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Clinical, Radiographic, and Histological Assessment of Socket Preservation Using Melatonin with Beta-Tri-Calcium Phosphate for Receiving Dental Implant

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Abstract: Aim: The clinical, 3D volumetric, and histological evaluation for effectiveness of addition of melatonin to β-tri calcium phosphate (β-TCP) in socket preservation after tooth extraction. Patients and methods: 24 patients were treatment planned for extraction of isolated hopeless mandibular teeth followed by delayed implant placement. They were divided randomly into two equal groups as follows: Group (A) sockets were grafted with β-TCP mixed with 1% melatonin, Group (B) included sockets were grafted with β-TCP alone. Clinical evaluation and Cone beam computed tomography (CBCT) were done immediately and 6 months postoperatively. Microscopic evaluation was performed after 6 months before implant insertion. All readings were recorded and analyzed statistically. Results: After 6 months, all clinical and radiographic parameters showed significant difference between the tested groups where Group (A) produced the highest mean values of bone density, bone height, and width followed by Group (B). Histological study referred to more maturation of bone in group A than group B. Where complete bone maturation occurred later in group II than group I. Conclusion: The results clearly concluded that melatonin had promotion effect for bone formation. Therefore, addition of melatonin to β-TCP has high successful effect in decrease bone resorption with increased bone density of alveolar ridge leading to preserve on 3-D volume of alveolar ridge after tooth extraction.

Keywords: Socket Preservation, Beta-tri-calcium Phosphate (β-TCP), Melatonin, Cone Beam Computed Tomography (CBCT)

1. Introduction

Post extraction resorption of the alveolar ridge is a progressive and irreversible process occurs in both the alveolar height, and width. It is accelerated in the first six months following tooth extraction. Techniques to preserve natural bone and soft tissue contours are of great interest for both clinician and patient because even subtle post-extraction buccal plate resorption may have significant clinical effects, particularly in the esthetic zone. Loss of ridge height and width results in prosthetic instability and complicated tooth replacement with implants which may require extensive reconstructive surgery later on. So, it has the potentiality to either complicate implant placement or impair the final esthetic result [1].

Alveolar ridge preservation is a procedure undertaken following tooth extraction, which is designed to modulate and minimize the early stage ridge resorption, increasing bone density and facilitating future implant placement [2-4]. Several modalities have been proposed for preserving extraction socket including; a traumatic tooth extraction, immediate implant placement, grafting materials with or

without barrier membrane, and also barrier membrane alone can used without grafting materials [5-8].

An ideal bone substitute should be biologically compatible, non-supportive for local pathogens or cross infection, osteogenic or osteoinductive or even osteoconductive to serve as a scaffold for the ingrowth of capillaries, perivascular tissue and osteoprogenitor cells from the recipient bed. In addition, it should matches the physical and chemical composition of natural bone trabeculae, resorbable and osteotropic [9-11].

It has been known that calcium phosphate compounds show specific affinity for vital tissues and showed promising results among other alloplastic graft materials [12]. The extraction sockets grafted with the pure phase β-TCP is a predictable method for preserving alveolar dimensions and the graft material resorbs to a high percentage in the timeframe desired between extraction and dental implant placement, as shown clinically, radio graphically, and histologically. In addition, the regenerated material in the sockets has enough density to support implant placement with subsequent loading in the 4th to 6th months after implant insertion [13].

Recently, to accelerate healing of bone graft in the bony defect, numerous adjunctive materials have been applied in the literature such Melatonin (N-acetyl-5-methoxy tryptamine). It is a hormone secreted by different organs including the pineal gland, bone marrow, retina, and immune system to regulate the day & night cycles (circadian rhythm). (14) In the same time it plays an antioxidant, immunomodulatory and anti-inflammatory effect through the down-regulation of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and receptor activators of nuclear factor kappa-B ligand/osteoprotegerin ratios (RANKL/OPG) and up-regulation of alkaline phosphatase, osteopontin and osteocalcin. These actions collectively led to stimulation and proliferation of osteoblasts with subsequent promotion of bone formation [15-17].

Regarding the evaluation of normal anatomical structures, detection of pat hoses in proximity to proposed implant locations and available bone estimation in terms of quantity and quality, CBCT provides a valuable tool in craniofacial region with low radiation dose [18, 19].

