Clinical evaluation of simvastatin-gelatin sponge application in preservation of alveolar bone after tooth extraction

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Abstract

Alveolar bone resorption after tooth extraction is a natural healing process resulting in aesthetic and functional problems when extracted tooth is replaced by artificial prosthesis. Recent research works are focusing on developing new materials and strategies that are simple, effective, easily available and less expensive in preserving remaining alveolar bone. Topically applied simvastatin, a cholesterol-lowering drug, has been shown to stimulate BMP-2, TGF-beta and VEGF mRNA expression in osteoblasts and promote bone regeneration. Gelatin sponge is widely used for the prophylaxis of wound infections and secondary bleeding after extractions. The present study was aimed to evaluate alveolar bone preservation after application of simvastatin-gelatin sponge combination after tooth extraction. The material was placed in the extraction socket of 30 participants immediately after extraction of diseased tooth. Cone-beam Computed Tomography radiographs were taken immediately, 1 and 3 months after extraction. Bone height and width of remaining alveolar bone were measured at different levels in radiographs. Repeated measure ANOVA was employed to evaluate the differences in measured parameters between study time points. The results showed that there was no significant change in bone height and bone width during study period. It is concluded that application of simvastatin-gelatin sponge combination in extracted socket effectively preserves remaining alveolar bone after extraction until 3 months.

Keywords: simvastatin, alveolar bone preservation, gelatin sponge, extracted socket

INTRODUCTION

The resorption and remodeling of the alveolar ridge after tooth removal is a natural healing phenomenon, which is physiologically undesirable and possibly inevitable and it can negatively impact the rehabilitation by artificial tooth replacement.[1, 2, 3] This includes but not limited to inadequate bone volume to accommodate dental implants, unstable dentures and unaesthetic dental restorations. Roots of maxillary premolar and molar teeth usually have very close relation with the floor of the maxillary air sinus and extraction of these teeth result in alveolar bone resorption both crestally and from floor of the maxillary sinus, due to accelerated pneumatization of maxillary sinus after tooth extraction. Bone augmentation

procedures are performed during or before prosthetic rehabilitation procedures in order to achieve desirable bone volume for satisfactory and successful dental restorations; however, these procedures are technique-sensitive, time-consuming, costly and post additional trauma and discomfort to the patient.

Recent research works are targeting to develop new materials and strategies to augment the deficient bone and to preserve the remaining alveolar ridge after tooth extraction by bone regeneration. To be practically applicable in daily clinical practice, the material or strategy should be simple, effective, easily available and less expensive. Bone regeneration requires three essential components: signaling molecule, scaffold which acts as osteoconductive surface to support osteoblastic bone formation, and cells responsible for bone formation. One strategy is to use *in situ* tissue regeneration approach in which new tissue formation is induced by specific scaffold with external stimuli that are used to stimulate body's own cells and promote local tissue repair. Topically applied simvastatin, a cholesterol-lowering drug, has been shown to stimulate BMP-2, TGF-beta and VEGF mRNA expression in osteoblasts[4] and promote bone regeneration.[5, 6, 7, 8, 9, 10, 11] Statins have been used in medicine for the treatment of hypercholesterolaemia and its safety has been well-documented. Gelatin sponge is widely used for the prophylaxis of wound infections and secondary bleeding after extractions. In the present study, gelatin sponge (Gelatamp, Coltene, Brasil) was used as carrier for simvastatin and as a scaffold. It contains colloidal silver and is therefore distinctly different from pure gelatin sponges. The silver leads to a broad antibacterial effect over the entire absorption time. The advantages are rapid initial hemostasis, stabilization of the coagulum, broad bactericidal depot effect and complete resorption. It is less expensive and readily available.

Single topical application of simvastatin-gelatin sponge material would be cost-effective and beneficial for the patients who undergo tooth extraction and who will have prosthodontic tooth replacement in the future by preserving the remaining alveolar bone after tooth extraction.

The objective of this research is to evaluate the effect of simvastatin-gelatin sponge on preservation of post-extraction dental alveolar bone dimension after 1 and 3 months after extraction.

MATERIALS AND METHODS

A before-and-after clinical study was carried out. The study participants were selected from the adult patients who seek the dental treatment for extraction and replacement of natural tooth or teeth at Dental Department, Mandalay General Hospital (n=30). Proper informed consent was taken after thorough explanation of detail procedure, benefits and potential risks of surgery such as pain and discomfort. Only medically fit patients were selected to include in the study. Proper pre-operative medical assessment and necessary pre- and post-operative medication were provided. After finishing the research, the participants were routinely treated with appropriate prosthodontic rehabilitation.

Simvastatin-gelatin sponge material was prepared as followed; Gelatin sponge (Gelatamp, Coltene, Brasil)) was used. One Gelatamp gelatin sponge has a dimension of 14 × 7 × 7 mm and it contains hardened gelatin Ph. Eur. 9.5 mg and colloid silver Ph. Eur. 0.5 mg. Simvastatin-gelatin sponge was prepared by crushing simvastatin tablet (10 mg), dissolving in ethanol and dropping into gelatin sponges in a concentration of 1 mg simvastatin in one gelatin sponge. Ethanol

was dried out and the material was stored in sterile container.

