Validity of Growth hormone and Melatonin mixture locally applied around immediate implants: Aclinical study

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Abstract: Background: There is no uniform strategy about the optimal implant yet. The foundation of implant success is osseointegration, the quality, quantity and rate of which is of importance. **Aim:** The aim of the study is to evaluate the effect of growth hormone and melatonin mixture on osseointegration around immediate implants after 3,6 and 9 months in human. **Material and methods**: Five patients were included in this study, to whom eight immediate implants were inserted in their posterior mandible. They were divided into two groups, test group including five implants and control group including 3 implants. The test group received the growth hormone and melatonin mixture before implant incersion, while the control group was not. **Results** as regard bone density were statistically non significant in all test periods, while the transition period 3-6 months was statistically significant in test and control. In conclusion, Growth hormone and melatonin mixture in a single large dose at time of surgery did not affect bone density of the new bone formed around an immediate implant.
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1. Introduction

The application to replace missing and lost teeth, becoming a more demanding situation specially for aging population with suspected systemic diseases and increased occlusal discrepancies that in turn bring about tempro-mandibular disorders.[1]When an implant is surgically placed into jaw bones the mechanical environment is altered, which assumed that osteocytes are sensitive to mechanical loading and active in controlling adaptation of bone mass. Bone mass is determined by bone remodeling and bone growth under the influence of external loads, bone is capable of optimizing its internal structure by redistributing its apparent density (bone remodeling) to fulfill maximum function. There is no uniform strategy about the optimal implant yet.[2,3] The foundation of implant success is osseointegration, which was defined microscopically as direct contact between living bone and implants. Implant surfaces have been developed in the last decade in a concentrated effort to provide bone in a faster and improved osseointegration process.[4]The term biomimetics (bio-integration) is now increasingly used in modifying the surface treatment of titanium implant. Biomimetics are bioactive molecules stimulating new bone formation.[5] Coming to sight growth hormone as an endocrine that has a rule in bone formation and melatonin as an antioxidant in the surgical bed, also stimulating bone formation. Growth hormone (GH) stimulate the recruitment of preosteoblasts and osteoblast proliferation *invitro*. Melatonin stimulate bone formation by stimulating [osteoblastic differentiation and stimulate gene expression of certain bone proteins (osteopontain, osteocalcin and alkaline phosphatase)] and inhibiting osteoclasts function.[7-8] Thus, suggesting the combination between GH and melatonin.Computed tomography CT provides a unique means of image analysis of implant sites. After axial Ct images are required, they undergo computer manipulation termed “Multiplanar reformatting MPR” to create tangential and cross sectional tomographic images of the implant site. This advanced computer technique allows the formation of two dimensional images in multiple images planes.[3,8-9]

Studies have demonstrated that the observation of clinical procedures such as atraumatic extraction followed by implant stabilization in an extraction socket must be carefully considered to allow healing in the form of defect like gap, which is considered to be filled with woven bone that allows structural continuity between bone in contact with implant surface (contact osteogenesis) and new bone formed due to socket healing (distant osteogenesis).[10,11]

Updated reviews and conferences on immediate implantation in fresh extraction socket suggest that there is no need to wait for complete healing of the socket before implant insertion.[12,]

