Simvastatin Effects on Dental Socket Quality: A Comparative Study

Abstract

Background: The shrinkage of the alveolar ridge might be minimized by the ridge preservation stages and applied alloplasts, after tooth extraction. According to studies on statins, angiogenesis and osteogenesis are observed as a topical application of these drugs. Objectives: The aim of this study is to the application of simvastatin in terms of bone regeneration of the alveolar ridge after tooth extraction. Materials and Methods: This study assessed this issue through the split-mouth method which assessed 10 dental sockets filled with simvastatin and collagen and 10 others filled just by collagen postextration. The histological process of bone samples was observed under light microscope after 2 months at the time of fixture insertion to evaluate live and dead bone, trabecular, amorphous, and nonosteoblastic. The statistical analysis was assessed using Mann–Whitney U-test and level of significance was considered <0.05. Results: Normal bone was detected in both groups. In simvastatin group, the percentages of vital bone, amorphous, and trabecular bone were more than the other group and the percentages of dead bone and nonosteoblastic were lower, although there was no significant difference in the results. Conclusion: Based on study results, simvastatin possibly can improve the quality of osteogenesis in the jaw bone; however, further studies are necessary to definitively result.

Keywords: Dental socket preservation, regeneration, statin

Introduction

After tooth extraction, decreasing in amount of alveolar bone and socket occurs as the result of bone loss.[1] Bone loss comes as an inevitable consequence of tooth extraction that is the result of changes in physiological status of bone.[2] If do not take action to preserve bone and bone regeneration, severe bone loss will happen that makes fixture insertion difficult and makes the requirement of aggressive and costly treatments essential such as bone graft.[3] The best time to preserve the alveolar ridge is at the time of extraction. Bone preserving guarantees success of implant.[4] Bone preservation can prevent 40%-60% of the jaw bone atrophy that normally happens 2–3 years after tooth extraction and continues at a rate of 25%-15% per year until death.[5]

The use of autogenous bone graft to repair bone defects mentioned as the golden standard but has limited sources, also has complications such as bleeding, pain, and infection.[3] The existing methods of ridge preservation include the use of autogenous, allogenic, xenogenous grafts, and alloplasts.[6] The biological mechanisms that support the use of bone graft materials include: osteogenesis, osteoconduct, and osteoinduction.[7] Although autogenous bone graft unambiguously accepted as the standard, extensive studies are in progress in relation to allogenic, xenogenous grafts to avoid autogenous bone resection.[8,9] For many years, the golden standard for bone grafting was autogenous bone sources from inside or outside of the mouth. Researchers for suitable bone alternative materials due to lack of autogenous bone, surgical instruments and limited available bone volume have increased in recent years.[10]

3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors or statins are widely used to reduce blood cholesterol levels that is an important factor in the treatment of hyperlipidemia and atherosclerotic disease. Most recently, other effects of statins are taken into consideration to related systemic side effects as common forms including atrial fibrillation, bronchitis, muscle pain, muscle problems, acute infection of the nose, throat or sinus, constipation, diarrhea, dizzy, feel like throwing up, gas, head pain, heartburn indigestion, infection, intense abdominal pain, rash, and stomach

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It has been shown in various studies that statins increase differentiation of osteoblasts by stimulating bone morphogenetic protein 2 (BMP-2) that show their potential as new osteogenic drugs.\textsuperscript{[12-16]} Statins are expected to be used as a new treatment to replace BMP-2 since they produce 16,000 times cheaper than BMP-2.\textsuperscript{[12]} Various methods have been tested for the local insertion of statins, which include the use of collagen gel, polyglycol, etc.\textsuperscript{[17-19]} New bone formation around the compound of gelatin hydrogel containing fluvastatin has been reported.\textsuperscript{[20]} Furthermore, reports of acceleration in wound healing related to the enhancement of angiogenesis after application of topical simvastatin might be notable.\textsuperscript{[21]} On the other hand, the biological effects of statins on bone metabolism have been evaluated in other studies.\textsuperscript{[22-27]}

Despite proving the effectiveness of statins on bone metabolism, direct study on the use of these drugs to preserve the tooth socket has not been done. Therefore, the present study has been done to evaluate the effect of simvastatin on bone quality of extracted tooth to the achievement of better postextraction socket healing.

