Comparative Evaluation of Simvastatin Gel in Enhancing Peri-implant Osteoblastic Activity During the Osseointegration Phase Using Bone Scintigraphy: A Prospective Case-Control Double-Blinded Study

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Purpose: To estimate the effect of simvastatin gel in the osseointegration of dental implants using bone scintigraphy. ***Materials and Methods:*** A total of 20 participants with missing mandibular first molars and D2 type bone were assigned equally to two groups. Group A received 1.2% simvastatin and group B received placebo gels during the placement of implants. The participants were subjected to bone scintigraphy to determine the osteoblastic activity at baseline, 30 days, and 90 days after implant placement. ***Results:*** Group A had a significant increase in osteoblastic activity between baseline, day 30, and day 90 ($P < .05$), with a higher mean of 100.06% ± 21.644% on day 30. Group B had a significant increase in osteoblastic activity only between baseline and day 30 and between baseline and day 90 ($P < .05$). There was no difference between days 30 and 90 ($P > .05$), with a higher mean of 79.20% ± 18.255% on day 30. A bivariate analysis performed at different time periods revealed a significant difference between groups A and B on day 30. ***Conclusions:*** Implants placed with 1.2% simvastatin gel showed enhanced osteoblastic activity in the 4th week after implant placement, indicating that there was a faster rate of osseointegration at an early stage. *Int J Oral Maxillofac Implants 2024;39:707–712. doi: 10.11607/jomi.10741*

Keywords: osseointegration, osteoblastic activity, simvastatin

Proper implant design and the use of bone-growth enhancers in compromised bone has been shown to improve osseointegration.[1] The use of bone-growth enhancers without allogeneic or xenogeneic bone graft material has led to the application of drug compounds that could upregulate bone growth factors.[1,2] Simvastatin (SMV), an antilipemic drug, increased the expression of bone morphogenetic protein mRNA to promote bone formation and is researched widely for its osteopromoting properties.[3] Mundy et al[4] reported that SMV stimulated bone regeneration and promoted bone formation in a mouse calvarial defect model due to its anti-inflammatory, osteoblast-promoting, osteoclast-inhibiting, and neovascularization properties.

The systemic administration of statins presents a limited effect on bone healing due to their rapid hepatic excretion. Hence, a majority of animal studies favored the local administration of SMV to enhance bone regeneration.[5–9] Clinical trials performed with 1.2 mg of locally administered SMV gel in patients with type 2 diabetes mellitus for the management of grade II furcation defects demonstrated significant bone fill and improved periodontal attachment without any adverse reactions.[10–13] The osteogenic potential of SMV around dental implants in animal trials also proved promising.[14,15] However, the extrapolation of similar effects in humans would be ambiguous due to the limited amount of published data. Hence, the present study was conducted to assess the osteoblastic activity of locally administered SMV in the peri-implant region.

The null hypothesis was that there would be no statistical difference in the osteoblastic activity around dental implants that were treated with SMV compared to the control. This prospective double-blinded case-control study evaluated the effect of SMV on the osteoblastic activity around implants in vivo using bone scintigraphy.

The objective of the study was to assess the changes in the osteoblastic activity at different periods of assessment, including at baseline, on day 30, and on day 90 within the group as well as during each time period between the groups.

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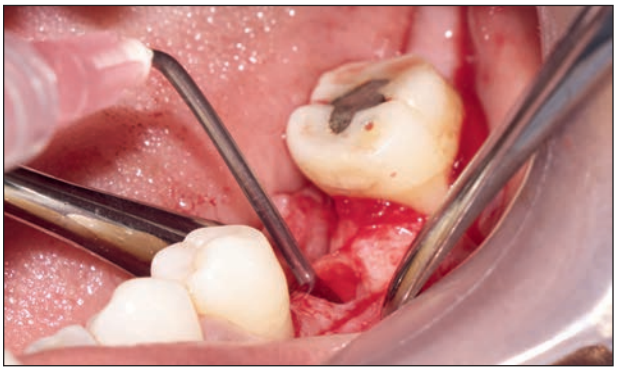

Fig 1 Injection of SMV gel around the osteotomy site.