Therefore, the present study was a trial to assess clinical and 3D volumetric efficacy of a mixture of Melatonin with β-tri calcium phosphate versus β-tri calcium phosphate alone in socket bone preservation using CBCT.

2. Patients and Methods

This study was designed as a randomized controlled clinical over a period of 2 years (July 2018 to July 2020). CBCT study carried out on total twenty four patients of both sexes (14 females and 10 males ranged in age from 32-48 years) from those attending at the Oral and maxillofacial surgery department, Faculty of Dental Medicine, Al-Azhar University- Assiut and planned for extraction of isolated hopeless tooth followed by delayed implant placement. All patients received a description of the nature, potential risks and benefits of their participation in the study and signed a written informed consent form. The study protocol was approved by the ethical committee, Faculty of Dental Medicine, Al-Azhar University- Assiut, Egypt.

2.1. Selection Criteria

Inclusion criteria:

Adult patients with isolated hopeless tooth indicated for extraction (badly decayed tooth, endodontic complications, root fracture, sever untreatable periodontitis or for prosthetic reasons) and planned for delayed implant placement. The patients were systemically and locally free from any disease/condition that would compromise post-operative healing.

Exclusion criteria:

Soft tissue recession at the extraction site, perforation and/or loss of labial bony plate following tooth removal, un-cooperative patients, and smoking patients. Also, patients with history of radiotherapy or chemotherapy in the head, and neck region and use of bisphosphonate therapy.

2.2. Patients Grouping

Patients classified randomly into the following two equal groups using online software (https://www. randomizer.org):

Group A: 12 patients with 12 fresh extraction sockets of mandibular first molar grafted by mixture of beta-tri-calcium phosphate (IngeniOs ß-TCP Bioactive Synthetic Bone Particles, Zimmer Biomet Dental, USA) with 1% melatonin powder ((VIVAMAX3® product of AMOUN Pharmaceutical industries co (APIC)) and covered by collagen membrane (GENOSS, Dentium. Co. Ltd, Suwon, South Korea)

Group B: 12 patients with 12 fresh extraction sockets of mandibular first molar grafted by beta-tri-calcium phosphate alone and covered by collagen membrane.

2.3. Preoperative Phase

Patients' data were collected and, medical and dental histories were taken. Also, all patients underwent pre-operative clinical and radiographic examination to exclude any pathosis and evaluate the dimensions of the socket. All patients were submitted to phase one periodontal therapy 2weeks prior to extraction to prepare the desired sites for the study.

2.4. Surgical Procedures

After local anesthesia had been administered, sulcular incisions were given around the premolars with a sharp instrument such as a No. 15 scalpel.

Periotome was used to dissect the attached fibers. The blade had to be angled at 20 degrees to ensure that the tip of the periotome was within the crest of the alveolar bone.

The instrument was inserted first in the gingival sulcus, and then in the periodontal ligament space. The periotome was moved repeatedly in a mesio-distal direction, along the circumference of the root.

Finally, the extraction of the tooth was performed with forceps without distorting or damaging the alveolar bone.

After tooth extraction, any soft and hard tissues debris was curetted, and then all patients underwent CBCT imaging before tooth socket grafting.

In *Group A patients;* the granules of β-TCP were mixed with 1% melatonin powder and applied to fill the socket up the level of crestal bone.

In *Group B patients;* the granules of β-TCP were applied to fill the socket up the level of crestal bone.

Finally, socket covered by collagen membrane and wound closure was performed by interrupted 0/4 non resorbable suture [Figure 1].

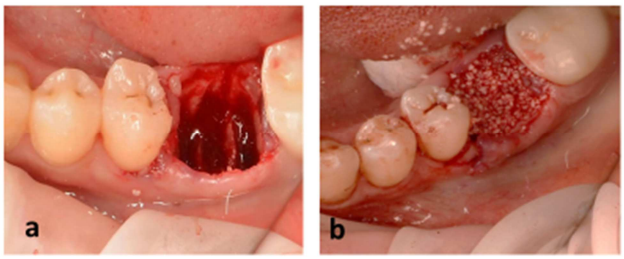

Figure 1. *(a) Lower first molar socket after ataumatic extraction (group A) (b) mixture of bone graft was placed in tooth socket and collagen membrane in position to cover bone graft.*

2.5. Postoperative Care

After surgical procedure, all patients were instructed to apply extra oral ice packs and preserve good oral hygiene. Patients were received augmentin (625 Amoxicillin Trihydrate, 125mg clavulanc corrosive. GSK Glaxo Smith kline, Egypt) for 7 days postoperatively twice/ day. Ibuprofen (Brufen kahira pharma & CHEM. IND. CO. Cairo-Egypt), was prescribed as an anti-inflammatory and pain relieving drug, 600mg twice every day for 1 to 3 days after medical procedure. Chlorhexidine mouthwash (Antiseptol Kahira CO. for pharm. what's more, Chem., IND organization, Cairo, Egypt) was utilizing twice every day for 3 weeks post operatively.

