



Evaluation of Controlled Release Simvastatin around Dental Implant in Controlled Type II Diabetic Patients

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ABSTRACT

Purpose: The goal of this study was to evaluate the clinical effect of topically controlled release simvastatin with dental implant in type II diabetic patients. **Materials and Methods:** Sixteen diabetic type II patients with missing teeth were selected according to inclusion and exclusion criteria. Patients were divided randomly into two groups using flip coin method. Group I (test group): 8 patients underwent implant placement for missed tooth with controlled released simvastatin around the implant. Group II (control Group): 8 patients underwent implant placement for missed tooth without controlled released simvastatin around the implant. All patients were followed up clinically and radio-graphically for 6 months postoperatively after implant placement. **Results:** The use of Simvastatin controlled release gel with delayed dental implants decrease postoperative pain and swelling **Conclusion:** This research showed that the drug delivery system of controlled release simvastatin improve the repair and healing of bone and soft tissue around dental implant in diabetic type II patients.

INTRODUCTION

Dental implants are the most successful and recent way to restore missing teeth. Initially, the survival rate of implant depends on successful Osseo-integration of bone around implant⁽¹⁾. The critical dependence on bone metabolism for implant survival leads us to evaluate a certain risk factors⁽²⁾. Among these risk factors is diabetes mellitus as increased prevalence of periodontitis and tooth loss is common finding in diabetic patients⁽³⁾, delayed wound healing and impaired response to infection⁽⁴⁾.

KEYWORDS

Dental implant, Diabetes type II,
Simvastatin.

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Type II diabetes mellitus is a chronic disease that has a high rate of morbidity and mortality. Its prevalence is quickly increasing as the general population ages, and it will soon become a global epidemic⁽⁵⁾. According to the International Diabetes Federation's (IDF) recently published (2017) data on the global burden of diabetes, there are around 425 million adults living with diabetes, with this number expected to rise to 629 million by 2045⁽⁶⁾.

According to recent surveys, the success rate of implants in individuals with T2DM has been compromised⁽⁷⁾. Insulin is well-known as a common treatment for diabetes, but its effect is restricted to alleviating all negative effects on bone metabolism while still resulting in poorer implant integration. As a result, there is a pressing need to investigate more effective strategies for treating people with T2DM who have poor osseointegration⁽³⁾. The use of hydroxymethylglutaryl-coenzyme A reductase inhibitors or statins is one such adjunct technique⁽⁸⁾.

Statins are specific inhibitors of 3-hydroxy 3-methylglutaryl-coenzyme reductase that are most typically used to prevent cholesterol formation in cardiovascular disorders. Statins offer a wide range of therapeutic activities, including vasodilatory, antithrombotic, antioxidant, antiinflammatory and immunosuppressive actions leading to the modulation of bone regeneration process at the molecular and cellular levels⁽⁹⁾. Statins were initially discovered to be effective stimulators of bone growth by in vitro study conducted in 1999⁽¹⁰⁾.

Statins stimulate bone formation by stimulating the production of bone morphogenetic protein-2 in Patients with: 1) poor bone quality, 2) inadequate bone, and 3) metabolic disorders present difficult cases for dental implant treatments⁽¹¹⁾.

Simvastatin is a lipid-lowering statin that is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor with a powerful impact⁽¹⁰⁾. Study conducted in 2017 demonstrated that simvas-

tatin inhibited osteoclastogenesis by inhibiting reactive oxygen species-mediated signalling pathways. Simvastatin has an anticatabolic and anabolic effect on bone metabolism as a result⁽¹²⁾.

A rather large daily dose of statins is required for systemic delivery. As a result, hepatic clearance is obstructed. Furthermore, in normal rats, topical use of simvastatin as a slow release carrier has demonstrated to improve bone around titanium implants⁽¹³⁾. Statins were 50–80 times more efficient in stimulating bone growth when administered topically or continuously released from an implant than when taken orally or injected subcutaneously⁽¹⁴⁾.

