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ORIGINAL ARTICLE

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Maxillary sinus lift using osteoinductive simvastatin combined with β-TCP versus β-TCP – a comparative pilot study to evaluate simvastatin enhanced and accelerated bone formation

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ABSTRACT

Purpose: The aim of this study was to evaluate available bone quality and quantity after performing sinus augmentation using simvastatin/β-TCP combination versus β-TCP alone.

Materials and methods: This study included eight sinus lift procedures conducted on six patients. The sinuses were divided into two equal groups. The patients were recalled one, two weeks two, five, nine months post-operatively for post-operative evaluation. Radiographic evaluation involved cone beam computed tomography (CBCT) radiographs taken for every patient one week and nine months post-operatively to evaluate the changes in bone height, while histomorphometric evaluation involved transcortical bone biopsies taken after nine months during the second-stage surgery for implant placement.

Results: The histomorphometric results showed that the amount of newly formed bone was higher in the simvastatin group when compared to the β-TCP group nine months after the surgery; the difference between the two groups was statistically significant. On the other hand, the radiographic evaluation showed that the rate of resorption of the simvastatin group was found to be higher than the control group; however, the difference between both groups was statistically insignificant.

Conclusion: These results showed that Simvastatin is safe to be used in sinus lift with promising osteoinductive capacity, yet further studies using larger sample size is needed.

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KEYWORDS
Simvastatin; sinus lift; tissue regeneration; implant

Introduction

Sinus lifting is a surgical procedure that aims to facilitate implant placement in the posterior maxilla following teeth extraction via superior repositioning of the sinus lining with the placement of bone graft in the created space to increase the available alveolar bone height, thus overcome the unfavourable local conditions that may interfere with obtaining sufficient primary stability of dental implants [1].

In spite of being the gold standard for bone regeneration owing to its superior osteogenic properties, yet various graft materials were widely used in sinus lift in order to avoid the donor site morbidity and other disadvantages of autogenous graft [2,3]. However, in addition to the associated antigenicity and lack of osteoinductive properties that represent major drawbacks of these graft materials [4,5], the risk of disease transmission – being harvested from cadavers and bovine sources – should always be kept in consideration in spite of using several methods of tissue processing [6] that decreased the risk of HIV transmission for instance to one case out of 1.6 million cases that received allografts [7]. The possibility of combining an osteoconductive bone substitute with a pharmacologic compound that will enhance the body's production and secretion of intrinsic growth factors appears to be a promising solution [8].

The ability of statins to stimulate osteoprogenitor cells proliferation and to upregulate the production of bone morphogenic protein (BMP-2) by osteoblast cell lines was first reported by Mundy et al in 1999 [9]. The bone anabolic actions of statins also involve increasing expression and synthesis of osteocalcin by reducing the inhibitory effect of Rho-associated protein kinase (ROCK) in osteoblasts [10]. Statins are also able to partially suppress osteoblast apoptosis through a TGF-β–Smad3 pathway [11] and regulation of oestrogen receptor α expression [12].

Beside its direct effect on bone, statins are also known for their other biological properties that may also play an important role in inducing bone formation including angiogenic and anti-inflammatory properties [13]. However, on addressing the anti-inflammatory effect of statins, it should be stated that, simvastatin in high doses can actually induce excessive inflammation around the site of local application that may adversely affect bone formation [14,15].

Several studies have been carried out to investigate the effects of systemically administered statins on bone healing and have found positive results [16–19]. However, because of their high hepatic targeting property, statins do not accumulate in bone and their effect after systemic administration appears to be minimal [20]. Exceedingly, high doses of

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systemically administrated statins can raise the risk of liver failure and kidney disease [21]. It was also noticed that locally applied statins were 50–80 times more effective in inducing bone formation than if given orally or injected subcutaneously [22].

In spite of the wide variety of simvastatin doses and carriers that were used in the studies [23–26] that evaluated the effect of locally applied simvastatin on bone formation in critical sized bone defects, still it is quite clear that the local effect of simvastatin is dose and carrier dependent [27] and what is considered to be the optimal dose and carrier have not yet been defined [28]. Simvastatin was not used until now in sinus lift or any other reconstructive procedures in humans, which makes this comparative study to be the first study to be reported in the literature that investigate both the safety and effectiveness of simvastatin as an osteoinductive material.

