



Evaluation of the Effect of Hyaluronic Acid Gel Loaded with Simvastatin on the Osseointegration and Stability of the Dental Implants

Wesam S. Ibrahim^{1*}, Fatma I. Mohammed², Hanan M. Reda³

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azhardentj@azhar.edu.eg

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ABSTRACT

Purpose: The purpose of this study was to assess the clinical and radiographic outcomes of mandibular posterior edentulous area rehabilitation by fixed implant-supported prosthesis with or without use of Hyaluronic Acid Gel loaded with Simvastatin. **Subjects and methods:** Twelve implants were inserted in mandibular posterior edentulous region that required rehabilitation with fixed implant-supported prosthesis were included in this study. The patients were divided into 2 groups: Group A; the edentulous sites were treated by 6 implants which were inserted with the application of Hyaluronic acid (HA) gel loaded with Simvastatin (SMV) in the drilling site. Group B; Six dental implants were placed in edentulous sites without the use of HA gel containing SMV. The clinical follow-up was done at three and six months, whereas the radiographic follow-up was done at three and twelve months. Treatment changes were evaluated for each group and a comparison was done between the 2 groups. Data were analyzed to assess difference and association of qualitative variable by Chi square test (X^2), paired by sign test and Differences between quantitative independent groups by paired t test. **Results:** Radiographically; at 3 and 12 months, there was a statistically significant difference in bone density between two groups. While, there was no statistically significant difference in implant stability between two groups immediately and after 3 months. **Conclusion:** Application of HA gel loaded with SMV around dental implant improves the implant stability and bone density around the implant which enhances the osseointegration of implant.

KEYWORDS

Stability, Hyaluronic acid,
Simvastatin.

INTRODUCTION

Because dental implants are connected directly to the bone and provide entire stability, they are a far superior option for tooth loss

1. Oral and Maxillofacial Resident at Al-ahrar Teaching Hospital, Zagazig , Egypt.
2. Professor of Oral and Maxillofacial Surgery Department, Faculty of Dental Medicine for Girls, Al-Azhar University, Cairo, Egypt and Faculty of Dentistry, Deraya University, Minya, Egypt
3. Lecture of Oral and Maxillofacial Surgery Department, Faculty of Dental Medicine for Girls, Al-Azhar University, Cairo, Egypt

* Corresponding author email: wesammandor34@gmail.com

replacement than standard dental appliances. They serve to keep the alveolar bone's height and width, which helps to keep the face from collapsing. ⁽¹⁾.

Direct bone anchorage to an implant body for therapeutic purposes is referred to as osseointegration. Osseointegration is influenced by a variety of parameters, including the biomaterial and surface composition of dental implants, implant design, heat generation, primary stability, bone quality, epithelial downgrowth, and loading ⁽²⁾. One of the most critical aspects influencing implant osseointegration is implant stability, this refers to the lack of mobility that occurs immediately after the implant has been placed. Implant stability is essential for long-term success ⁽³⁾.

Implant stability is divided into two stages: primary and secondary. The main source of primary stability is mechanical contact between the implant and the surrounding cortical bone. The quality and density of the bone in the implant site, as well as the implant designs, all play a role. To evaluate primary stability, torque at the time of implant placement, reverse torque resistance, and resonance frequency analysis (RFA) can all be used. Secondary stability is achieved through bone regeneration and remodeling, which gives biological stability ⁽⁴⁾.

SMV is an inhibitor of 3hydroxy3methylglutaryl-CoA (HMG-CoA) reductase. It is primarily used to reduce serum cholesterol levels in the treatment of hyperlipidemia and arteriosclerosis. It also causes BMSCs to differentiate into osteogenic cells and inhibits osteoclastic activity in bone tissue ^(5,6). SMV has been shown to enhance bone regeneration in bony defects when applied locally and orally ⁽⁷⁾. Additionally, when applied topically, it promotes osseointegration around dental implants ⁽⁸⁾.

HA is considered a natural organic material because it makes up the bulk of the extracellular matrix in a variety of tissues, such as the skin, synovial joints, and periodontal tissues. It's a glycose made up of sequential chains of d-glucuronide acid and N-acetyl glucosamine monosaccharide that

create a linear polymer. It encourages cell motility, adhesion, proliferation, and differentiation, all of which contribute to the development of bone. During bone regeneration, it exerts an osteoinductive effect. Osseointegration is also aided by it ^(9,10). Therefore, the present randomized clinical study aimed to assess the effect of hyaluronic acid loaded with SMV on the osseointegration and stability of the dental implant.