Local administration can bypass hepatic degradation of statins and attain the therapeutic concentrations in bone, avoiding the negative effects associated with systemic administration. The local drug delivery system, on the other hand, is a means of making the active component available at the site of action for as long as possible⁽¹⁵⁾. Numerous studies have used local delivery of simvastatin to improve bone repair and found that statins had a favorable effect locally⁽¹⁶⁾.

Based on the advantage of controlled released drugs and topical use of simvastatin, this study was carried to evaluate clinically and radio-graphically the effect of controlled released simvastatin with dental implant in diabetic type II patients.

MATERIALS AND METHODS

Patient selection

16 diabetic patients with missing teeth were chosen from the out-patient clinic of the Oral Medicine and Periodontology department at Al-Azhar University's Faculty of Oral and Dental Medicine for Girls.

Prior to any procedure, all subjects were informed about the nature and benefits of their participation in the study. All of the patients gave

their written consent, indicating that they were OK with the planned research program and study design. Approval number **REC-ME-21-03** from the Research Ethic Committee of the Faculty of Dental Medicine for Girls, Al-Azhar University was received.

The patients were selected according to the following inclusion criteria: Missing teeth (lower posterior teeth), Patients age was in the range from 35 up to 50 years old, Controlled diabetic patients, No periodontal therapy, systemic antibiotics or non-steroidal anti- inflammatory agents during the preceding 6 months. Patients who were excluded are smokers, Pregnant or lactating women, Patients with variation in anatomical landmarks. Patients with bad oral hygiene, Patients with abnormal habit, Patients with systemic disease other than diabetes and Patients with neuromuscular disorders.

Sample Size Calculation:

The sample size was calculated according to the research (Influence of Simvastatin-Loaded Implants on Osseointegration in an Ovariectomized Animal Model⁽¹⁷⁾) using CDC Epi Info program version 7.2.0.1 (Atlanta, USA) it was 8 patients in each group including the dropouts. Patients were divided randomly into two groups using flip coin method by throwing a coin into the air and seeing when land facing up head this patient was group I and when land facing tail this patient was group II. Group I (test group; n=8) underwent implant placement for missed tooth with controlled released simvastatin around the implant. Group II (control group; n=8) underwent implant placement for missed tooth without controlled released simvastatin around the implant.

Clinical Evaluation:

All patients were followed up clinically for 6 months postoperatively after implant placement to record the following clinical parameters: Patient

Satisfaction⁽¹⁸⁾, Pain assessment: pain were assessed in the first 7 days after surgery by the aid of visual pain scores⁽¹⁹⁾, Swelling assessment: swelling were assessed in the first 7 days after surgery by the aid of swelling scores⁽²⁰⁾, Modified gingival index⁽²¹⁾ (MGI): Reading were obtained twice using a periodontal probe. First measure were taken after implant placement by 3 months and after loading by 3 months, Modified plaque index⁽²¹⁾ (MPI): Reading were obtained twice using a periodontal probe. First measure was taken after fixture placement by 3 months and after crown by 3 months, Probing depth⁽²²⁾ (PD): Reading were obtained twice using a periodontal probe. First measure was taken after implant placement by 3 months and after loading by 3 months.

Materials used in the study:

1. Implant:

Neo biotech (Neo Biotech Co, Seoul, Korea) implant system was used in this study. Implants were made of pure titanium with length ranging from (8.5-13mm) and diameter ranging from (3.5-5mm). Neo biotech implant is designed with tapered body and sandblasting with large grit and acid etched (SLA) surface treatment. Double threaded design. Tapered form implants achieve excellent bone response and harmonize with surrounding bone anatomically. While threads help to increase initial stability. The Neo biotech implant has internal hex connection between implant fixture and abutment interface ensure hermetic sealing. This biological connection distributes the load of the fixture evenly leading to minimizing the micro movements and marginal bone loss.

2. Simvastatin gel:

Simvastatin gel was applied topically in the test group in a gel form into the osteotomy site before implant placement, gel was supplied in a sterile plastic syringes, one syringe for each patient.