Materials and methods

Study setting

This study included eight sinus lift procedures conducted on six patients (4 females and 2 males aged between 48 and 62 years with a mean of age of 56 years, SD ±5.33). The patients were selected from the outpatient clinic of the Oral and Maxillofacial Surgery Department – Cairo University. The sinuses were divided into two equal groups, four sinuses each (test and control groups), both groups underwent maxillary sinus lift procedures using either combination of β-TCP[1] and simvastatin[2] for the test group or β-TCP only for the control group. The study was a double blind one (participants and outcome assessors were blinded throughout the study).

The patient selection (eligibility criteria)

The selected patients had missing posterior maxillary teeth with insufficient available bone – less than 8 mm – for implant placement indicating the need for open maxillary sinus augmentation. The patients were apparently free from any systemic disease or sinus disease that may affect normal healing of bone and predictable outcome. The study was approved by the Ethics Committee of Scientific Research, Cairo University. An informed signed consent was also obtained from the patients.

Intervention

Pre-operative preparation

A pre-operative cone beam computed tomography (CBCT) scan[3] was performed to every single patient in both groups in order to evaluate the amount of available bone in the maxillary posterior edentulous area. The residual bone height was measured from the crest of the ridge to the floor of the sinus. (Figure 1(a,b)) Fabrication of both a study model and a radiographic stent (which was used as a surgical stent in the second stage surgery) were also performed.

Preparation of β-TCP-simvastatin complex

Simvastatin powder was dissolved in 97% ethanol. Then, the solution was applied by a mean of a dropper to the β-TCP particles so that each gram of β-TCP contained 7.21 mg of simvastatin, afterwards ethanol was allowed to evaporate completely. The entire procedure was done in laminar flow hood to ensure completely sterile conditions.

Intra-operative procedures (for both groups)

Immediately before the surgery each patient was instructed to rinse with chlorohexidine gluconate 0.1%[4] mouth wash. All the surgical procedures were performed under local analgesia (articane 4% with 1: 100,000 epinephrine[5]) using maxillary nerve block with buccal and palatal infiltration. Then, the maxillary sinus floor elevation using the lateral window technique was performed. The created space was filled with the previously prepared β-TCP- Simvastatin complex after being hydrated with saline for the test group while for the control group, β-TCP was used to fill all of the new available volume after being hydrated with saline. Resorbable collagen membrane[6] was used to cover the osteotomy window followed by wound closure using 3-0 black silk suturing material. (Figure 2(a–d)).

Post-operative medications included Augmentin 1 g[7] (one tablet every 12 h for one week), Ultrafen 600 mg[8] (one tablet every 12 h for one week) and Afrin nasal spray[9] (2–3 sprays every 12 h for one week).

Follow-up

All the patients were recalled a week after surgery for suture removal. Wound was thoroughly examined for any sign of inflammation or infection.

Post-operative clinical examination

Face-to-face adherence reminder session took place to stress on the post-operative instructions and for clinical evaluation including assessment of complications during surgery and postoperative healing period (inflammation, wound dehiscence and loss of grafted bone particles) at the following time intervals.

- 1 and 2 weeks post-operative
- 2 and 5 months post-operative

Criteria for discontinuing or modifying intervention

If the test group showed an intensive inflammatory reaction, the simvastatin dose was to be re-evaluated. There was no protocol for the discontinuation of the procedure.

Concomitant care

The test group did not receive any concomitant care.

Post-operative radiographic evaluation

Postoperative CBCT radiographs were taken for every patient one week (T_0) and nine months (T_9) postoperatively.