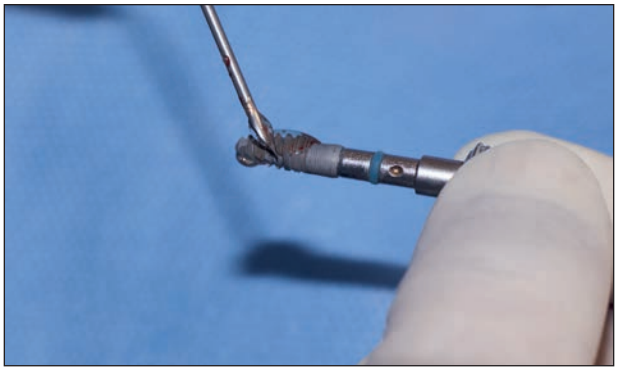

Fig 2 Coating of the implant with SMV gel.

MATERIALS AND METHODS

Study Design

A prospective double-blinded case-control study design was conducted in the Department of Prosthodontics and Implantology at Sri Ramachandra Dental College and Hospital in Chennai, India, following the STROBE guidelines. Ethical clearance with the declaration of Helsinki involving human subjects was obtained from the Institutional Ethics Committee (reference number CSP/16/NOV/52/288). Written informed consent was obtained from the participants before commencement of the study.

Based on a previous study,[16] the statistical power analysis was performed assuming the power of the sample at 95% with an alpha (α) error of 5% and an effect size of 1.8542, which led to a sample size of seven for each group. Considering the dropout of the participants, a total of 20 male and female participants with a unilateral missing mandibular first molar and type D2 bone were selected. The age group of the participants was between to 25 and 40 years, as the density of the bone in this age range remains stable without either bone growth[17] or bone mass reduction.[18] The participants were assigned to two treatment groups (10 in group A and 10 in group B), and they received SMV and the placebo gels, respectively. Allocation of the case and control groups was concealed from the clinician and investigator of scintigraphy. Any occlusal imbalances due to supraeruption or tilting of teeth were corrected prior to implant placement.

The exclusion criteria included *(1)* chronic smoking habits or alcohol/drug abuse; *(2)* liver disease; *(3)* systemic conditions that contraindicate implant placement, including use of medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and bisphosphonates that affect osseointegration; *(4)* bruxism; and *(5)* systemic statin therapy.

Preparation of the SMV and Placebo Gel

Commercially available methyl cellulose 4000 cPs powder (HiMedia) and SMV (Kniss Laboratories) powder were prepared into gels in a sterile environment at Kniss Laboratories. As specified by Thylin et al[14] and Hyeong et al,[19] 1.2% SMV gel in 4% methyl cellulose gel carrier was prepared to form a clear gel. The placebo gel was prepared by dispersing 2 g of methyl cellulose powder in 50 mL of distilled water with continuous stirring until a clear gel was formed. Then 1 mL of each gel (SMV and placebo) was loaded into insulin syringes under sterile conditions and sealed individually in airtight pouches. These pouches were marked A or B by an individual not involved in the study, and the investigator and participants were blinded about the groups to prevent bias.

Surgical Procedure and Scintigraphy Evaluation

Myriad Plus (Equinox, Straumann) two-piece root-form implants (3.8 × 11 mm) were placed by sequential osteotomy. Prior to implant placement, either 1.2% SMV (group A) or placebo (group B) gel was injected into each osteotomy site (Fig 1). The implants were also coated with the gel (Fig 2) before being placed in the osteotomy sites and torqued to 40 to 50 Ncm. The flap was closed for conventional healing of the implant with a delayed loading protocol, and a panoramic radiograph was taken (Fig 3).

The participants were recalled for multiphase bone scintigraphy to evaluate the osteoblastic activity 30 and 90 days after implant placement (Fig 4). An intravenous dose of 10 millicuries (mCi) of technetium-99m-methyl diphosphonate (Tc-99m-MDP) was administered while the patient was in the supine position; after 2.5 hours, nuclear images of the anterior and lateral views of the head and neck region were taken using a dual-headed gamma camera (Siemens Symbia Evo Excel). The osteoblastic activity was evaluated by drawing a region of interest (RoI) around the implant-bone interface that

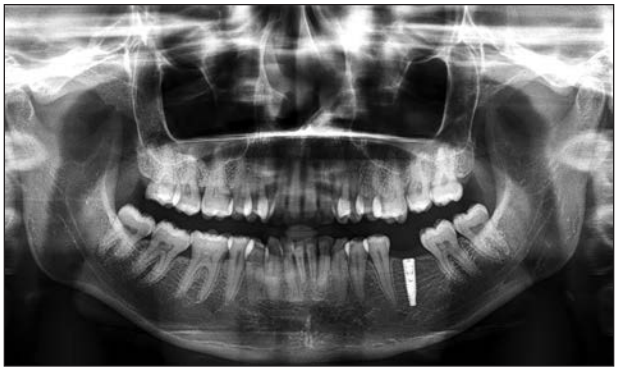

Fig 3 Postoperative panoramic radiograph showing an implant placed in the mandibular left first molar site.

