Journal of Dentistry Indonesia

Volume 29 | Number 2 Article 5

8-31-2022

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Journal of Dentistry Indonesia 2022, Vol. 29, No. 2, 105-112
doi: 10.14693/jdi.v29i2.1319

ORIGINAL ARTICLE

The Effect of Melatonin on Implant Stability and Marginal Bone Level around The Implant

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ABSTRACT

Dental implants have been used for missing teeth replacement with a high success rate. Melatonin is an antioxidant and acts as a free radical scavenger. It retards the resorption of bone by regulating RANKL and OPG synthesis, and increases the BIC (Bone to implant contact) and also bone perimeter and bone mineralization. **Objective:** The aim of the study was to assess if topical melatonin application at the osteotomy site has any influence on the stability and marginal bone level around the implant **Methods:** In this split mouth double blind randomized control trial 30 implants were placed on either side of the mandible in which test sites were irrigated with melatonin solution prior to the implant placement and the control site on the other side was irrigated with normal saline. Crestal bone level and implant stability assessment was done at baseline and 3 months. **Results:** A significant difference was observed between the groups with respect to crestal bone loss scores at 3 months. Regarding implant stability a significant difference($p<0.05$) was observed within the groups at baseline and 3 months and also between the groups at 3 months only. **Conclusion:** Melatonin showed a statistically significant reduction in crestal bone loss and an increase in implant stability.

Key words: crestal bone loss, implant, implant stability, melatonin

How to cite this article: Ravella H, Rao MVR, Manthena S, Koneru S, Preethi PL, Anumolu VNSH. The effect of melatonin on implant stability and marginal bone level around the implant. J Dent Indones. 2022;29(2): 105-112

INTRODUCTION

Oral health and oral health care are very important to maintain proper mastication, phonation, esthetics and psychological well-being. The replacement of missing teeth with dental implants has now become a treatment modality for fully and partially edentulous patients. Branemark in the year 1969 defined osseointegration as "a direct structural and functional connection between ordered living bone and the surface of the load bearing implant".[1]

Preservation of the bony support around the implants determines the long-term success of dental implants. Albrektsson proposed that 1 to 2 mm of crestal bone loss could be expected in the first year after the implant placement, and then 0.2 mm of crestal bone loss as an average might occur each year after that.[2] The other important parameter that influences the successful osseointegration of the implant is stability. The stability is categorized into two classes. First, the initial stability that is gained during the implant installation and the second, secondary stability during the healing process. Initial stability is a mechanical phenomenon, and secondary stability is a biological phenomenon and is the result of osseointegration.[3]

Melatonin is chemically recognized as N-acetyl-5-methoxytryptamine and is a compound which occurs naturally in plants, microbes, and animals. It neutralizes a variety of reactive oxygen species (ROS), including superoxide anion radical(O_2^-), Hydrogen peroxide (H_2O_2), and Hydroxyl radicle (-OH) and reduces the degree of tissue damage.[4,5] Melatonin enhances the production of bone sialoprotein, alkaline phosphatase, osteocalcin, osteopontin and reduces the

period of differentiation of osteoblasts from 21 days to 12 days through located receptors on preosteoblasts and this reaction is mediated by the membrane receptors for the indole.[6] The molecular mechanism of melatonin on bone resorption is that melatonin downregulates the expression of RANKL and upregulates the expression of OPG. RANKL is a potent activator, and OPG is a potent inhibitor of not only osteoclastogenesis but also osteoclast activity.

For successful osseointegration, implant stability plays a critical role. Achievement and maintenance of implant stability are prerequisites for a successful clinical outcome. Implant stability is achieved at two different stages: primary and secondary. Primary stability refers to the stability of a dental implant immediately after implantation. Secondary stability which reflects the value of strengthening of mechanical connection between implant and bone induced by a successful osseointegration process.[7] Primary stability is accomplished when the implant is placed in bone in such a position that it is well seated. This allows the implant to adapt mechanically to the host bone until secondary stability is achieved. Impaired implant stability has shown to jeopardize the osseointegration process. During osteotomy preparation, the preservation and maintenance of bone lead to enhanced primary mechanical stability, enhanced BIC, thereby enhancing the implant secondary stability.[8]