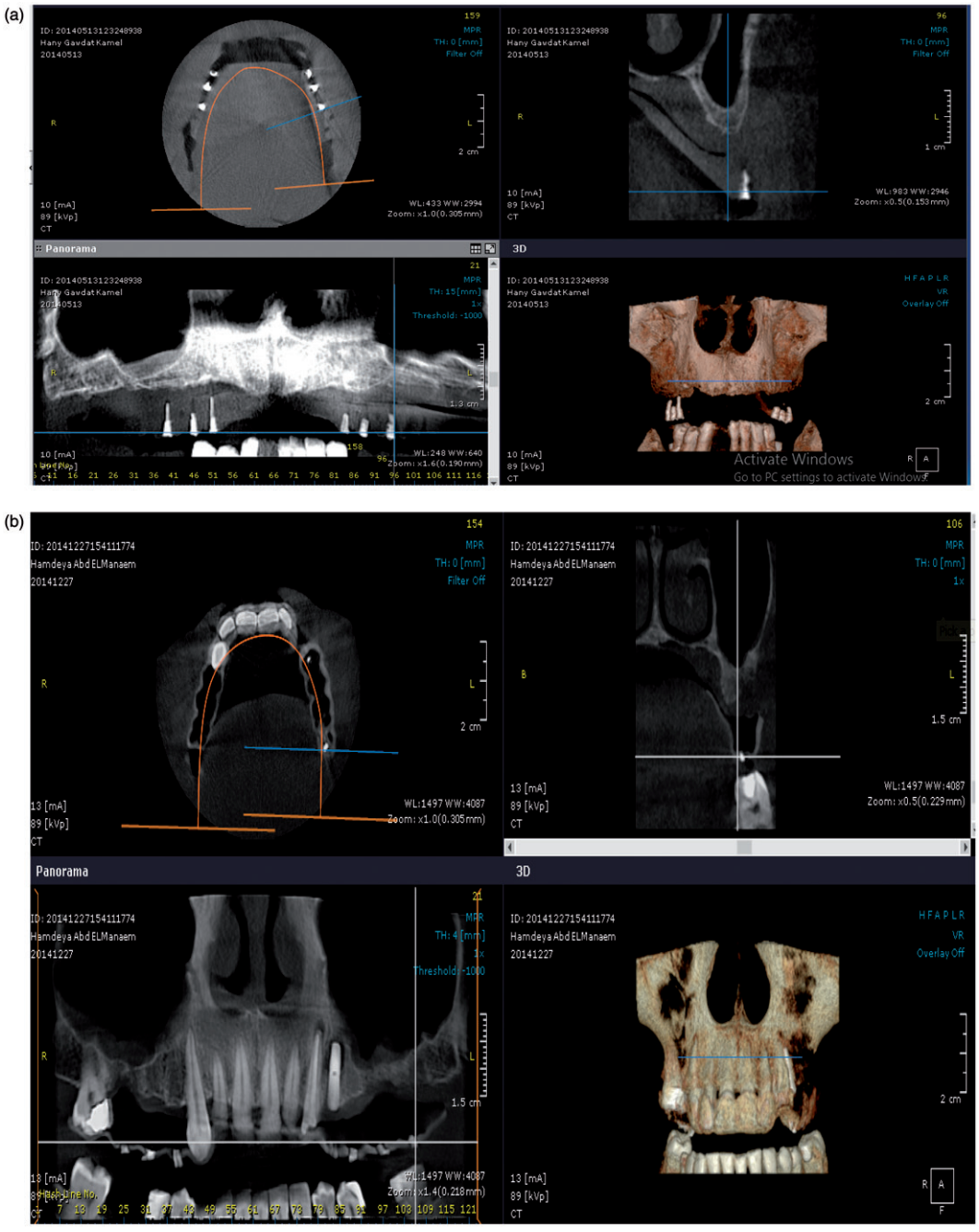

Figure 1. (a) Pre-operative CBCT of case number 1 (test group) and (b) Pre-operative CBCT of case number 3 (control group).

The radiographs were made with the same machine and same exposure parameters. Image reconstruction was performed using special software {Ondemand3D software (cybermed Inc – Korea)}.Radiographic evaluation was focused on bone quantity.

All measures were performed at the highest point of new sinus floor using the software with a millimetre scale. For each sinus, the measures were recorded in both orthopantomogram and cross-sectional views (Figures 3 and 4). Alveolar crest, original sinus floor and grafted sinus floor were traced and the following measures were recorded in T_0 and T_9

- Residual bone height: The distance from the marginal bone crest to the original sinus floor.
- Bone graft height: The distance from the original sinus floor to the new sinus floor.
- Total bone height: The distance from the marginal bone crest to the new sinus floor.
- Bone loss: The difference between graft height at immediate and 9 month radiographs.
- Percentage of bone loss: The percentage of the bone loss to the bone height of the graft at immediate radiographs.