2.6. Patient Evaluation

All clinical and radiographic evaluations were performed in Oral Medicine, Periodontology, Oral Diagnosis and Dental Radiology departments, Faculty of Dental Medicine Al-Azhar University, Assiut, Egypt. All clinical and radiographic parameters were recorded at the baseline and after 6 months prior to implant placement.

a- Clinical parameters

Acrylic stent for the extraction site was fabricated on the cast model up to 1/3rd of the crowns of the teeth adjacent to the surgical site. Two perpendicular lines were drawn through the center of the alveoli, one in the mesio-distal direction and another one in the bucco-lingual direction. The point of intersection of bucco-lingual line on mesio-distal line was recorded for reproducibility. A corresponding hole to the central part of the alveoli and 2 grooves on the mid-buccal and mid-palatal/lingual were made in the prepared acrylic resin stent, corresponding to the respective cortical plates [Figure 2].

Mid-buccal crestal height

Mid-buccal crestal height was measured as the distance in millimeters from a fixed reference point (FRP) on the acrylic stent to the most coronal mid-point on the buccal cortical plate using graduated periodontal prob.

Mid-palatal/lingual crestal height

Mid-palatal/lingual crestal height was measured as the distance in millimeters from a fixed reference point (FRP) on the acrylic stent to the most coronal mid-point on the palatal/lingual cortical plate using graduated periodontal prob.

Relative socket depth

Relative socket depth was measured as the distance in millimeters from the central hole on the acrylic stent to the most apical end of the socket/ridge, using (no. 20) spreader with a stopper.

Bucco-lingual width

Bucco-lingual width was measured corresponding with the line 2 mm apical to the most coronal point on the socket/residual ridge using Ridge Mapping Caliper.

All base line clinical measurements were taken immediately after extraction and before placement of the graft material.

Local infiltration anesthesia was used during recording the clinical measurements at 6 months follow-up.

b-Radiographic Parameters

Cone beam computed tomographies (CBCT) were performed and handled for all patients with New Tom cone beam 3D system within 24h after the surgery and after 6 months prior to implant placement. All images were marked and traced in cross-sectional and axial view, and same reference points and lines were used both at baseline and at 3 months [Figure 3]. The sagittal and coronal reference lines where intersected at each other at the center of the socket. The axial reference line was adjusted at the exact view to be parallel to the lingual cortex of bone at crestal level.

Bone Height measurements

At the generated cross-sectional view, two tangential lines were drawn passing through the highest and lowest point of the socket, and then the distance between these two lines was measured in millimeters.

Bone width measurements

At the generated cross-sectional view, two tangential lines were drawn passing through the most buccal and most lingual/palatal points of the socket and then the distance between these two lines was measured in millimeters.

Bone density measurements

At the generated cross-sectional view, three density readings were taken for each site (crestal, middle and apical) then the mean of the three readings was acquired.

c- Histological evaluation

Bone biopsies were harvested using a trephine bur at the site that will prepare for implant placement in the future. The trephine burs including the bone biopsies were fixed in 4% formalin for 5–7 days, rinsed in water, and dehydrated in serial steps of ethanol (70, 80, 90, and 100%), the specimens were then stained by hematoxylin- eosin for light microscopic evaluation.

2.7. Statistical Analysis

Data was represented as a mean and standard deviation. Paired Student's t-test was used when comparing between the two groups. Unpaired t-test was used to compare numeric variables within both groups during intervals of the study. Data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Result was considered statistically significant if the p- value was less than 0.05.