SUBJECTS AND METHODS

Study Design

A prospective study was conducted on 9 patients with mandibular posterior edentulous region that required rehabilitation with fixed implant-supported prosthesis. These patients were selected from Al-Azhar University's Faculty of Dental Medicine for Girls' Oral and Maxillofacial Surgery Department's outpatient clinic. This research was approved by the Research Ethics Committee (REC) of Al-Azhar University's Faculty of Dental Medicine for Girls (code: REC-SU-21-03). A written consent was signed for each included patient. The patients were divided into 2 groups: Group A; 4patients where the edentulous sites were treated by 6 implants which were inserted with the application of HA gel loaded with SMV in the drilling site. Group B; 5patients in which Six dental implants were placed in edentulous sites without the use of HA gel containing SMV.

Inclusion and Exclusion Criteria ⁽¹¹⁾

All selected patients had mandibular posterior edentulous region, adequate bone quantity and quality for implantation, adequate oral hygiene, and absence of systemic diseases. Medically compromised patients; patients with any systemic diseases that could affect bone healing, patients with periodontal diseases, patients had history of allergy to the SMV, patients on systemic lipid lowering medication, pregnant women or lactating mothers, smokers and alcohol users, patients with para-functional habits or deep bite and bruxism were excluded from the study.

Patient Management Protocol

Both groups of patients were submitted to the following procedures:

1. Pre and postoperative intra and extra oral clinical examinations of area selected for implant insertion regarding to: mucosal color, texture, periodontal condition of neighboring teeth (if present), ridge contour and relation with adjacent teeth. In addition, oral hygiene, type of occlusion, and the presence of any pathological condition were evaluated. Palpation over the covering mucosa was done to detect any sharp ridges, or extremely thin mucosa.
2. Perioperative maxillary and mandibular diagnostic study models were fabricated and mounted to evaluate the centric relationship and inter arch space. They were also employed to make a mandibular vacuum (surgical) stent.
3. All patients were recalled for measuring probing depth (PD), and gingival index (GI) at 3rd, 6th, and 12th months postoperative period.
4. All implants were evaluated for stability twice: first immediately after insertion and again three months later, just before implant loading, using OSSTELL.
5. All patients in both groups had CBCT scans prior to surgery, three months after surgery, and twelve months after surgery.

Preparation of hyaluronic acid gel loaded with SMV for study group (Group A):

HA (OPTIVISC 20, IPC, International Pioneers Company, Egypt) gel loaded with SMV (SIMVASTATIN, Hetro Labs Limited Company, India) was prepared by adding 2.5g of methylcellulose (Methylcellulose Powder, Reacher-Lab Fine Chem Industries Company, India) to 100g of hyaluronic acid slowly and stirring continuously to attain the gel consistency. This is followed by the addition of 20mg of SMV slowly with continuous stirring to obtain the final form of the gel ⁽¹²⁾.

Preoperative preparation:

The following procedures were performed on all of the patients who participated in this study: (1) Full mouth scaling was performed before surgery, (2) All patients were motivated to follow the proper oral hygiene measurements by regular brushing, flossing, and the use of chlorhexidine mouth washes, (3) The patients received a prophylactic dose of antibiotic Amoxicillin 875 + clavulanic acid 125 (Augmentin 1g, GlaxoSmithKline S.A.E, Egypt) one tablet two hours before surgery.

Surgical Procedure

Before receiving local anesthesia (LA), all patients were instructed to rinse their mouths with 0.2 percent Chlorhexidine mouthwash for 5 minutes. LA was achieved by inferior alveolar nerve (IAN) block technique by using Articaine hydrochloride (Septanest SP, European Medicines Agency E.M.A) 4%, 40.00 mg/ml and epinephrine 1:200,000. The surgery was performed under complete aseptic condition. Made a single-step sharp clean cut crestal incision through the mucous membrane and periosteum., a mucoperiosteal flap was delicately elevated, revealing the bone. The prefabricated vacuum stent was placed and adjusted in the patient mouth according to the preoperative preparation. The pilot drill was inserted through the splint and alveolar bone to locate the proper site of the implant and then sequential drilling was performed as described by the manufacturer. Once the implant site had been prepped in the study group, HA gel loaded with SMV was placed on the implant site by insulin plastic syringe before the implant placement. Then the implant (in both groups) was transferred using implant mount and inserted into implant site. And then, it was secured with ratchet. The initial implant stability was measured immediately for both groups after implant insertion using the OSSTELL (ISQ). After that, the flap was adjusted and sutured with Vicryl interrupted tension free sutures (3-0).