Second-stage surgery (after 9 months)

Second-stage surgery involved biopsy harvesting (one biopsy was taken from each sinus) and implant[10] placement.

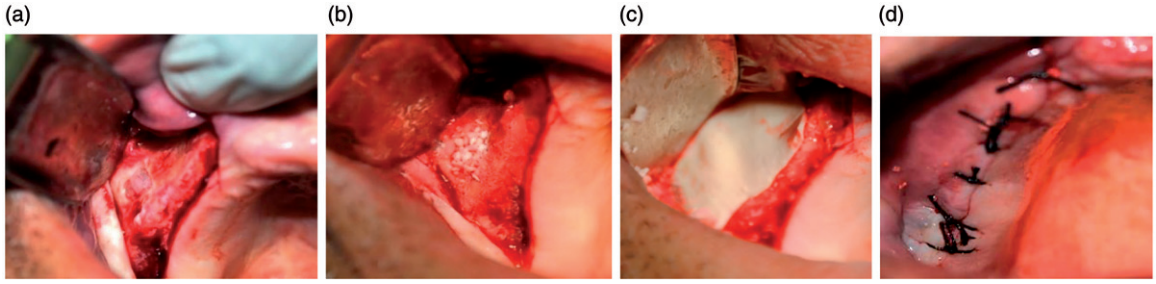

Figure 2. (a,b,c and d) showing the sinus membrane lifted, Grafting of the created space, covering the bone window with collagen membrane and the surgical flap repositioned and sutured.

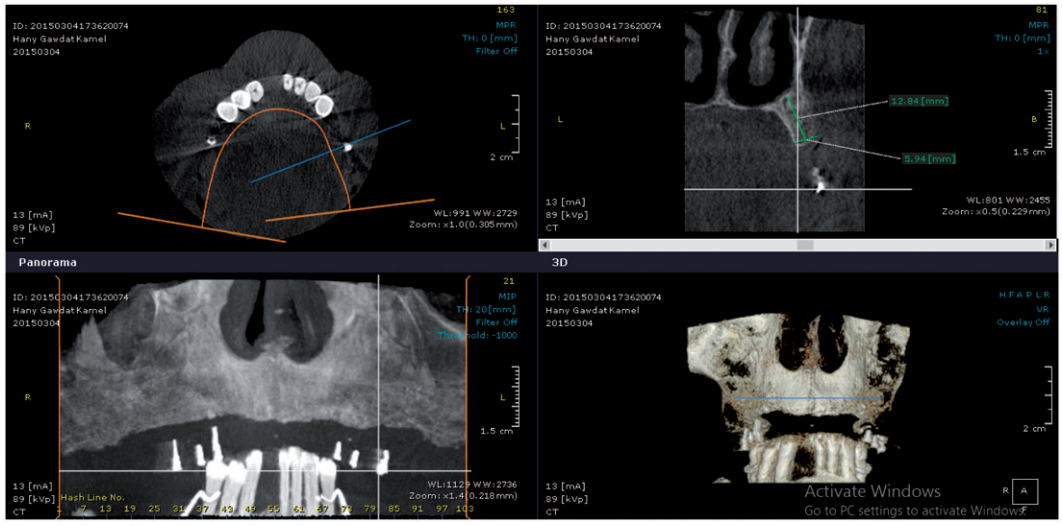

Figure 3. Post-opertive CBCT of case number 1 (test group- 9 months).

A 3 mm diameter trephine bur was used to collect the transcortical bone biopsy from the grafted sinuses. The drilling depth was planned from the CBCT to ensure that the biopsy contains newly formed bone and native bone. Biopsy samples were fixed immediately in 10% buffered formalin.

Specimen processing

Specimen decalcification was achieved by suspension in EDTA 10% solution for one week with regular renewal of the solution daily. After decalcification, the specimens were dehydrated using ascending alcohol, followed by clearing in xylol. Then, it was embedded in paraffin wax to form a block. The paraffin block was sectioned longitudinally using a microtome into thin paraffin sections, each of approximately five microns thick. Sections were stained using Masson Trichrome stain for histomorphometric analysis.

Histomorphometric analysis

Histomorphometric analysis was performed through using image analyzer computer system using software Leica QWin 500[11]. Areas of newly formed bone and remnants of bone substitute as a percentage of the total area was measured at 40X power field.