The molecular aspects in the mechanism of bone fracture healing and the role of melatonin were explained by Mehmet Halici.[9] According to this, the inflammatory phase is characterized by clot formation, reperfusion injury and inflammatory cells such as leukocytes, macrophages and mast cell infiltration. During this period, neutrophils produce free radicals that initiate a chain reaction leading to cell membrane damage via lipid peroxidation, which has a negative effect on bone healing. Malondialdehyde, superoxide dismutase and myeloperoxidase play a key role in oxidant production. Melatonin helps in suppressing the effects of free oxygen radicals and regulating antioxidant enzyme activity, thereby accelerating bone formation in the fracture healing process. Melatonin also acts as a powerful biomimetic mediator in the placement of endosseous dental implants and prevents ion leakage and particle residues. They also suggested that melatonin increases the BIC and also bone perimeter and bone mineralization.

Very few clinical studies were conducted measuring the effect of melatonin on implant stability and marginal bone level around the implant. Therefore, this study is designed to assess if topical melatonin application at the osteotomy site has any influence on the stability and marginal bone level around the implant.

METHODS

This double-blind split-mouth randomized control trial was conducted in the Department of Periodontics & Implantology, Drs. Sudha & Nageswara Rao Siddhartha institute of dental sciences. A total of 10 periodontally stable subjects with 30 bilaterally edentulous sites in the mandibular region willing for replacement were taken into consideration. The sites of the mandible that require implant were randomly assigned as test and control sites using a flip coin method to maintain randomization. To keep the trial as a double-blind study design, allocation site to control and test group, placement of dental implant was done by one examiner and the radiographic and stability measurements were taken by another examiner. The patients were also maintained blind towards the allocation of the site to test or control group. The edentulous sites should have an adequate bone height (at least 10mm) and bone width (at least 5.5mm) and bone crest healing period of minimum 4 months prior to implant placement. Bone quality and density was assessed by using CBCT. Patients with systemic diseases contraindicating any type of surgery, under bisphosphonate therapy, chronic smokers, any evidence of pathology or active diseases of the implant bed, subjects who underwent radiation therapy were excluded from the study. Treatment plan was explained to all the patients and written informed consent was obtained. The study protocol was approved by Drs. Sudha & Nageswara Rao Siddhartha institute of dental sciences institutional ethical committee. (21/2018)

A brief case history was taken and all the patients were selected based on inclusion and exclusion criteria. General medical examination was done to ascertain the absence of any medically compromising conditions. Proper diagnosis and treatment planning was done for all the implant patients. Investigations such as complete hemogram, INR, Hb%, ESR, PCV, bleeding time, clotting time and blood sugar levels were done to evaluate fitness of the patient for implant surgery. IOPA, OPG, CBCT scan were done to evaluate quality and quantity of bone and also to select the size of the implant with respect to the edentulous site. Surgical site was examined and implant length and diameter were selected for each patient based on individual clinical and radiographical needs (CBCT). Local anesthesia was given i.e., lignocaine 20mg/ml with adrenaline 1:80,000. After achieving adequate local anesthesia at the implant site, crestal incision was given with No.15 BP blade and full thickness muco-periosteal flap was elevate using periosteal elevator. Osteotomy site preparation was done through sequential drilling as per the manufacturer's instructions, and the length and diameter were prepared to the pre- planned measurements in the CBCT in both the groups.

Preparation of melatonin solution
A 3mg melatonin tablet (meloset®) was crushed in a sterilized mortar pestle. Melatonin solution was prepared in a sterilized container by mixing the obtained powder with normal saline in a concentration of 3mg/ml.

In test site after preparation of the osteotomy, melatonin solution (3mg/ml) was irrigated until the osteotomy site is filled (figure 2) and then the implant is carried from the packaging to the osteotomy site and is positioned to the desired depth with a torque ratchet. In the control side, after preparation of the osteotomy, the site is irrigated with saline solution (placebo effect) the implant is carried from the packaging to the osteotomy site and is positioned to the desired depth with a torque ratchet. A minimum of 3mm inter implant distance and 1.5mm distance from the adjacent tooth was maintained. Flaps were approximated, and simple interrupted sutures were placed with 3-0 BBS suture material. it was made sure that all the implants were placed at an equicrestal level.