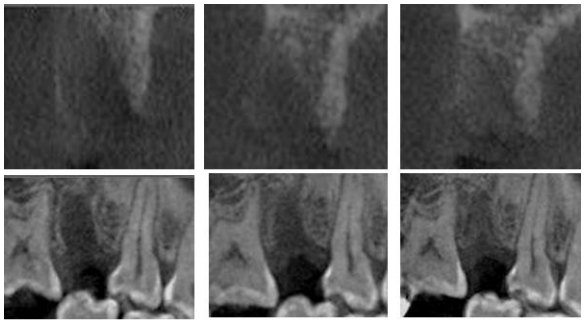
Pre-extraction periapical radiograph were taken. Tooth or teeth with active infection was excluded. Extraction of indicated tooth was performed atraumatically. The extracted socket was thoroughly scraped so that no granulation tissue was left inside. Then, the prepared material was packed into the socket and sutured with vicryl sutures in figure 8 pattern to retain the graft. Post-extraction cone-beam computed tomography (CBCT) radiographs were taken immediately, 1 month and 3 months after extraction. Alveolar bone height and width of the residual alveolar ridge were measured in the CBCT radiographs. Change in alveolar bone height was measured in the sagittal view of CBCT radiographs by determining the distance from the occlusal plane joining adjacent remaining teeth to the crests of remaining alveolar bone. The distance at baseline was denoted as (D-0), at one month post-extraction as (D-1) and at 3 months post-extraction as (D-3). If D-1 and D-3 become longer than D-0, it means that alveolar bone height was reduced and the reverse is true if D-1 and D-3 become shorter. Alveolar bone width was measured at three different regions of remaining alveolar bone (apical, middle and coronal) in axial view of CBCT radiographs. Data was calculated as mean $\pm$ standard deviation and repeated measure ANOVA test was employed to analyze the data.

Ethics approval and consent to participate

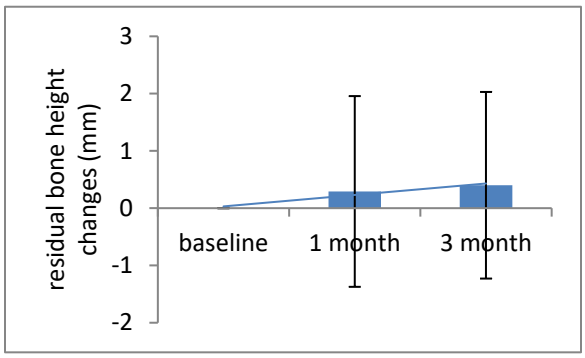
The study received human subjects approval from Research and Ethical Committee, University of Dental Medicine, Mandalay with ERC approval date: 7th June, 2019 and ERC approval number: Ethical/UDMM/2019/05. All participants provided written informed consent to participate.

RESULTS

All participants were female with mean age of 41 years (ranging from 16-73 years old). Among them, 75% of participants were under 60 years of age and the remaining 25% were over 60 years old. All participants reported uneventful healing of extracted socket without pain and swelling. Clinically, the residual alveolar ridges were similar in shape and volume through the observation period until 3 months. In CBCT radiographic images, extracted socket appeared as radiolucent root-formed space immediately after extraction. After 1 month, the slightly radiopaque new bone was seen forming from the sides of the sockets as well as from the base rendering the socket size smaller compared with the baseline. At 3 months, CBCT images revealed that the extracted sockets were almost completely filled with relatively less radiodense newly formed bone (figure 1).



Changes in the residual alveolar bone height at the extraction site were illustrated in figure 2. Slight but not statistically significant increase in bone height was observed at 1 month and 3 months after extraction.



As demonstrated in table 1, the width of residual bone at coronal region of extracted socket was slightly decreased from baseline to 1 and 3 months after extraction, but the difference was not statistically significant. In contrast, the width of residual bone at middle and apical regions of extracted socket showed slight increase at 1 month and decrease again at 3 months the final width being similar to baseline value. Again, the differences were not statistically significant.

Taken together, the results indicated that the dimensions of remaining alveolar bone after extraction were not significantly changed until 3 months.

DISCUSSION

Bone resorption after tooth extraction is an unavoidable physiological process. It seemed to be more pronounced during the initial phase of socket healing than during later periods following tooth extraction.[9] Johnson (1969) and Schropp et al. (2003) reported that most of the dimensional alterations – horizontal as well as vertical – of the alveolar bone took place during the first 3 months of extraction[15, 16]. According to a systemic review, the weighted mean changes as based on the data derived from the individual selected studies show the clinical loss in width (3.87 mm) to be greater than the loss in height, assessed both clinically (1.67–2.03 mm) as well as radiographically (1.53 mm) during the post-extraction healing period.[17] In the present study, the bone height was not obviously reduced; it was slightly increased but not to a clinically significant level. This may be partly due to the osteopromotive effect of simvastatin release from the gelatin sponge and partly due to presence of adjacent teeth proximal to extracted socket that can retain periodontal tissues and bone. Since the results showed a slight increase in bone width at apical and middle regions of the socket at 1 month after extraction and declined again at 3 months, the osteopromotive effect of simvastatin seemed to last until 1 month of healing while bone remodeling took place at 3 months. Nevertheless, the residual alveolar bone volume was maintained by the use of simvastatin-gelatin material.