Simvastatin gel preparation:

The gel prepared under aseptic condition using sterilized laminar flow system. The gel was prepared with 0.3 gm. of the carbopol 940 polymer. For appropriate dissolving of the polymer, the required amount of carbopol 940 was added to warm distilled water with vigorous stirring and left overnight. 20 mg of simvastatin (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in sterile distilled water were incorporated into gel base with continuous stirring. Mixing at 300 rpm using a magnetic stirrer (Dubuque, Iowa, USA). For around 15 minutes, the beaker was covered with aluminum foil and left to mingle. A homogenizer was used to homogenize the mixture for 5 minutes at low speed. The PH was corrected to 7 with the addition of 1 percent triethanolamine solution after complete addition of the polymer and good mixing, and gel formed spontaneously. The gel was permitted to set at room temperature for 15 minutes to allow the air bubbles created by the mixing to escape, until it formed a clear gel. To create homogeneous gel formulations, stirring was continued until no lumps were visible, and the contents were placed in the refrigerator (4°C) overnight⁽²³⁾.

Preoperative assessment:***Clinical assessment***

Visual examination and palpation of the entire oral mucosa. All patients received full mouth scaling and root debridement followed by proper oral hygiene instruction.

Surgical steps:***1- First phase:***

All surgical steps were carried out under strict condition. The implant area was anaesthetized by inferior alveolar nerve block technique using local anaesthesia (mepavecaine with epinephrine

1:100.000). After testing anaesthesia using explorer to assure the patient numbness, using #15 blade, crestal incision which slightly located lingually on the ridge of the missing lower posterior tooth was performed, followed by intrasulcular incision around adjacent teeth (one tooth mesial and one tooth distal) were made, the full thickness mucoperiosteal flap was raised using mucoperiosteal elevator to expose underlying bone. Osteotomy site preparation through sequential drilling. The surgical sequence were followed the protocol described by the implant company surgical kit until reaching the desired diameter of the implant under copious saline irrigation and at (1500rpm) speed. Drilling direction must be parallel to the adjacent mesial teeth; parallelism must be checked with parallel pins from the implant company surgical kit. After a proper osteotomy site was prepared, the implant removed from its sterile packing, then held using fixture driver, inserted into the prepared osteotomy and screwed manually with apical pressure until there is resistance (Fig. 1A). At this stage the Ratchet was attached to adaptor at the implant screw in clockwise manner until complete seating of the implant to its final depth with platform placed 1mm apical to alveolar crest. The cover screw is placed into its position and tightened using screw driver. Flap was returned to its position covering the implant and sutured with 4-0 vicryl (absorbable) suture material. Postoperative digital periapical radiography was taken to check the implant position and its relation to adjacent structure and anatomical landmarks⁽²⁴⁾.

Regarding test group (group I):

Same steps were followed except After preparation of osteotomy site and before implant placement, simvastatin gel in plastic syringe was applied inside the osteotomy (Fig. 1B) until the gel fill the whole osteotomy site, then the implant inserted and screwed within its place⁽²⁴⁾.

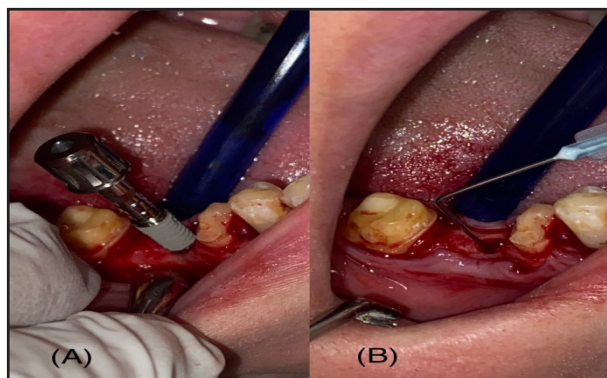


Figure (1): A) showing the insertion of implant into the osteotomy site, B) showing the administration of simvastatin gel to osteotomy site.