All the patients were prescribed with Amoxicillin + Clavulanic acid 625mg twice daily for 5 days, Ibuprofen 400mg thrice daily for 5 days along with 0.2% chlorhexidine mouth rinse twice daily until complete oral hygiene habits were resumed. Patients were asked not to brush on the operated site for a week and other post- surgical instructions were given and recalled suture removal.

Mean crestal bone loss was assessed radiographically using standard intra-oral periapical radiographs taken using paralleling technique with customizable film holder along with grid (figure 7). Radiographs were taken at baseline and 3 months post-operatively (figure 5 and 6). Crestal bone level was measured at mesial and distal implant surfaces using IOPA with grid and averaged to yield mean marginal bone loss for that implant at baseline and 3 months. Intraoral periapical grid measures exactly the size of IOPA (3×4 cm) and is made up of 2 strands of lead (thicker and thinner) incorporated both vertically and horizontally throughout its measurements. Thicker strands are incorporated exactly at 5mm distance, and thinner strands are built in between thicker stands precisely at a distance of 1mm both vertically and horizontally. The stability of implants was measured using an Osstell device and smart peg (figure 8 and 9). ISQ values are recorded at the mesial, distal, buccal and lingual sides of the implant, and an average of all the values is calculated. Implant stability is measured immediately after placement and at 3 months.

Data analysis
Statistical analysis was performed using SPSS software version 23. To determine the normality of the data Shapiro-Wilk test was used. As the distribution of data was not normal for the implant length, implant width and crestal bone loss, a nonparametric Mann-Whitney U test was applied for intergroup comparison. The data distribution was normal for the stability, so parametric Paired t-test was applied for intragroup comparison and Unpaired t-test for intergroup comparison.

RESULTS

Among these 10 patients, 3 were male (30%) and 7 patients were female (70%) aged between 25-65 years (mean: 45 years). Among these 10 patients, 5 patients received 4 implants, and 5 patients received 2 implants. There was no significant difference on comparing the mean diameter and length of implants between test and control groups. (Table 1, 2 and 3).

A significant difference was observed between inter groups comparison with respect to crestal bone loss scores at 3 months. The results of our study suggest that melatonin application at implant sites showed lesser crestal bone loss than the control sites which was statistically significant. (Table 4)

A significant difference was observed between intra group comparison with respect to mean implant stability at baseline and 3 months. A significant difference was observed between inter group comparison with respect to mean implant stability at 3 months only. The results of our study suggest that melatonin application at implant sites showed greater implant stability than the control sites which was statistically significant. (Table 5 and 6).

Table 1. Implant demographic data

Implant diameter × length in mm	No. of implants in control group	No. of implants in test group
3.75x11.5	3	0
3.75x13	1	2
4.2x10	1	0
4.2x11.5	6	6
4.2x13	1	2
4.65x10	1	1
4.65x11.5	0	2
5.3x6	2	2

Table 2. Comparison of control group and test group with diameter of implants using Mann-Whitney U test

Group	n	Implant Diameter		Mean Rank	U value	Z value	p
		Mean	SD				
Control	15	4.26	0.49	14.10	91.5	-0.95	0.38
Test	15	4.38	0.46	16.90			

$p<0.05$

Table 3. Comparison of control group and test group with length of implants using Mann-Whitney U test

Group	n	Implant Length		Mean Rank	U value	Z value	p
		Mean	SD				
Control	15	10.77	2.09	14.4	96	-0.76	0.51
Test	15	11.06	2.23	16.6			

p<0.05

Table 4. Inter group comparison of crestal bone loss at 3 months using Mann-Whitney U test

Group	n	Crestal Bone Loss (mm) At 3 months		Mean Rank	U value	Z value	p
		Mean	SD				
Control	15	1.4	0.34	21.33	25	-3.93	<0.0001*
Test	15	0.83	0.24	9.67			

p<0.05

Table 5. Intra group comparison of Stability from baseline to 3 months using Paired t-test

Group	Stability	n	Mean	SD	SE	t value	p
Control	Baseline	15	69.05	2.09	0.54	-6.48	0.001*
	3 months	15	70.33	2.39	0.61		
Test	Baseline	15	70.28	2.29	0.59	-11.49	0.001*
	3 months	15	72.43	2.04	0.52		

p<0.05

Table 6. Inter group comparison of Stability at Baseline and 3 months using Unpaired t-test