Prosthetic Phase

After 3 months postoperatively, all patients were recalled for the second stage surgery (loading)

procedures. The cover screw was exposed and removed by crestal incision, and the implant stability was measured by using OSSTELL (ISQ). Then, gingival former was inserted for 1-2 weeks to provide good gingival contour around the implant collar. The gingival former was removed, and the implant's abutment analogue was attached. An appropriate tray was chosen, and the closed tray impression process was used. To make the impression, light and heavy rubber base materials were used. The abutment analogue was removed and attached to an implant analogue of the same size, then both were placed into the impression and the gingival former was re-placed intraorally, as well as the upper impression was taken. Both impressions were sent to the dental laboratory. At the end, the abutment was connected to the implant, and cement-retained final restorations were delivered in place after full check of occlusal interferences.

All radiographic CBCTs were superimposed together (in both groups) between preoperative and 3 months postoperative CBCTs, preoperative and 12 months CBCTs using OnDemand 3D software, to assess the value of bone density around the dental implants at 3 and 12 months postoperative. The following procedure was used to superimpose the images in three planes (axial, coronal, and sagittal): One image was designated as the primary

image, while the other was defined as a secondary image. In order to execute image superimposing, both primary and secondary images in the axial plane had to be in approximately the same plane. The images were superimposed in the coronal view using established reference points such as the cusp tips of molars, and the axial level was then properly adjusted so that the primary and secondary images are on the same exact axial plane. Both images were examined in 3D projection as a final confirmation, and the primary and secondary images were fused together (automatic). The primary and secondary images' bone density values were obtained at the same bone site (Fig.1,2).

Statistical Analysis

To summarize the demographic preoperative measurement data, data was displayed as means, standard deviations, ranges, and percentages. Also, the probing depth, gingival index, implant stability and the bone density were analyzed, difference and association of qualitative variable by Chi square test (χ^2), paired by sign test and Differences between quantitative independent groups by t test paired by paired t test. If the p-value was 0.05 the result was judged statistically significant and 0.001 for a high significant outcome. SPSS software version 20.0 was used to perform all statistical calculations.

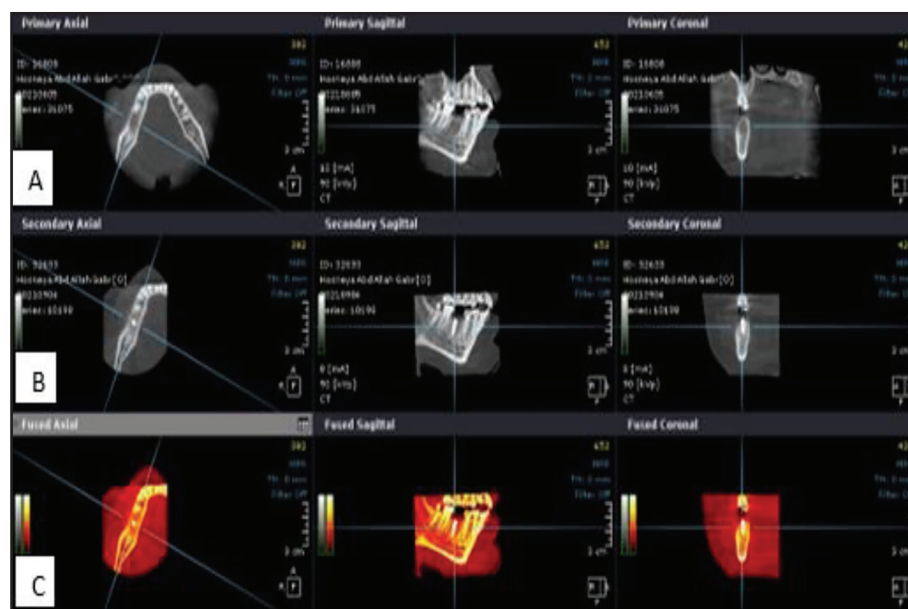


Figure (1) Photograph of axial, sagittal and coronal CBCT cuts showing: (A) the preoperative image, (B) the secondary image, (C) fusion between primary and secondary images.