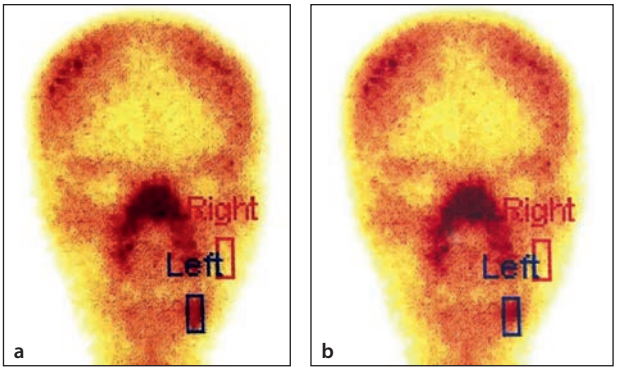

Fig 4 Bone scintigraphy analysis performed 30 days *(a)* and 90 days *(b)* after implant placement in the test group.

measured 66 pixels. A duplicate RoI of 66 pixels was placed in the mandibular ramus region to enable a scintigraphy comparison between the implant site and the native bone.[20] The mandibular ramus––known to have high osteogenic potential with low proliferative activity ––was used as a guideline to reduce bias due to the inherent osteoblastic activity in edentulous patients and the test site.[21] The osteoblastic activity was evaluated as counts/pixel using Syngo Siemens MI software, and the output was measured as the percentage (%) of radioactive isotopes. The participants were instructed to hydrate and empty the bladder frequently.

Intraoral periapical radiographs were taken on the day of implant placement and 90 days after stage-two surgery at the control and test sites. These radiographs were evaluated for changes in the crestal bone level (in millimeters) between the groups.

Statistical Analysis

The collected data were analyzed with IBM.SPSS statistics software, version 29.0. Descriptive statistics were performed to calculate the mean and SD. The Shapiro-Wilk test for normality showed that the data was normally distributed; hence, parametric analysis was conducted for the scintigraphy analysis. The Levene test was performed to test the assumption for equality of variance. The independent sample *t*-test was used to find the significant difference between the bivariate samples in independent groups (the study and control groups) during each time period. Repeated measures of ANOVA with a Bonferroni correction were performed to control the type I error on multiple comparisons of the osteoblastic activity between different time periods. To find the significant difference between the bivariate samples for analysis of changes in crestal bone level in independent groups, the Mann-Whitney *U* test was used. In all of these statistical analyses, the probability value of .05 ($P < .05$) was considered significant.

Table 1 Descriptive Statistics of Test and Control Groups for Osteoblastic Activity

Time period	Group A (test)		Group B (control)	
	Mean (%)	SD	Mean (%)	SD
Baseline	45.43%	6.109	41.19%	6.149
Day 30	100.06%	21.644	79.20%	18.255
Day 90	74.37%	15.149	67.26%	12.328

Table 2 Multivariate Analysis with Repeated Measures of ANOVA Between Various Time Periods in Test Group A

Time period	Mean difference (%)	SE	*P* value
Baseline – day 30	–54.627%	5.472	.000*
Baseline – day 90	–28.939%	4.285	.000*
Day 30 – 90	25.688%	7.251	.019*

SE = standard error.
*$P < .05$ is significant.

RESULTS

The Levene test revealed no significant difference between the test and control groups, depicting equality of variance among samples. The descriptive statistics for groups A and B are presented in Table 1. Multivariate analysis revealed a significant increase in osteoblastic activity in group A between baseline and 30 days, between 30 and 90 days, and between baseline and 90 days ($P < .05$), with a higher mean of 100.06% ± 21.644% at 30 days (Table 2). The multivariate analysis in group B, on the other hand, revealed a significant increase in osteoblastic activity only between baseline and the 30-day mark and between baseline and the 90-day mark ($P < .05$). There was no difference between 30 and 90 days ($P > .05$), and a higher mean of 79.20% ± 18.255% on day 30 was found (Table 3).