Postoperative medication, care and instructions:

Augmentin (625 mg Amoxicillin trihydrate, 125 mg Clavulanic acid GSK, Egypt.) 1gm tablets every 12 hours every day for 5 days after surgery to guard against infection. Ibuprofen (Kahira CO. for pharma and Chemo., IND Company, Cairo, Egypt.) 600mg tablets every 12 hours every day if needed postoperatively, as an analgesic and an anti-inflammatory. Chlorhexidine mouth wash (Kahira CO. for Pharma and Chemo., IND Company, Cairo, Egypt.) was prescribed twice daily for two weeks after surgery. In the day of surgery instruct the patient to apply extra oral ice bags (15-20) minutes over implantation site to prevent hematoma formation. About eating, instruct the patient to follow cold drinks and soft diet on the other side and avoid hot drinks and foods. Brushing the teeth with soft toothbrush except surgical site. Suture removal was done 10 days after surgery.

2- Second phase (healing abutment):

Two months after surgery the second phase surgery was performed include: Identification of cover screw position by palpation and probing was made. Circular incision was made around the identified position of cover screw, using #15 blade. Cover screw was removed using screw driver. Gingival former (healing abutment) was placed to allow gingival margin formation⁽²⁴⁾.

Follow up and outcomes measures:

Patients were recalled for clinical parameters 7 days after surgery for pain and swelling assessment. 3-months and 6-months after surgery for gingival index, probing depth and plaque index.

Clinical assessment

1. Pain assessment: The visual analogue scale was used to examine the patient in the first seven days after surgery⁽¹⁹⁾.
2. Swelling assessment: Swelling score assessment was used in the first seven days after surgery⁽²⁰⁾.
3. Modified gingival index (MGI): Readings were recorded for each implant at 3 and 6 months after implant placement. The gingival conditions were scored by using periodontal probe⁽²¹⁾.
4. Modified plaque index (PI): Readings were recorded around the healing abutment for each implant at 3 and 6 months after implant placement⁽²¹⁾.
5. Probing depth (PD): With the least probing force, measurements were taken from the gingival margin to the base of the sulcus. Readings were recorded at 3 and 6 months for each patient around the healing abutment and final prosthesis⁽²²⁾.

Statistical analysis:

Clinical results were collected and tabulated for statistical analysis at the end of the study period (6 months).

RESULTS

1. Pain Scale

The Pain scale mean value was (6.5 ± 0.55) in control group ranged from 6 to 7 meaning all patients were suffering from severe pain. While the Pain scale for tested group decreased to (2.00 ± 0.89) ranged from 1 to 3 meaning all patients were suffer-

ing from mild pain. According to the Independent sample t- test, the result of the p-value was 0.000 ($P < 0.01$) which indicates that there was statistically highly significant differences in the mean of Pain scale at the 0.01 level ($P < 0.01$ & confidence 99%) between Control and Test group in favor control group which have a higher mean of Pain scale, figure 2.

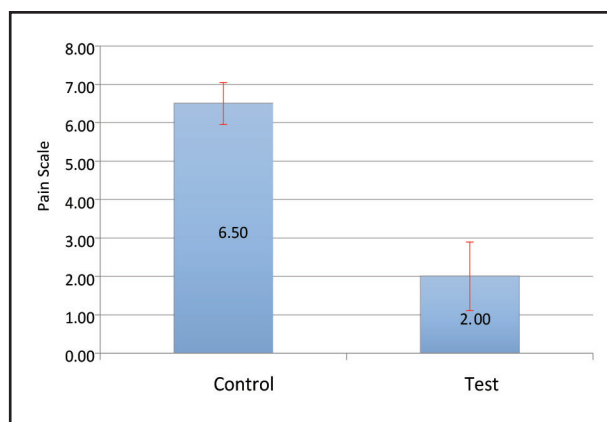


Figure (2): Bar chart showing Mean and SD of Pain Scale for Control and Test group.