Statistical analysis

Statistical analysis was performed using SPSS[12] (Statistical package for the social sciences- IBM Corp., Armonk, NY). The data were represented as mean ± standard deviation. Mann–Whitney *U*-test was used to compare variables between the two groups. The results were considered statistically significant if the *p* value was less than .05.

Results

Clinical assessment

No complications occurred during the surgical procedure and the healing period of the two groups.

Histomorphometric results

The histomorphometric analysis of the samples showed that the percentage of newly formed bone was higher in the test group compared to that of the control group (26.25 ± 4.35 vs. 19.5 ± 2.38) and there was a statistical significant difference between both groups. To the contrary, remaining bone substitute was lower in the test group compared to that of the control group (24.5 ± 4.51 vs. 26 ± 2.71) with no statistical significant difference between both groups. (Table 1)

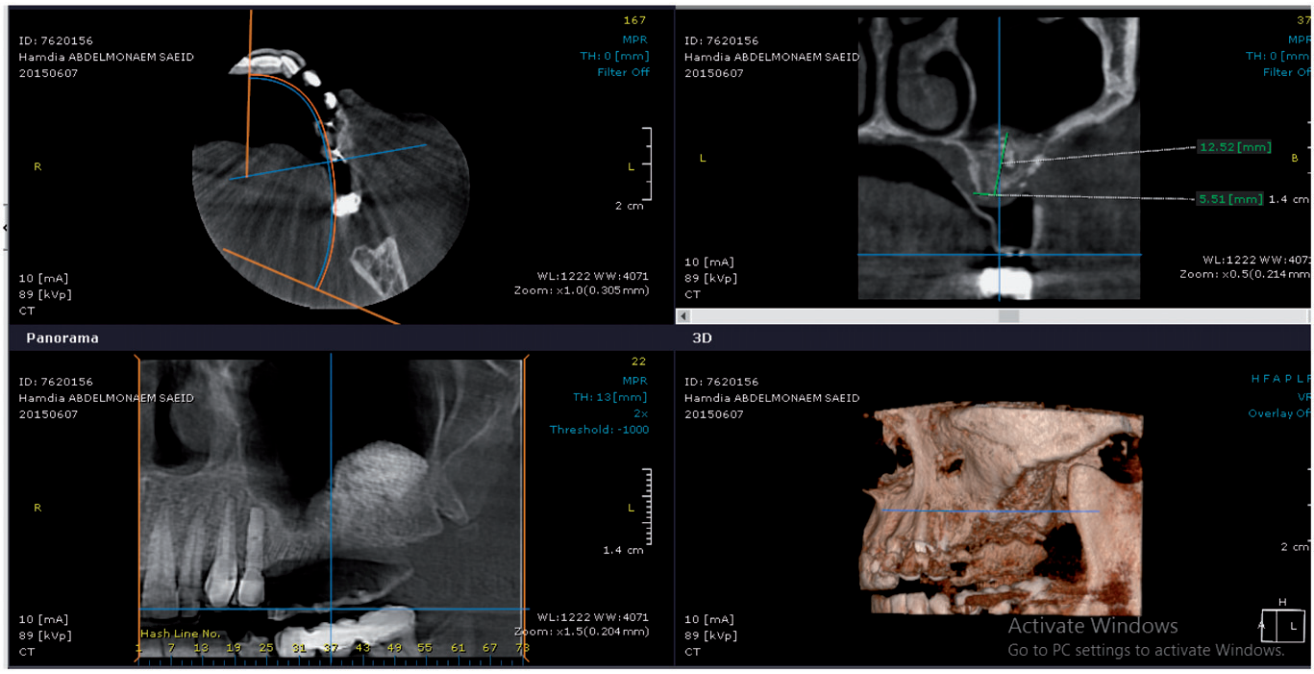

Figure 4. Post-opertive CBCT of case number 3 (control group- 9 months).

Radiographic evaluation

The pre-operative radiographic evaluation of both groups showed that the mean value of the residual bone height was 4.92 mm for the test group and 5.2 mm for the control group. The post-operative evaluation of the test group showed that one week after the procedure the mean value of the bone graft height was 10.93 mm with total bone height of 15.85 mm. Nine months post-operatively, the mean value of the bone graft height dropped to 9.56 mm with total bone height of 14.48 mm with average bone loss of 1.37 mm.