Table 3 Multivariate Analysis with Repeated Measures of ANOVA Between Various Time Periods in Control Group B

Time period	Mean difference (%)	SE	*P* value
Baseline – day 30	–38.013%	5.229	.000*
Baseline – day 90	–26.072%	4.578	.001*
Day 30 – 90	11.941%	6.017	.235

SE = standard error.
*$P < .05$ is significant.

Table 4 Bivariate Analysis Using Independent Sample *t*-test between Group A (Test) and Group B (Control) at Various Time Periods

Time period	Mean difference (%)	SE	*P* value
Baseline	4.24%	2.741	.139
Day 30	20.86%	8.954	.032*
Day 90	7.11%	6.177	.265
Baseline – day 30	16.48%	7.430	.040*
Baseline – day 90	2.87%	6.270	.653
Day 30 – 90	13.75%	9.422	.162

SE = standard error.
*$P < .05$ is significant.

Bivariate analysis at different time periods revealed a significant difference between groups A and B on day 30 ($P < .05$), with a high mean score of 100.06% ± 21.644% for group A. In addition, the mean difference between baseline and day 30 in the osteoblastic activity of groups A and B showed a significant difference in the comparative analysis between the groups ($P < .05$; Table 4).

Bivariate analysis of the crestal bone level showed a significant difference between the two groups ($P < .05$), with a mean of 0.15 ± 0.10 mm for group A and –0.22 ± 0.06 mm for group B.

DISCUSSIONS

The null hypothesis was rejected, and we found that local administration of SMV at the implant site improved osteogenesis. We also observed no signs of inflammation or untoward consequences in our study with the local delivery of SMV gel during the evaluated 3 months. This research is in agreement with previous research conducted regarding periodontal therapy.[11] SMV, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor in the mevalonate pathway, indirectly promotes bone morphogenetic protein 2 (BMP-2) synthesis by activation of the membrane-bound Ras/Smad/Erk/BMP-2 pathway to differentiate osteoblastic cells.[3] SMV administered systemically also resulted in improved bone-to-implant contact (BIC), greater bone density, and higher mechanical strength around titanium implants in rats (but with rapid hepatic excretion).[22,23] On the other hand, local administration of SMV in the animal model delivered an adequate dosage to the desired area and proved to be more efficient in promoting bone formation.[24,25] SMV improved implant osseointegration in numerous animalstudies,[6–10] but there is a lack of substantial evidence on its effect on dental implants in humans.[26]

SMV, a lipophilic drug, is usually combined with a carrier at varying concentrations of 4%, 5%, or 6% to allow a sustained release of the drug and improve its absorption into local sites.[13,25] In vitro kinetics has also proved the sustained release of the drug.[27] However, the viscosity is 28 Pa-s for 4% and 87 Pa-s for 6% gel,[25] and such viscosity would prevent the flow of material through a sterile syringe, so 1 mL of 4% methyl cellulose gel with 1.2% SMV concentration was used in the present study to maintain the volume of drug delivered at an equal quantity.[13,27]

Bone scintigraphy is a highly sensitive nuclear medicine imaging technique that shows significant bone changes in the dynamic state compared to the static images of CT and MRI.[28] Although histologic and histomorphometric analysis depicts specific static bone changes, it is not possible in human clinical research. Bone scintigraphy enabled dynamic longitudinal observation of bone metabolism in the present study to evaluate osteoblastic activity around the implants.[29–33] Tc-99m-MDP molecules are bone-seeking agents that are absorbed by the crystalline hydroxyapatite minerals in bone proportionate to local blood flow to exhibit active osteoblastic activity.[30,34,35] The outcome was considered to be in concurrence with the static histologic analysis in estimating bone turnover.[29,36] However, pathologic changes or anatomical details are relatively low with scintigraphy.[36] Tc-99m-MDP has a half-life of 6 hours, and the injected dose leaves the body in a short period.[29] Moreover, the amount of ionizing dose is less than 0.02 mSv, which is far less than the annual natural radiation dose of 3 mSv that an individual receives.[37] Parihar et al[38] reported that radiopharmaceutical extravasation of patients with Tc-99m-MDP was only 0.37% at a 12-year duration and only 0.009% of patients had short-term local symptoms in reported cases with no long-term adverse events.