Stability	Group	n	Mean	SD	SE	t value	p
Baseline	Control	15	69.05	2.09	0.80	-1.53	0.13
	Test	15	70.28	2.29	0.80		
3Months	Control	15	70.33	2.39	0.81	-2.58	0.01*
	Test	15	72.43	2.04	0.81		

p<0.05

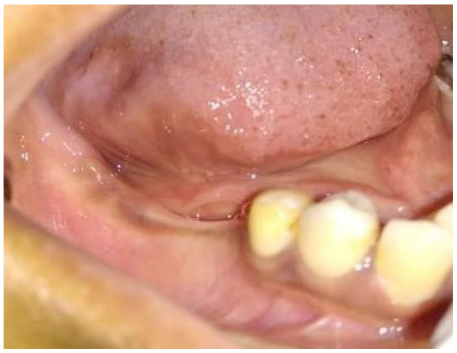

Figure 1. Pre-operative

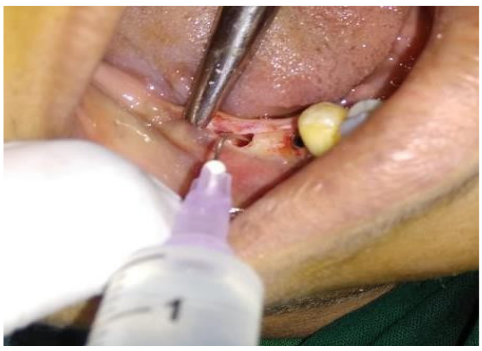

Figure 2. Irrigation of melatonin solution in osteotomy site

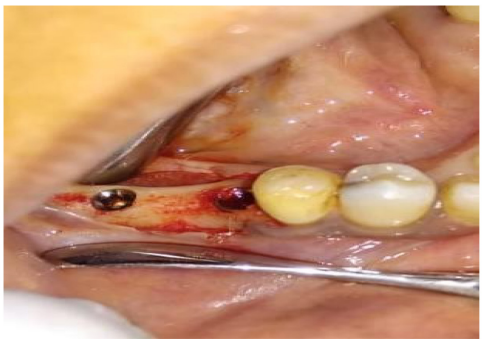

Figure 3. Implants placed

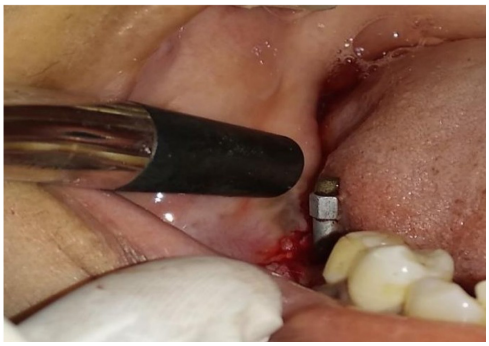

Figure 4. Stability measurement

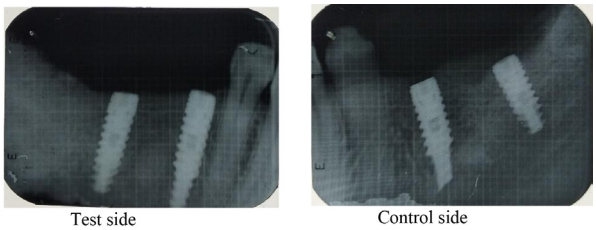

Figure 5. IOPA with grid at baseline

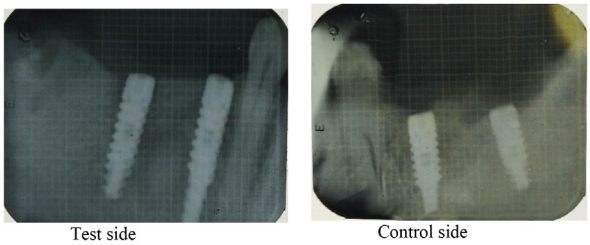

Figure 6. IOPA with grid at 3 months

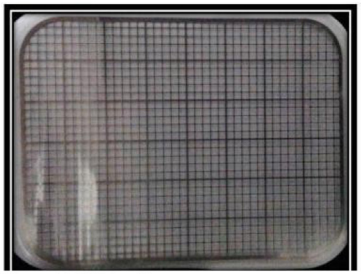

Figure 7. IOPA grid

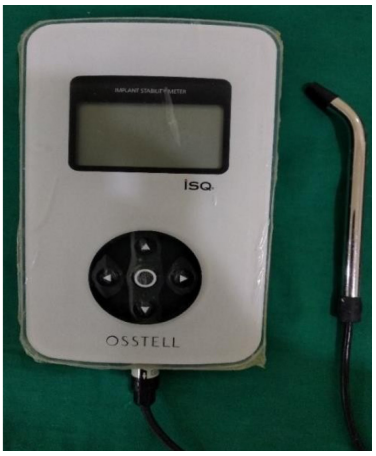

Figure 8. Osstell device

Figure 9. Smart peg

DISCUSSION

Implant supported rehabilitation has gained much attention in the contemporary clinical scenario to restore the patient's oral health to normal function, comfort and esthetics. The long-term clinical success of dental implants depends mainly on preservation of bony support around the implant. Early crestal bone loss depends mainly on the surgical trauma during the placement of implant which includes excessive reflection of the periosteal flaps, prolonged exposure of the osteotomy site to the external environment and due to excessive pressure, that is applied on the bone during the placement of implant.[10] To minimize these factors it was made sure that all the implants in the study were placed in the least traumatic way possible.

The implants used in this study were Alpha Bio ICE implants which consists of micro rings at the coronal part which itself helps to increase the bone-implant contact at the crestal region. These implants have double threaded design with 2mm step and the apical part of the implant is narrow with sharp and deep apical threads and has a flat apical border. These implants were sand blasted and double acid etched which increases the surface area on the implant enabling a more intense absorption of blood and plasma proteins directly into the implant micropores immediately after the implant placement which ultimately enhances the bone-implant contact. This micro structure and roughness created by the sand blasting and acid etching process greatly influences the dynamic wet ability of implant surfaces during the initial contact with the host.