Regarding the post-operative radiographic evaluation of the control group showed that the mean value of the bone graft height recorded after one week was 12.2 mm with total bone height of 17.4 mm. Nine months post-operatively the mean value of the bone graft height was 11.1 with total bone height of 16.3 mm with average bone loss of 1.1 mm.

The test group showed more bone loss when compared to the control group, but there was no statistical difference (p value = .294)

Percentage of bone loss

The percentage of bone loss was recorded for the test and control groups with an average of 12.53% (SD ±4.65) and 9.02% (SD ± 5.9), respectively. However, this difference was statistically insignificant. (Table 2)

Discussion

The process of bone regeneration requires the harmonious cooperation of three main components: signalling molecule, scaffold and cells responsible for bone formation. The 'in situ tissue regeneration approach' involves inducing new tissue formation by specific scaffolds with external stimuli that are used to stimulate body's own cells and promote local tissue repair [27].

Table 1. The histomorphometric results of both groups.

	Test		Control		
	Mean	Std. deviation	Mean	Std. deviation	p value
New bone	26.25%	4.35	19.5%	2.38	*.029
Bone substitute	24.5%	4.51	26%	2.71	*.306

*Results suggested statistically different if $p < .05$.

The direct effect of statins on bone was discovered for the first time by Mundy et al [9] in 1999. Their study, along with others, suggest that statins, administered either locally or systemically, act as potent stimulators of bone formation and regeneration [9,23,24]. Simvastatin was found to upregulate BMP-2 [29], vascular endothelial growth factor (VEGF) gene expression [10] and alkaline phosphatase expression in osteoblasts, [30] it was also found to inhibit osteoclastogenesis [31].

Since the external sinus floor elevation technique was first introduced by Boyne Tatum [32] and Boyne [33], several grafting materials have been used in sinus augmentation procedures including autogenous bone [34]. Nevertheless, the morbidity involved in its use, leads many patients to refuse this line of treatment [35]. For this reason, different osteoconductive synthetic materials have been developed [36]. Among them is the pure phase of β-TCP used successfully in maxillofacial and implantology surgery, where it has demonstrated its capacity to form bone on reabsorption by the organism [37].

In this study, we evaluated the osteoinductive power of simvastatin when combined with β-TCP in sinus lift. To select the optimal dose of simvastatin, we reviewed previous studies that had evaluated different simvastatin doses. The

Table 2. The average percentage of bone loss in both groups.

	Mean	Std. deviation	*p* value
Test	12.53%	±4.65	*0.56
Control	9.02%	±5.9	–

*Results suggested statistically different if $p < .05$.

highest dose of simvastatin (2.2 mg) was applied by Thylin et al [23] over mice calverium using methyl cellulose membrane as a carrier. Simvastatin group showed a significant increase in bone thickness and bone area, yet this was associated with an intense inflammatory reaction that persist for seven days followed by ulceration and crust formation.

Using the same carrier, Stein et al [24] applied different doses of simvastatin (0.1, 0.5, 1.0, 1.5 or 2.2 mg) on the lateral aspect of the mandible of mature rats. The results showed that although using 0.1 mg simvastatin was associated with the least inflammatory reaction yet the highest amount of bone formation was recorded with 0.5 mg simvastatin. Guided by the results of the aforementioned studies, Nyan [25] introduced his theory that assume that combining an ideal dose of simvastatin with a gradually biodegradable bone substitute may results in achieving the maximum anabolic effect of simvastatin while eliminating or limiting the associated inflammatory reaction.

Nyan [25] used different doses of simvastatin (0.01, 0.1, 0.25 and 0.5 mg) with α-TCP as a carrier to fill critically sized calverial defects in adult Wistar rats. The results of the study were consistent with Stein's observation regarding the least amount of inflammation encountered with the use of 0.1 mg of simvastatin; however, regarding the amount of bone formation, the results showed that using 0.1 mg of simvastatin had induced the highest amount of bone formation. Nyan [25] attributed the difference between his observation and Stein's findings to the different carrier and experimental model.