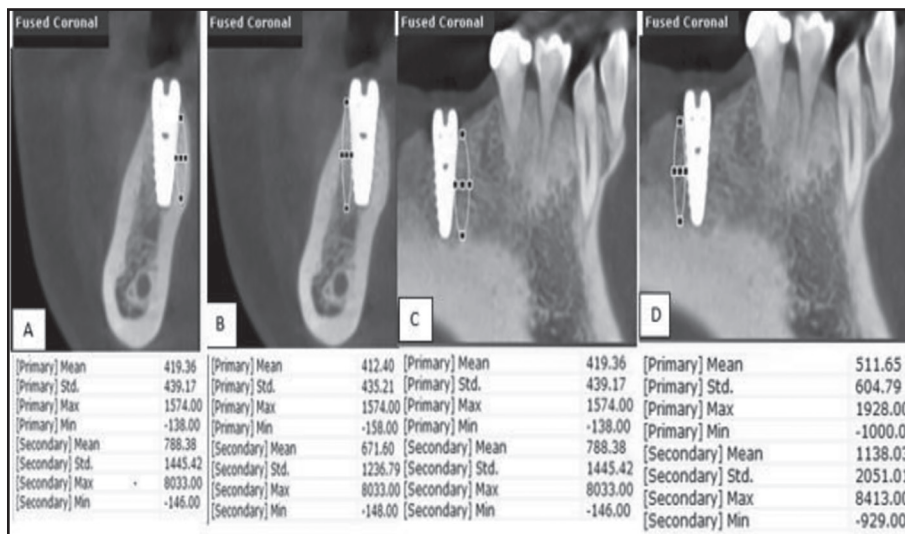


Figure (2) Superimposed coronal and sagittal CBCT cuts showing the measurements of Bone density in group A at the base time (preoperative) and at three months after implant at (A) the buccal aspect, (B) the lingual aspect, (C) the mesial aspect, and (D) the distal aspect.

RESULTS

The study included 9 patients (8 females and 1 male), 4 in the study group and 5 in the control group, all of whom had a mandibular posterior edentulous region that required rehabilitation with a fixed implant-supported prosthesis. The average of patients' age in study group was 38.0 ± 11.7 years. While, in control group the mean of patients' age was 39.0 ± 10.3 years (table 1).

Table (1) Demographic and clinical data of the patients

	Group A	Group B
Sample size	4 patients	5 patients
Age (years): Mean $\pm$ SD	38.0 ± 11.78	39.0 ± 10.39
Gender:		
Male	0	1
Female	4	4

SD: Standard Deviation

Non-significant values; $P > 0.05$

During the follow-up period of up to 6 months, all patients were assessed at regular intervals. There

were no post-operative problems in any of the cases where healing was uneventful. The probing index, gingival index, implant stability, and bone density are all factors to consider.

There was no statistically significant difference in all features between the study and control groups at 3 months and 6 months when it related to the mean of the probing depth. Also, the mean of the gingival index; At 3 months ($P=0.54$) and 6 months ($P=0.29$), there was no statistically significant difference between the study and control groups.

The mean of the immediate implant stability (primary stability) in the study group was 76.16 ± 14.62 . The primary stability for the control group was 78.66 ± 15.14 . The mean implant stability value in the study group was 96.33 ± 6.50 at 3rd month after surgery, while in control group the mean of implant stability at 3rd month postoperative was 84.83 ± 11.32 . The results show that there was no statistically significant change in ISQ values between the study and control groups immediately and after 3 months, with P-values of ($P=0.777$) and ($P=0.065$) correspondingly. However, between the immediate and postoperative 3rd month readings in the study group, there was a considerable increase (table2).

Table (2) Immediate and 3rd month Postoperative Implant Stability in the two Groups

	Group A	Group B	P-value
Immediate	76.16±14.62	78.66±15.14	0.8
3rd month	96.33±6.50	84.83±11.32	0.07
P- value	0.01*	0.28	

Data presented as mean and standard deviation (mean±SD)

*Statistically Significant Difference ($p < 0.05$)

The study group's mean preoperative bone density was 569.2±113.04, and the study group's mean postoperative bone density was 1096.5±213.6 at 3 months, and 1420.1±3175.7 at 12 months. The mean preoperative bone density in the control group was 586.3±185.6, and the mean postoperative bone density was 667.9±242.9 at 3 months, and 717.5±219.6 at 12 months. This result shows that there were no statistically significant differences between the study and control groups in relation to changes in bone density preoperatively ($P = 0.351$), but there was a statistically significant difference between the study and control groups in relation to changes in bone density from the baseline (pre-operative) to the 3 months postoperative period before loading ($P = 0.047$). Also, through related to changes in bone density at 12 months postoperative period, there was a statistically significant difference between the study and control groups. ($P = 0.001$) (table 3).