According to Sennerby and Meredith[11] Resonance frequency analysis stability measurements essentially apply a bending load, which mimics the clinical load and direction and provides information about the stiffness of the implant-bone junction. Stability of the implants was measured using Osstell device and a transducer. The transducer has a magnetic peg on top and is fixed to the implant. By the activation of the magnetic resonance frequency probe, the peg is activated, which vibrates and induces electric volt sampled by magnetic resonance frequency analyzer. Values are expressed as ISQ of 0 to 100. It provides baseline reading at the time of implant placement and for further comparison and post-surgical placement of the implant. In this study, ISQ values are measured at the time of implant placement (primary) and after 3 months (secondary).

Aaron Lerner and colleagues 1958 found the chemical structure of Melatonin as N-acetyl-5-methoxy-tryptamine.[12] Melatonin, an endogenous hormone rhythmically produced in the pineal gland under the control of the suprachiasmatic nucleus and the light/dark cycle. It is also produced by several tissues, including retina, thymus, spleen, ovaries, testicles, gastrointestinal tract. Its actions are mediated by the binding of indoleamine to nuclear receptors or membrane receptors. It also binds to some cytosolic proteins such as kinase, calmodulin and calreticulin.[13]

Melatonin because of its antioxidant properties and capacity to counteract the active species, it retards the resorption of bone by downregulating the RANKL, as RANKL is the main source of formation and regulation of osteoclast lacunae. The anti-inflammatory and the antioxidant properties have a reinforce action by the minimum production of reactive species and hence prevents bone resorption. Melatonin also suppresses the pain from inflammation by blocking the pathways of nitric oxide production.[14]

Melatonin being a pleiotropic multitasking molecule, on topical application it suppresses the effect on IL-6, IL-β which are the inflammatory mediators, causing soft tissue destruction by stimulating the production of PGE and collagen synthesis. Melatonin increases preosteoblast/osteoblast-like cell proliferation by regulating RANKL and OPG synthesis and also improves the expression of type I collagen and bone marker proteins such as alkaline phosphatase, osteopontin, bone sialoprotein, osteocalcin and stimulates the mineralized matrix in these cells. Once these bone markers are developed in the osteoblast, they, in turn, helps in differentiation of osteoblasts by reducing the time from 21 days to 12 days through located receptors on preosteoblasts and this reaction is mediated by the membrane receptors for the indole.[6]

Lobna M.conducted a study to evaluate the effect of autogenous bone graft on the osseointegration of early loaded dental implant either alone or combined with melatonin gel. They concluded that the adjunctive topical use of melatonin seems to have a more valuable outcome in promoting the early osseointegration.