2. Swelling Score

The Swelling Score mean value was (3.17 ± 0.41) in the control group ranged from 3 to 4 meaning patients were suffering from moderate to intense swelling (83.3% of patients was moderate and 16.7% was intense). While the Swelling Score for tested group decreased to (2.17 ± 0.41) ranged from 2 to 3 meaning patients were suffering from slight moderate swelling (83.3% of patients was slight and 16.7% was moderate). According to the Independent sample t- test, the result of the p-value was 0.002 ($P < 0.01$) which indicates that there was statistically highly significant differences in the mean of Swelling Score at the 0.01 level ($P < 0.01$ & confidence 99 %) between Control and Test group in favor control group which have a higher mean of Swelling Score, figure 3.

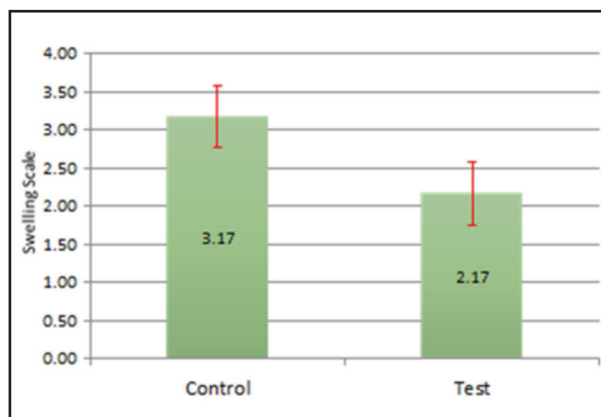


Figure (3): Bar chart showing Mean and SD of Swelling Scale for Control and Test group.

3. Modified Gingival index (MGI), table 1:

Inter group comparison:

Table (1) Mean $\pm$ SD and Range of Modified Gingival Index for Control and Test groups at different time intervals.

Time interval	Control	Test	Range	P-value**
3 months	1.00 $\pm$ 0.89	0.67 $\pm$ 0.52	Control 0-2 & Test 0-1	0.448 ^{NS}
6 months	1.17 $\pm$ 0.75	0.83 $\pm$ 0.41	Control 0-2 & Test 0-1	0.363 ^{NS}
P-value*	0.611 ^{NS}	0.364 ^{NS}		

NS: non-significant ($p > 0.05$)

* P-value from paired t test for intragroup comparison.

** P-value from independent sample t test for intergroup comparison.

- After 3 months, The MGI mean value was (1.00 ± 0.98) for control group, this value decreased in the test group to (0.67 ± 0.52). Also, the index rang for control group was from 0 to 2 while in test group was from 0 to 1. According to the Independent sample t- test, the result of the p-value was 0.448 ($P < 0.05$) which indicates that there was no statistically significant differences in the mean of MGI between the Control and Test group after 3 months.

- After 6 months, The MGI mean value was (1.16 ± 0.75) for control group, this value decreased in the test group to (0.83 ± 0.41). Also, the index rang for control group was from 0 to 2 while in test group was from 0 to 1. According to the Independent sample t- test, the result of the p-value was 0.363 ($P < 0.05$) which indicates that there was no statistically significant differences in the mean of MGI between the Control and Test group after 6 months.

4. Modified Plaque index (MPI), table 2:

Inter group comparison:

Table (2) Mean $\pm$ SD and Range of Modified Plaque Index for Control and Test groups at different time intervals.

Time interval	Control	Test	Range	P-value**
3 months	1.67 ± 0.52	1.17 ± 0.75	Control 1-2 & Test 0-2	0.209 ^{NS}
6 months	1.00 ± 0.63	0.83 ± 0.41	Control 0-2 & Test 0-1	0.599 ^{NS}
P-value*	0.175 ^{NS}	0.363 ^{NS}		

NS: non-significant ($p > 0.05$)

* P-value from paired t test for intragroup comparison.