**Materials and Methods**

This study with stratification randomized single-blind design was conducted to evaluate the histomorphometric effect of simvastatin on bone formation in patients seeking implant insertion, after obtaining approval from ethics committee, Dental branch of Tehran, Islamic Azad University. Sampling was done by purposive sampling method and sockets with simvastatin were randomly selected. In patients with indication of two teeth extractions, after tooth extraction, curettage and washing the cavity with saline, the statin drug, simvastatin in the study (Sivastrol 20, 20 mg, manufactured by Tehran Chemie Pharmaceutical Co.,) with collagen was placed in one of the sockets (one 20 mg tablet in the form of powdered), and then, flap was returned and sutured so that the opening be blocked. In the other socket, only collagen was placed. At the next visit after 2 months later for the insertion of implants, samples from the tooth cavities were taken to histological checking of bone quality.\textsuperscript{[22]} In this study, the patients who referred to Tehran Islamic Azad University of Dentistry, for tooth extraction and implant placement, from 2015 to 2016, in the case of patient satisfaction, if there were no exclusion criteria (including systemic diseases, diabetes, pregnancy, periodontitis, history of radiation therapy, and the use of steroids, there is need for allergy prophylaxis), participated in this the project. In this study, 20 tooth sockets, in two groups of 10 teeth, were evaluated. Selection of socket which was going to be filled with simvastatin was using the stratification randomized. The next stage of work was performed 2 months later. In spite of placing implant, with surgical trephine, bone samples were taken from the middle part of socket for histologic evaluation and were put in 10% formalin for 48 h to fixation. The samples were placed in 10% formic acid for decalcification for a week then they were cut longitudinally to a thickness of 5 micron, then stained with hematoxylin and eosin method under magnifications of 100 of the Nikon YS-100 optical microscope by the use of scaled lens to determine live and dead bone, trabecular, amorphous, and nonosteoblastic. Figures 1-3 demonstrate histological section of evaluated samples and Figure 4 exhibits clinical feature related to the application of simvastatin.

Changes in bone regeneration rate in both groups were performed using t-test and the quality of bone generation was performed using Mann–Whitney U-test and \( P < 0.05 \).

**Results**

This study was performed on 20 dental sockets which of 10 contained simvastatin and 10 of them without that. The patients were of two men and a woman with an average age of 41. Data about histological study are gathered in Table 1 that shows the percentage of vital bone in simvastatin group is 20.3 ± 12.90 and in the other group is 17.2 ± 10.019 that the difference is not statistically significant (\( P < 0.7 \)) and the percentage of nonvital bone in simvastatin group is 33.7 ± 21.57 and in the other group is 35 ± 18.55 that the difference is not statistically significant (\( P < 0.7 \)).

The percentage of amorphous bone in simvastatin group is 20.3 ± 12.90 and in the other group is 17.2 ± 10.019 that the difference is not statistically significant (\( P < 0.7 \)).

The percentage of trabecular bone in simvastatin group is 10.3 ± 9.83 and in the other group is 10.1 ± 10.59 that the difference is not statistically significant (\( P < 0.9 \)).

The percentage of amorphous bone in simvastatin group is 10 ± 7.31 and in the other group is 7.3 ± 5.27 that the difference is not statistically significant (\( P < 0.9 \)).

The percentage of nonosteoblastic in simvastatin group is 46 ± 12.05 and in the other group is 47.8 ± 10.71 that the difference is not statistically significant (\( P < 0.9 \)).

**Discussion**

This study showed that the use of simvastatin increases the rate of vital bone and reduces necrotic bone in the samples containing simvastatin compared to other group; however, the differences are not significant. In the literature review, there is no article in relation to the effect of the drug on