Rojabani [26] used Nyan's simvastatin optimal dose (0.1 mg) with different carriers (α-TCP, β-TCP and hydroxyapatite). The results of the study supported Nyan's theory as the highest amount of bone formation was found in the α-TCP group followed by the β-TCP (without statistically significant difference) with the least amount of bone found in the hydroxyapatite group. These results were in line with the known different rate of degradability of the three carriers.

The dose of simvastatin used in the present study was based on studies performed by Nyan et al. [25] in 2009 and Rojabani et al [26] in 2010, in which they used 0.1 mg simvastatin per 14 mg either α and/or β-TCP. Although there was other studies [8,38] that used higher dose of Simvastatin (0.5 mg) with other scaffold (collagen graft) and report a significant increase in bone formation as well, yet this dose/scaffold combination was selected as it is the lowest dose that was reported in the literature to induce bone formation since it was the first time in the literature to use Simvastatin in human sinus and its effect on the sinus lining is still unknown.

In the present study, the simvastatin powder was dissolved in ethanol in order to hydrolyse it into simvastatin acid that is the medically active form of Simvastatin [39,40].

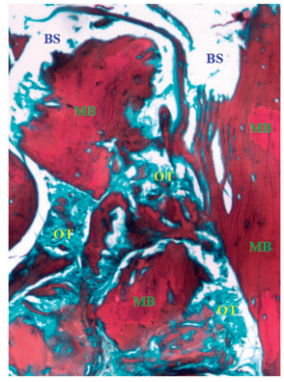

Figure 5. Masson trichrome stain of test group showing osteoid tissue (OT), mature bone (MB) and bone substitute (BS) remnants.

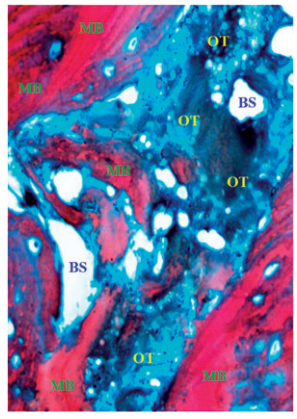

Figure 6. Masson trichrome stain of control group showing osteoid tissue (OT) , mature bone (MB) and bone substitute (BS) remnants.

On applying the graft material into the sinus in both groups, it was mixed with saline and not blood. Since growth factors capable of stimulating bone formation are present in blood, it can be speculated that placement of additional venous blood collected from the patient during surgery may further facilitate and improve the results from the sinus membrane elevation technique [41], which may augment the osteoinductive capabilities of the Simvastatin.

The average bone volume (BV) formed in the augmented sinus at the control side was 19.5% (17–21%). This result is supported by the studies performed by Zerbo IR et al [42] and Zijderveld SA [43]. The amount of newly formed bone in the simvastatin group was significantly higher than that formed in the β-TCP group. In addition to the significant difference in the total bone volume between the two groups, the newly formed bone in the test group showed areas of mature lamellar bone more than that in the control group which is formed mainly of immature-woven bone (Figures 5,6). These results agree with the result achieved by Rojabani et al [26] and prove the osteoinductive power of the simvastatin.

Nyan [25] and Rojabani [26] explained the effectiveness of this simvastatin dose when added to β-TCP due to its releasing profile which is affected mainly by the degradation rate of the graft material. Their studies showed that about half of the simvastatin was released from the graft particles in the

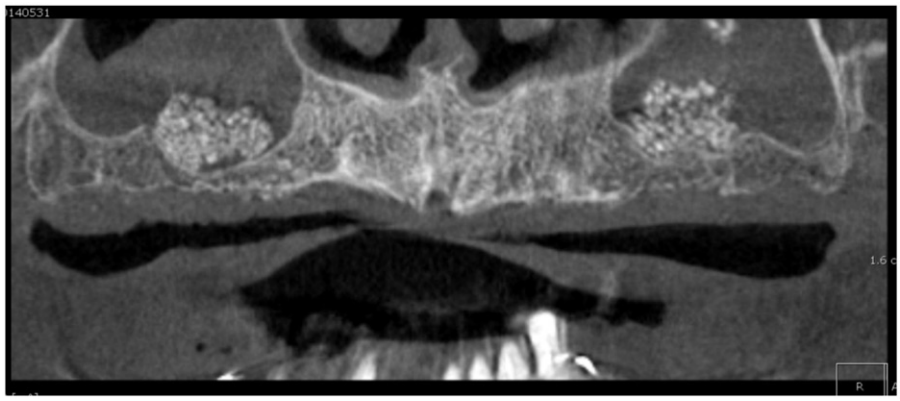

Figure 7. Radiographic signs of sinusitis observed in the simvastatin group in the one-week follow-up.

first day, which was then followed by slow release of the drug. Such a release of simvastatin may be advantageous in such dose for providing an optimal dose of the drug that could stimulate local responding cells to express BMP-2 without eliciting an inflammatory reaction.