** P-value from independent sample t test for intergroup comparison.

- After 3 months, The MPI mean value was (1.67 ± 0.52) for control group, this value decreased in the test group to (1.17 ± 0.75). Also, the index rang for control group was from 1 to 2 while in test group was from 0 to 2. According to the Independent sample t- test, the result of the p-value was 0.209 ($P < 0.05$) which indicates that there was no statistically significant differences in the mean of MPI between the Control and Test group after 3 months.
- After 6 months, The MPI mean value was (1.00 ± 0.63) for control group, this value

decreased in the test group to (0.83 ± 0.41). Also, the index rang for control group was from 0 to 2 while in test group was from 0 to 1. According to the Independent sample t- test, the result of the p-value was 0.599 ($P < 0.05$) which indicates that there was no statistically significant differences in the mean of MPI between the Control and Test group after 6 months.

5. Maximum Probing Depth (Max PD), table 3:

Inter group comparison:

Table (3) Mean $\pm$ SD of Maximum Probing Depth for Control and Test groups at different time intervals.

Time interval	Control	Test	P-value**
3 months	3.83 ± 1.72	3.00 ± 0.89	0.318 ^{NS}
6 months	2.83 ± 0.41	2.83 ± 0.41	1.000 ^{NS}
P-value*	0.203 ^{NS}	0.695 ^{NS}	

NS: non-significant ($p > 0.05$)

* P-value from paired t test for intragroup comparison.

** P-value from independent sample t test for intergroup comparison.

- After 3 months, The Max PD mean value was (3.83 ± 1.72 mm) for control group, this value decreased in the test group to (3.00 ± 0.89 mm) and according to the Independent sample t- test, the result of the p-value was 0.318 ($P < 0.05$) which indicates that there was no statistically significant differences in the mean of Max PD between the Control and Test group after 3 months.
- After 6 months, The Max PD mean value was equal for control and test group (2.83 ± 0.41 mm) and according to the Independent sample t- test, the result of the p-value was 1.00 ($P < 0.05$) which indicates that there was no differences in the mean of Max PD between the Control and Test group after 6 months.

DISCUSSION

The goal of this study was to evaluate the use of Simvastatin as anti-inflammatory, pain reducing agent, swelling reducing agent and promoter for healing of hard and soft tissue around dental implants. Simvastatin has been discovered to promote bone regeneration and soft tissue healing. This is accomplished by increasing osteoblastic differentiation, stimulating neovascularization via its effect on bone morphogenetic proteins (BMP) and endothelial growth factor⁽²⁵⁾, inhibiting tissue degrading enzymes such as matrix metalloproteinase (MMPs), promoting autophagy, and lowering ROS production⁽²⁶⁾.

The preparation of simvastatin as controlled release drug delivery system was to take an advantage of it. The most important of these advantages are sustained drug levels in situ, drug escape from stomach destructive acidic environment, increase local concentration of drug in situ and sustained release drugs offer a onetime application and have an advantage over repeated applications⁽²⁷⁾.

This study was performed on 16 T2DM patients as Diabetic patients have delayed wound healing, impaired response to infection and compromised bone and soft tissue healing. Impaired vascularity and T2DM-enhanced inflammation disturb a proper distribution of oxygen, nutrients, and osteoprogenitor cells to repair site. It is suggested that the function of osteoprogenitor cells is compromised in T2DM patients. And there is an alternation in bone turn over which in turns has a bad impact in bone formation and/or resorption. Additionally, advanced glycation end products (AGEs) which generated as a result of the hyperglycemia is capable of altering the bone matrix and decreasing the bone quality⁽²⁸⁾.

In this study Titanium dioxide implants was used. Which is the main material for dental implant that is surgically inserted into hard and soft tissues which provide a superstructure for esthetics and function purposes⁽²⁹⁾.

Regarding to results, the patients in test group who received the simvastatin gel, experienced less post-operative pain after the surgery. When assessed by pain scores 7 days after surgery. The control group mean value was (6.5 ± 0.55) , while the tested group decreased to (2.00 ± 0.89) . According to the Independent sample t- test, the p-value was 0.000 ($P < 0.01$) which indicates that there was statistically highly significant differences in the mean of Pain scale at the 0.01 level ($P < 0.01$ & confidence 99 %) between Control and Test group. It is worth highlighting that the majority of patients in test group stopped using the pain killers the second day after surgery. While the majority of the patients in control group used pain killers for 7 days after surgery and a few of them stopped using it after 5 days after surgery.