Table (3) The mean value of bone density of the two groups at different follow up periods

Bone density	Group A	Group B	P- value
Preoperative	569.2±113.04	586.3±185.6	0.4
-3rd month	1096.5±213.6	667.9±242.9	0.047*
P- value	0.001*	0.092	
Preoperative	569.2±113.04	586.3±185.6	0.4
-12th month	1420.1±175.7	717.5±219.6	0.001**
P- value	0.001*	0.06	
-3rd month	1096.5±213.6	667.9±242.9	0.047*
-12th month	1420.1±175.7	717.5±219.6	0.001**
P- value	0.001*	1.826	

Data presented as mean and standard deviation (mean±SD)

DISCUSSION

This prospective study was directed to evaluating the role of HA gel loaded with SMV on the osseointegration and stability of the dental implants. It was reported that the implant osseointegration is influenced by bone density and implant stability⁽¹³⁾.

The effect of a SMV-loaded HA gel on the stability and osteointegration of implants placed in the mandible's posterior areas was investigated in this study. In all patients, the postoperative ISQ value increased significantly during the healing period, indicating new bone apposition at the implant-bone contact. The ISQ results for the study group indicated high implant stability, while the ISQ readings for the control group indicated medium implant stability. As a result, when it related to implant stability, the study group outperformed the control group. This is because the HA gel containing SMV may promote better bone formation in the study group, enhancing implant stability. However, the ISQ values, on the other hand, were not statistically significant.

These results were consistent with those of Dundar S et al.,⁽¹⁴⁾ who described that SMV can improve osteoblastic differentiation of BMSCs by increasing autophagy and decreasing osteoclast activity, thus improving and speeding up the osseointegration of dental implants. Also, Yazan et al.,⁽¹³⁾ which reported that the use of HA gel, which is known to stimulate osteogenic cell differentiation, was found to have a more positive influence on Osseointegration surrounding dental implants. On contrary, Kalboush et al.,⁽¹⁵⁾ found that, local application of HA around the immediate implants did not improve implant stability or soft tissue regeneration.

The mean value of PD and GI were found to be statistically non-significant in both groups during the follow up period. These results were in agreement with the Yi Xu et al.,⁽¹⁶⁾ who observed that there was no clinical improvement in PD and GI with the subgingival administration of HA gel. On the other hand, this contradicts with the

kandil I et al.,⁽¹⁷⁾ which stated that by minimizing the probability of pathogenic strain resistance, HA subgingival administration reduces PD and improves GI. Also, this opposes with Kanoriya D et al.,⁽¹⁸⁾ which informed that subgingival application of SMV subgingivally decreases PD and enhances GI as it has several anti-inflammatory potentials.

The bone density at the 3rd and 12th months post-operative showed a significant difference between the two groups based on the change in bone density from the baseline (pre-operative). This might be attributed to the increased osteoblastic cell activity and associated bone apposition in the study group. These results are supported by Moraschini V et al.,⁽¹⁹⁾ it was conveyed that SMV has a variety of anabolic effects on bone metabolism, as they stimulate osteoblastic bone marrow stem cell development by increasing the gene expression of BMP-2. They also prevent osteoblast apoptosis, promoting bone formation. Also, the results of this study are in agreement with Yazan et al.,⁽¹³⁾ which found that HA protects osteoinductive growth factors in the local environment due to their physicochemical features. As a result, by promoting osteogenic cell differentiation new bone can be generated.

On the other hand, Xianqi L et al.,⁽²⁰⁾ disagree with the findings of the present study, as they found that SMV may cause the rebound phenomenon by inducing IL6 production, which is a pro-inflammatory and bone resorbing cytokine in bone tissues and enhances osteoclastogenesis, resulting in trabecular bone loss and a drop in new bone formation (NBF). Also, Boot W et al.,⁽²¹⁾ notified that HA underwent degradation over time, without variations in the quantity of bone apposition near the dental implants.

In term of the postoperative clinical outcomes, there was no statistically significant difference between the two groups.

The key finding of this study is that the use of HA gel loaded with SMV as a result of increased bone density and implant stability, implant osseointegration is improved.

CONCLUSION

Application HA gel loaded with SMV is a successful modality to be used in the prepared implant site. Compared to the previous approach, implant stability and peri-implant bone density are increased significantly.

RECOMMENDATIONS

Extra studies should be conducted to confirm that the use of the HA gel loaded with SMV improve the bone density around implant, implant stability, and decrease the implant failure rate.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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