2. Material and Methods

A total of eight immediate implants were carried out in the study. The patients were selected from the outpatient clinic, department of Oral Surgery, Faculty of Dentistry, Suez Canal University. All patients of the present study were given a detailed explanation of the treatment protocol and gave their written consent to carry out treatment of the described protocol. The surgeries were performed under local anesthesia. All implants were placed on the day of tooth extraction, using two stages surgery technique with submerged implant placement. Simple maneuvers were used for extraction; extraction forceps and fine elevators with gentile force was carried out to protect the socket wall. Preparation of implant bed was done to the bottom of the socket by 2-3mm. Preparation was at 4000 rpm with saline irrigation using the sequence of drills as advised by the manufacturer written protocols 2.2, 2.8, 3.4, 3.7 and 4.4. The right side was treated by a mixture of 4IU (1.6mg) **Growth hormone** (Somatotropin 4IU SEDICO Pharmaceutical Industries co.,6thoctober city. EGYPT)in a vial form and 3mg **Melatonin (**VIVA-MAX3® product of AMOUN Pharmaceutical industries co (APIC) El Salam city, Cairo, Egypt)in a powder formbefore implant insertion while the left side was left as a control. Melatonin tablet was crushed in a sterile dappen dish until powder form was established, GH powder was injected with 1mml of sterile water supplied by the manufacturer, gentile injection was important to allow all powder to dissolve without remnants.Both components were mixed and put in a plastic syringe for easy application in the wound.The implant shoulders were positioned at the level of the crestal bone or even lower than the crest of adjacent. Primary stability was important. The implant was sealed with conventional cover screw. Wound closure with interrupted sutures using 3.0 silk sutures.All patients were kept under antibiotic therapy foxime 1g*(*Tabuk Phrmacuticals.co, Saudi Arabia) for 3 days or more when needed, as well as metronidazole (Amrizole® 500mg, Amriya Pharma Pharmaceuticals. Co, Alexandria Egypt) and analgesic Cataflam 50mg(Novartis Pharma Pharmaceutical industries co, Cairo, Egypt).Five patients were included in the study, they were subjected to extraction of a posterior mandibular tooth, usually the second premolar. Five extraction sockets received growth hormone and melatonin treatment immediately before implant incersion, while the other three sockets received immediate implants without treatment to serve as control.

Computed tomographic analysis:

All patients were subjected to CT imaging immediately post operatively, 3 month, 6 month and 9 month. The study was carried out using (Hispeed dual CT system GE Medical system) according to the following parameters ; 120 kv, 120 ma and a slice thickness of 1mm. Bone density measurements by linux dental software using Hounsfield units (- 1000 to + 1000) were applied.

Bone density measurements:A central line of 5 mm was drown midway along the implant (perpendicular to the long axis of the implant) corresponding to the 3.7 mm implant. Moreover,a central line of 6 mm was drown midway along the implant (perpendicular to the long axis of the implant) corresponding to the 4.7 mm implant.

A rectangular area of a fixed dimension was drown mesially, distally, bucally and lingually perpendicular to the central line. Using Linux software the bone density along the rectangular area was recorded..

Statistical analysis The comparison between test and control groups at different healing periods were analyzed using non parametric tests; Mann-Whitney Test. Wilcoxon Signed test was used for comparing different groups in control and test separately. Differences were considered statistically significant when p value was < 0.05.

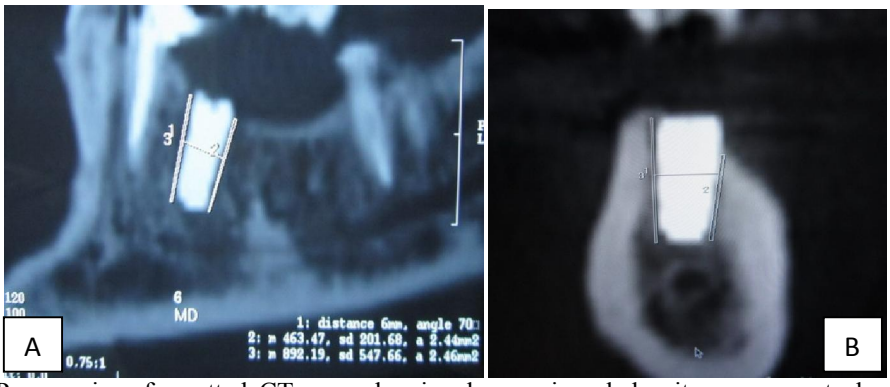

Fig.1a: Panoramic reformatted CT scan showing bone mineral density assessment along the mesial and distal surfaces of the implant. **Fig.1b:**Coronal CT scan showing bone mineral density assessment along the buccal and lingual surfaces of the implant

3. Results

The test group had higher bone mineral density than the control group in 3rd and 9th month periods, while after six months the control was higher. This difference was statistically non significant see (Table 1).