Also, patients in test group who received the simvastatin gel experienced less post-operative swelling. When assessed by swelling scores 7 days after surgery. The mean value was (3.17 ± 0.41) in the control group ranged from 3 to 4 meaning patients were suffering from moderate to intense swelling (83.3% of patients was moderate and 16.7% was intense), while the mean value for tested group decreased to (2.17 ± 0.41) ranged from 2 to 3 meaning patients were suffering from slight moderate swelling (83.3% of patients was slight and 16.7% was moderate). According to the Independent sample t- test, the result of the p-value was 0.002 ($P < 0.01$) which indicates that there was statistically highly significant differences in the mean of Swelling Score at the 0.01 level ($P < 0.01$ & confidence 99 %) between Control and Test group.

The modified gingival index mean value in the Control group was (1.00 ± 0.98) after 3 months & 1.16 ± 0.75 after 6 months). This value decreased to (0.67 ± 0.52) after 3 months & 0.83 ± 0.41 after 6 months) in the Test group. According to the Independent sample t- test, the result of the p-value was 0.448 ($P < 0.05$) after 3 months & was 0.363 (P

<0.05) after 6 months which indicates that there was no statistically significant differences in the mean of MGI between the Control and Test group after 3 & 6 months.

The modified plaque index mean value in the Control group was (1.67 ± 0.52 after 3 months & 1.00 ± 0.63 after 6 months). This value decreased to (1.17 ± 0.75 after 3 months & 0.83 ± 0.41 after 6 months) in the Test group. According to the Independent sample t- test, the result of the p-value was 0.209 ($P < 0.05$) after 3 months & was 0.599 ($P < 0.05$) after 6 months which indicates that there was no statistically significant differences in the mean of MPI between the Control and Test group after 3 & 6 months.

The probing depth mean value after 3 months in the Control group was (3.83 ± 1.72 mm). This value decreased to (3.00 ± 0.89 mm) in the Test group. According to the Independent sample t- test, the result of the p-value was 0.318 ($P < 0.05$) which indicates that there was no statistically significant differences in the mean of PD between the Control and Test group. While the PD mean value after 6 months was equal for both groups (2.83 ± 0.41 mm) and according to the Independent sample t- test, the result of the p-value was 1.00 ($P < 0.05$) which indicates that there was no differences in the mean of PD between the Control and Test group.

Study conducted in 2018 reported that topical simvastatin gel is a unique therapeutic method for palatal donor site wound healing after a free gingival transplant operation. This clinical study examined the effect of topically applied simvastatin/chitosan gel (10 mg/mL) intra-oral over the palatal donor site following a free gingival graft (FGG) procedure. Study reported statistically significant decrease in wound-healing scores (after 3, 7 days) in test group compared to other groups. And a significant decrease in the visual analog scale (VAS) score (1, 3, 5 days) when compared to the other groups on the same days⁽³⁰⁾.

In vivo study conducted in 2021⁽³¹⁾, the rates in test group received wound dressing contained controlled release simvastatin shown a faster and more efficient wound healing process than the rates in control group.

In 2020 a study showed that topical use of simvastatin at low concentrations (10 mg/mL) is safe and enhances wound healing. This also reduces the danger of bacterial infection throughout the wound healing process due to its antibacterial action and ability to control the inflammatory response. Finally, using statins topically to promote wound healing is a safe and promising therapeutic option⁽³²⁾.

CONCLUSION

The use of Simvastatin controlled release gel with delayed dental implants may be able to decrease postoperative pain and swelling in addition to improvement healing around dental implants by the anti-inflammatory properties.

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RECOMMENDATIONS

It is recommended to measure the periodontal measurements (Modified plaque index, Modified gingival index and probing depth) after 2 months from the dental procedure. Further long term studies are recommended for controlled release drugs around dental implant in diabetic type II patients.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

FUNDING

This research received no external funding.

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