Simvastatin has been shown to upregulate expression of BMP-2, TGF-beta and VEGF genes after local application in bone defects. [4, 5, 6, 7, 8, 9, 10, 11] It has been used to stimulate bone regeneration in pre-clinical peri-implant bone regeneration and osseointegration, treatment of human periodontal bone defects and alveolar bone preservation after extraction.[12, 13, 14] Saifi et al (2017) conducted similar study using simvastatin and gelatin sponge to evaluate the efficacy of simvastatin on bone formation in extraction sockets in a split mouth study design. In contrast to the present study, bone fill in the extraction sockets was measured immediately, 1 and 4 months after extraction. They concluded that local application of simvastatin induces bone formation in extraction sockets.[14] Direct comparison between two studies is difficult because the dose of simvastatin was different and the measured parameters were also different.

In previous studies, various carriers for simvastatin were used such as collagen sponge, PLGA, methyl cellulose, calcium phosphate and tri-calcium phosphate. [5, 6, 7, 8,

[9, 10, 11] Certain conditions must be considered when selecting an appropriate carrier or delivery system for drugs : (1) the ability of the system to deliver the drug at the appropriate time and in the proper dose, (2) the presence of a substratum that will enhance cell recruitment and attachment and will potentiate chemotaxis, (3) the presence of a void space to allow for cell migration and to promote angiogenesis, and (4) the ability of the delivery system to biodegrade without generating an immune or inflammatory response and without producing toxic waste products that would inhibit the repair process.[18] Gelatamp used in this study is a haemostatically acting gelatin sponge to which 5% colloidal silver is added. It facilitates optimum wound treatment when applied to a surgical cavity and can be cut to the required size to fit smaller wound cavities. The evenly porous foam structure absorbs its own weight in blood several times over, promotes thrombocyte aggregation due to the large surface and fills the wound cavity. The plug thus formed has a constant volume, fits snugly and stabilizes blood coagulum. This prevents the formation of fissures and secondary cavities which, without Gelatamp, could form by contraction of the blood coagulum and trigger infection due to the invasion of contaminated saliva. Callus formation is not hindered in this way. Impaired wound healing in larger surgical cavities is thus avoided. Gelatamp remains in the wound and is completely absorbed within four weeks. The addition of colloidal silver has an antimicrobial effect and does not develop resistance. Unlike other potential antimicrobial additives, colloidal silver cannot be washed away from the sponge so that its insolubility produces a long lasting depot effect. Being spongy in nature, gelatin can absorb simvastatin solution well and retain the drug after the solvent was dried out. Not only it acts as excellent drug carrier, it would had functioned well as scaffold for blood clot formation, cellular organization, neovascular formation and tissue regeneration owing to its porous structure. Since the drug can be released from the gelatin during early phases of wound healing, such molecular and cellular stimulation would result in enhanced tissue regeneration.

The limitations of the present study are; the observation time was of only short terms. It may be necessary to observe longer-term changes of the alveolar bone. Also histological analysis was not done to assess the quality of newly formed bone. In the future long-term studies, cases requiring dental implant placement for prosthetic rehabilitation can be included so that bone samples for histological examination can be taken during bone drilling for implant placement surgery.

Within the limitations of this study, it can be concluded that simvastatin-gelatin sponge combination effectively helps to maintain remaining alveolar bone dimension after tooth extraction until 3 months. It is advantageous to preserve the dimension of the post-extraction alveolar ridge immediately instead of reconstructing it thereafter, thus maintaining its ideal vertical and horizontal dimensions and decreasing patient morbidity and extra cost. Single topical application of simvastatin-gelatin sponge material would be cost-effective and beneficial for the patients who undergo tooth extraction and who will have prosthodontic tooth replacement in the future by preserving the remaining alveolar bone after tooth extraction. Dental practitioners can apply the material easily after extraction and thus preserve the remaining alveolar bone, enabling to prescribe more aesthetic and functional dental prostheses for the patients.

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Regions of alveolar socket	Bone width at baseline (mm)	Bone width at 1 month after extraction (mm)	Bone width at 3 months after extraction (mm)
Coronal region	9.29 (±3.42)	9.14 (±3.15)	8.29 (±4.12)
Middle region	8.92 (±3.03)	9.25 (±2.65)	8.52 (±3.4)
Apical region	8.36 (±3.8)	9.49 (±2.65)	9.00 (±3.69)

Table 1. Changes in remaining alveolar bone width from baseline (immediately after extraction) to 1 month and 3 months after extraction. Values were shown as mean (±standard deviation).