O. Salomo-Coll conducted a study to evaluate the effect of topical application of melatonin and vitamin D over surfaces of immediate implants.[16] Mandibular premolars were extracted bilaterally from six dogs. They concluded that topical applications of 5% Melatonin or 10% vitamin D improved bone formation around the implants placed immediately after extraction and helped to reduce CBL after 12 weeks of osseointegration.

In our study at 3 months, control group showed mean marginal bone loss of 1.4mm, and test group showed mean marginal bone loss of 0.83mm. In this study, implants with micro threads at the coronal part were used which itself helps to reduce the bone loss. These results were in accordance with the criteria for successful implant therapy reported by Albrektsson. These results showed that the test side in which melatonin was irrigated showed a significant reduction in crestal bone when compared to the control group. These results were in accordance with the study conducted by Mona Y. El-Gammal.[17] Serkan Dundar et al. conducted a study to evaluate the effect of local melatonin at different dosages of 1.2 mg and 3mg on BIC and found that there was higher BIC percentage at 3mg compared to 1.2mg.[18] In this study, the dosage and results were in accordance with the study conducted by Isabel F Tresguerres.[19]

Ahmed Fahmy conducted a study to compare the effect of PRF and melatonin on the stability of implants immediately placed in extraction sockets and loaded with implant retained overdenture.[20] Ten edentulous patients were restored with two immediately placed implants in the lower canine, first premolar region and were restored with implant-retained overdentures. A split-mouth technique was used where on one side melatonin was placed into the extraction socket prior to implant placement (group-1), and on the contralateral side, PRF was placed after implant placement (group-2). After loading the implants with locator attachments and mandibular overdentures, ISQ measurements were recorded at overdenture insertion after 2, 4 and 6 months. He concluded that the addition of PRF into fresh extraction sites in immediately installed implants showed better implant stability than the use of melatonin.

In our study at baseline control group showed mean stability of 69.05, and test group showed mean stability of 70.28. The stability scores at baseline were more or less similar and showed no significant difference. ISQ values greater than 65 have been regarded as the most favourable implant stability, whereas ISQ values below 45 indicate poor stability. [21] Both the test and control group showed ISQ values greater than 65 at baseline, which ensured that the implant was stable in the osteotomy site. Both test and control group showed a significant increase in the stability scores from baseline to 3 months. A significant increase in stability scores was observed in the test group when compared with control group at 3 months. These results were in accordance with the study conducted by Doaa Amr A. Heshmat Rostom (2016).[22]

Within the limitations of the study, though application of melatonin showed a statistically significant reduction in crestal bone loss and an increase in implant stability, translation of this statistical significance to clinical significance and its impact on long-term marginal bone preservation and stability maintenance have to

be explored. Till now, most of the studies were done to evaluate the effect of melatonin on crestal bone loss, and very limited studies were done on implant stability.

There are several limitations of the study. This study could not measure the bone density around the implant sites. Furthermore, this study only had minimal sample size, and short-term follow-up.

CONCLUSION

There is a statistically significant difference in crestal bone loss between the control group and the test group from baseline to 3 months, indicating that melatonin preserves the crestal bone in the early healing period. A significant increase in implant stability was found in the test group when compared to the control group at 3 months, indicating that melatonin helps to increase implant stability.

Within the limitations of the study, though application of melatonin showed a statistically significant reduction in crestal bone loss and an increase in implant stability, translation of this statistical significance to clinical significance and its impact on long-term marginal bone preservation and stability maintenance have to be explored. Till now, most of the studies were done to evaluate the effect of melatonin on crestal bone loss, and very limited studies were done on implant stability. Further long-term studies should be conducted to assess if melatonin can preserve the bone at the crestal region of the implants after the placement of the prosthesis.

CONFLICT OF INTEREST

No conflict of interest related to this study.

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(Received November 19, 2021; Accepted August 2, 2022)