| Experimental groups | Vital bone \( \overline{x} \pm \text{SD} \) | Nonvital bone \( \overline{x} \pm \text{SD} \) | Trabecular pattern \( \overline{x} \pm \text{SD} \) | Amorphous bone \( \overline{x} \pm \text{SD} \) | Nonosteoblastic \( \overline{x} \pm \text{SD} \) |
|----------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Simvastatin \((n=10)\) | 20.3 ±12.90 | 33.7±21.57 | 10.3±9.83 | 10±7.31 | 46±12.05 |
| Collagen only \((n=10)\) | 17.2±10.019 | 35±18.55 | 10.1±10.59 | 7.3±5.27 | 47.8±10.71 |
| \( P \) | <0.7 | <0.8 | <0.9 | <0.3 | <0.9 |
human model to analyze the similarities and contrasts, but all similar studies in animal models or related studies on human have reported that the use of simvastatin improves bone quality.\(^{24,29-31}\) Rao et al., in 2012, studied on simvastatin local drug delivery in smokers with chronic periodontitis. Clinical parameters at baseline and at 3, 6, and 9 months later were recorded including modified sulcus bleeding index, probing depth (PD), and clinical attachment level (CAL). At baseline and at 6 and 9 months later, radiographic evaluation of internal bone defect was performed by computer software. The results showed that the rate of reduction in PD and the return of CAL in simvastatin group was more than placebo group in entire examinations. Thus, greater average of bone filling in the simvastatin group was observed compared to placebo.\(^{29}\) Study is valuable since was done on human model but in terms of method is different with present study and the drug has not been used in the socket also the follow-up times are different. Tanabe et al., in 2012, studied on osteogenic effect of fluvastatin combined with biodegradable gelatin hydrogel. Two circular defects were surgically created on 15-week-old male rats calvaria. All defects of each rat were randomly filled with two of three treatments, specifically: fluvastatin incorporated into a GH disk (Flu-GH), distilled water incorporated into a GH disk, and no treatment. A highly osteogenic effect was observed in the Flu-GH group. The results showed that the fluvastatin incorporated into a biodegradable GH scaffold promoted osteogenesis in rat calvarial bone, indicating its potential for bone regeneration.\(^{30}\) This study was done on animal models that reduces its diagnostic value, also workspace was outside of the mouth. Behzad Houshmand et al. performed a study by title of simvastatin and lovastatin induce ectopic bone formation in rat subcutaneous tissue. Cartilage formation was observed in simvastatin-treated area in one rat after 6 weeks. Bone formation was also evident in lovastatin-treated area in one rat and simvastatin-treated area in another after this period. No hard tissue formation was detected in muscles.\(^{31}\) Study shows the improvement of bone quality in relation to drugs although samples are animal models, workspace was outside of the mouth and the follow-up times are different too. Wu et al., in 2008, studied on effect of simvastatin on remodeling of the...
alveolar bone following tooth extraction. A total of 60 male Wistar rats were randomly divided into experimental and control groups (n = 30). Polyactic acid/polyglycolic acid copolymer carriers, with or without simvastatin, were implanted into extraction sockets of the right mandibular incisors. The rats were killed at 1, 2, 4, 8, or 12 weeks after implantation. The relative height of the residual alveolar ridge was significantly greater in the experimental group compared to the control group at 2, 4, 8, and 12 weeks. The bone mineral density in the experimental group was significantly higher than that in the control group at 4, 8, and 12 weeks. A larger newly formed bone island was observed in the experimental group at 4 weeks, and higher bone formation rate and quality were found than in the control group at different time points except 1 week. The findings indicate that the local application of simvastatin would effectively preserve the residual alveolar bone by promoting bone formation in the extraction socket.

The type of material used (simvastatin) is consistent with present study, but samples are animal models that reduces the generalizability of man. Contrary to Wu research, in the present study, case and control groups are related to one person and also follow-up times are different.

In the present study, although osteogenesis has been done within 2 months with no trace of drug, but for longer duration of study, changes in bone quality in relation to drug may be seen. In addition, a higher number of samples may provide a more reliable population. Finally, in the case of this study, it should be noted in this issue for the first time in human samples since research on animal models certainly is not generalizable to humans. Furthermore, the study has been done by the best way of matching and the most powerful version of study which is split mouth that minimizes intervening variables. Although it is recommended to examine the osteogenesis of different statins for longer than 2 months, and a higher number of samples in another study. At the end, according to the results, the use of these materials is recommended to control of alveolar ridge bone loss and improvement of results in the loading of the implant.

**Conclusion**

Based on the results of this study, simvastatin could possibly improve the quality of osteogenesis in the jaw bone are, however, more studies are necessary to the certainty of the result.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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