Regarding the comparison between the follow up periods along the study in both control and test groups, a statistically significant difference was noticed between the 3rd and the 6th months postoperatively in both groups. While a statistically significant difference was recorded only between the 3rd and the 9th month postoperatively in the control group only (Table 2)

Table (1): Comparison between the bone mineral density means in the control and experimental groups in the clinical study

Study periods	Groups		*P*- value
	Exp.	Cont.	
	Mean ± SD	Mean ± SD	
3M	508 ± 186	471 ± 75	0.55
6M	582 ± 169	647 ± 101	0.48
9M	760 ± 186	643 ± 86	0.121

*Values considered significant when the *p* value ≤ 0.05, SD standard of deviation

Table (2): Comparison between the bone mineral density means along the study periods in the control and experimental groups each alone.

Study periods	Control			Exp		
	3-6	3-9	6-9	3-6	3-9	6-9
p-value	*0.028	*0.028	0.753	*0.025	0.18	0.18

*Values considered significant when the *p* value ≤ 0.05

4. Discussion

The present study was carried out on five male patients. The female patients were not included in this study, to overcome the direct effect of estrogen loss on bone resorption. Moreover, lower bone mineral densities in female have been observed throughout adult life. Ideal bone mineral density value for bone strength has not yet been determined, increasing mineralization density increases the ability of bone to absorb impact energy although the relation is not linear. Within the limitation of this study, bone at the interface of unloaded dental implants after 3, 6and 9 months showed statistically non significant increase of bone mineral density in the 3rd and 9th month in test over control while in the 6th month the control showed statistically non significant increase over the test group. This may be attributed to insufficient dose or the need of further repeated local applications. Moreover, The circulating half life of melatonin and growth hormone were 23 and 20 min respectively. It is challenging to explore the concept of a single large dose of Growth hormone GH and melatonin in fresh extraction socket. Such information will be key to developing biomimetic materials.[13,14] Growth hormone GH and Melatonin are examples of biomimetics. Growth hormone (GH) could exert an impulse effect in the first hours of the process of osseointegration by accelerating the recruitment of preosteoblasts. Concerning the GH and its binding peptide that had a network shape that favors osteoconduction, cells to settle down and tissue to mineralize. Suggestions of synergy between different stimulating agents is a working concept as GH itself cannot keep a long term effect. Hence the trial of synergy between melatonin and GH in this study. Many authors documented the link between melatonin and bone metabolism, stated that melatonin acted on bone as a local growth factor with paracrine effect on neighboring cells. Melatonin stimulate gene expression of certain bone proteins (osteopontain, osteocalcin and alkaline phosphatase). The relation between melatonin, growth hormone and bone have been demonstrated in many studies.[15,16-20]They act as bone stimulators by increasing osteoblastic lineage differentiation and proliferation, matrix production and potentiating mineral deposition. Bone healing around immediate implants involves bundle bone that possesses a high remodeling capacity. New research protocols suggesting mandatory initial stability, five walls

defect was mandatory to maintain a firm blood clot which is an indicator for immediate implant (adequate bone room), to enhance the primary stability, immediate implant should be stabilized using the surrounding socket wall and bone beyond the root apex at least 3mm.[21-23]On the other hand, the follow up recalls for the human group were 3, 6 and 9 months postoperatively. This was attributed to fact that the loss of 33% of alveolar ridge width in posterior sites at first 3 months and 50% after 12 months.[4]The average length of the remodeling phase in cancellous bone is about 200 days.[20]

Further investigations as regard different imaging techniques, different (smaller) study periods and more control on the local application of such biomimetics around the immediate implant.

Conclusion,

A single large dose of growth hormone and melatonin mixture at immediate implant site insertion did not increase the bone mineral density .

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