We evaluated the osteoblastic activity at baseline, day 30, and day 90, because osteoblastic activity is at its peak 3 to 4 weeks after implant placement followed by a rapid decline toward baseline values at week 16, which indicates near completion of the osseointegration process.[7,15] We observed a nonsignificant increase of 4.245 counts/pixel of osteoblastic activity between

the two groups at baseline, depicting the homogeneity of participants in both groups. We observed peak osteoblastic activity in both groups 30 days after implant placement, which declined by day 90. This indicated peak osteoblastic expression on day 30 with a gradual decrease to normal physiologic levels after 4 months. However, we observed significantly higher osteoblastic activity in the SMV group than the control group. Tc-99m-MDP molecules are specific markers for the anabolic phase of bone remodeling during increased organic matrix formation suggestive of increased osteoblastic activity.[33] Ayukawa et al[6] found that there were abundant, thick bony trabeculae with a meshlike structure as well as greater BIC on day 30; likewise, this was observed as peak osteoblastic activity in the present study.

Higher osteoblastic activity was noted in the SMV group compared to the control group at both day 30 and day 90, but maximum osteoblastic activity was observed on day 30 in the SMV group. Ayukawa et al[7] and Du et al[15] also showed evidence of significant osteogenic potential on days 30 and 90 in an animal model. This could also be attributed to the release kinetics of the SMV in methyl cellulose that was observed at 30 days. Du et al[15] investigated the effect of SMV around titanium implants in rats using bone-formation markers and concluded that SMV induced greater bone formation 4 weeks after implant placement compared to the control group, with increased expression of bone alkaline phosphatase and bone Gla protein, indicating an increased osteoblastic response. Xu et al[39] also reported greater trabecular bone formation and an accelerated osseointegration process in a rat model at week 4. This was in concurrence with our radiographic finding that the control group experienced more bone loss than the SMV group.

There was a significant decrease in the osteoblastic activity in the SMV group on day 90 in comparison to day 30, whereas there was a nonsignificant decrease in the osteoblastic activity in the control group between the evaluated days. Stein et al[27] observed that the administration of SMV in a methyl cellulose carrier on the lateral aspect of the rat mandible demonstrated a drastic increase in bone formation within the first 7 days, and Gutierrez et al[24] reported a 150% increase in bone formation at the end of week 4. The present study also observed that osteoblastic activity was more similar between the groups on day 90 of the evaluation. This indicated increased osteoblastic activity, enhancing the osseointegration process at a faster rate and at an earlier stage, in the presence of SMV. However, our outcome contradicted the conclusion of previous studies that showed a continual increase in osteoblastic activity markers in the serum even on day 84 in an animal model.[15]

Although the osteoblastic activity in the SMV group was not equivalent to the baseline values on day 90, its rapid decline indicates that the osseointegration process was in its final phase. Brånemark et al[40] stated that the development of intimate bone contact presents as an increase in collagen fibers and osteoblasts within 4 weeks, indicating abundant bone turnover and mineralization. Three months after implantation, a mixed bone texture of woven and lamellar matrix can be found around the implants with reduced osteoblastic activity, indicating that the osseointegration process is almost complete.[41,42] Therefore, a significantly higher peak in osteoblastic activity on day 30 indicated near completion of the osseointegration process on day 90 in the SMV group. Furthermore, increased bone density at the early stage of healing can improve implant stability and successfully disperse the stress applied to the implant.[43]

Bone scintigraphy reflects the cellular-level changes in osteoblastic activity and bone metabolism that are essential for osseointegration; it does not measure the level of bone-implant integration directly, which is certainly a limitation of this study. However, the enhanced osteoblastic activity observed with scintigraphy was correlated with radiographic data that showed bone gain and thereby confirmed the results of scintigraphy. In addition, the effects of bone quality and loading were not evaluated, which may be an avenue for future research.

The findings of the present study showed the osteogenic potential of 1.2% SMV in increasing the rate of osseointegration of dental implants in humans. Indicators for early implant placement include improved BIC with greater bone density of trabecular bone and a higher bone turnover rate during the early stages of osseointegration, as these indicate the bone's ability to distribute the occlusal load.[8,22] However, its implications on the quality of bone formation, bone-implant interface, and response to early loading in humans need to be studied. Further research on the effect of SMV gel in immediate implant placement and loading would provide in-depth knowledge on the effect of accelerated osteoblastic activity in bone healing.

CONCLUSIONS

The topical application of 1.2% SMV gel in a 4% methyl cellulose carrier promoted osteoblastic activity around dental implants. The peak osteoblastic activity observed within 4 weeks of implant placement depicted an increased rate of osseointegration that reached near completion by 12 weeks.

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