This burst release of simvastatin may explain the presence of radiographic signs of sinusitis in the post-operative CBCT taken one weeks after the surgery (Figure 7). Such finding was not associated with any clinical signs of sinusitis which indicates that this simvastatin dose can result in the inflammatory reaction needed as the first step of bone healing yet in the accepted clinical levels.

An ideal maxillary sinus bone-grafting material should provide biologic stability, ensure volume maintenance and allow the occurrence of new bone infiltration and bone remodelling [44]. The most important factor influencing reduction in vertical bone height on the time axis after sinus augmentation is the grafting material, followed by the presence of a functional implant [45].

The maxillary sinus is a type of 'contained-type defect', and most biocompatible bone grafting materials can be used successfully [44]. However, with time maxillary sinus bone-grafting materials may undergo resorption [46]. Hatano et al. [47] reported that, in the initial 2–3 years, the material may undergo pneumonization; to avoid this, grafting materials should be non-absorbable or only slowly absorbed.

Complete resorption of the bone substitute, with subsequent replacement by new bone formation at a later stage, is preferable. However, rapid revascularization and complete resorption of a grafting material may adversely affect their long-term goals, especially in certain augmentation cases as maxillary sinus grafting [48]. Zerbo et al. [42] reported that in sinus floor elevation, the first few β-TCP particles, lying directly over the residual or original bone of the maxilla, were often partially or even completely replaced by bone after 6 months. The particles more apical to these were progressively less infiltrated or surrounded by bone. This slow rate of resorption allows the β-TCP to act as a scaffold for new bone formation.

In this study, the simvastatin group showed a higher resorption rate when compared to β-TCP group. As it is the first time to use simvastatin in a maxillary sinus, there are not any previous studies to compare this result. However, Rojbani et al. [26] reported that combining Simvastatin with β-TCP will increase its degradation rate for the benefit of new bone formation. This finding may explain the difference in the resorption rate between the two groups.

Conclusions

Simvastatin is safe to be used in sinus lift with promising osteoinductive capacity that appears to have beneficial effect on graft maturation without affecting its volumetric stability, yet further studies using larger sample size and histological evaluation is needed.

Notes

1. Bioresorb classic – Herrlichkeit 4.28199 Bermen – Germany.
2. Simvastatin – Supplied by Molekula Limited. Brickfields Business Park. Gillingham, Dorset – United Kingdom.
3. Scanora3D, Soredex- Nahkelantie 160, P.O. Box 148, Tuusula-Finland, 15 mA, 85 KV.
4. Antiseptol, Kahira Pharma Co, 4 Abdel-Hamid Eldeeb st .Shoubra, Cairo, Egypt.
5. UbistesinTM forte, 3M ESPE, Espe Platz, Seefeld – Germany.
6. Biocollagen, Bioteck, Torquato Taramelli, 23, 20025, Legnano MI – Italy.
7. Each tablet contains 875 mg amoxicillin and 125 mg Clavulanic acid by Glaxosmithkline, Fifth district – New Cairo, Cairo – Egypt.
8. Each tablet contains 600 mg Ibuprofen by Glaxosmithkline – Fifth district – New Cairo, Cairo – Egypt.
9. Oxymetazoline HCl) 0.05% Nasal Spray 20 ml by Medical Union Pharmaceuticals – Egypt.
10. IBS implant, Innobiosurg co., Ltd, 518 Yongsan-dong (Daedeok Techno Vally) Korea.
11. Leica Microsystems Inc. Buffalo Grove, IL 60089 United States.
12. IBM® SPSS Statistics® version 20 for windows:
    ®IBM Corporation, NY, USA.
    ®SPSS, Inc., an IBM Company.

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Disclosure statement

The authors report no conflict of interest. The final version of this manuscript was revised and approved by all authors.

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