Figure 2. *Clinical parameters measurements.*

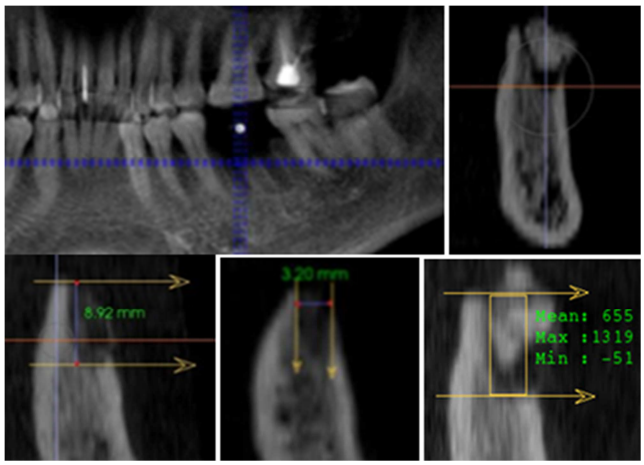

Figure 3. *Radiographic parameters measurements.*

3. Results

3.1. Clinical Parameters

Table 1 illustrated the changes in mean values± SD, P-values and t-values of clinical parameters for both groups at base line and after 6 months.

Paired Sample t-test showed statistically significant differences after 6 months when compared with the baseline in group A and group B in both relative socket depth (*p-value <0.001)* and bucco-lingual width (*p-value 0.043 and 0.008 respectively)* with no statistical significant difference in mid-buccal crestal height (*p-value 0.802 and 0.537 respectively)*, mid-palatal/lingual crestal height (*p-value 0.794 and 0.613 respectively).*

Independent sample t-test showed statistically significant differences in group A when compared with group B after 6 months in all clinical parameters including; mid-buccal crestal height (*p-value 0.015)*, mid-palatal/lingual crestal height (*p-value 0.048)*, relative socket depth (*p-value 0.024)* and bucco-lingual width (*p-value 0.019)*.

3.2. Radiographic Parameters

The changes in mean values± SD, P-values and t-values of radiographic parameters for both groups at base line and after 6 months were illustrated in Table 2.

Paired Sample t-test showed statistically significant differences after 6 months when compared with the baseline in both group A and group B in both bone height (*p-value <0.001)* and bone width (*p-value 0.029 and 0.008 respectively)* while bone density showed a statistically significant difference after 6 months when compared with the baseline in group A only (*p-value 0.038)*.

Independent sample t-test showed statistically significant differences in group A when compared with group B after 6 months in all radiographic parameters including; bone height (*p-value 0.041)*, bone width (*p-value 0.017)* and bone density *(p-value 0.005).*

Table 1. *Mean differences±SD, t-values and P-values of Mid-buccal crestal height, Mid-palatal/lingual crestal height, Relative socket depth and Bucco-lingual width in mm in Group A and Group B at baseline and after 6 months.*

			Paired t. test		Independent t. test	
	Baseline	**After 6 months**	**t-test**	**p-value**	**Base line p-value**	**6 months p-value**
Group A						
Mid-buccal crestal height	9.54±3.06	8.21±2.80	1.976	0.802	0.236	0.015*
Mid-palatal/lingual crestal height	9.72±2.19	8.40±2.71	1.083	0.794	0.346	0.048*
Relative socket depth	22.81±2.94	9.02±3.54	7.438	<0.001**	0.786	0.024*
Bucco-lingual width	8.66±3.51	7.23±1.89	7.014	0.043*	0.937	0.019*
Group B						
Mid-buccal crestal height	9.28±2.07	9.98±3.24	3.941	0.537		
Mid-palatal/lingunl crestal height	9.12±2.34	9.83±2.85	2.874	0.613		
Relative socket depth	22.03±2.96	10.17±3.15	7.056	<0.001**		
Bucco-lingual width	8.50±2.63	6.55±2.12	9.682	0.008		

*Statistically significant: (P < 0.05)
**High statistically significant: (P < 0.01).

Table 2. *Mean differences± SD, t-values and P-values of Bone height, Bone width in mm and Bone density in CT unit in Group A and Group B at baseline and after 6 months.*

			Paired t. test		Independent t. test	
	Baseline	**After 6 months**	**t-test**	**p-value**	**Base line p-value**	**6 months p-value**
Group A						
Bone Height	11.04±4.55	2.65±0.62	2.124	<0.001**	0.871	0.041*
Bone Width	8.35±3.09	7.02±1.63	3.901	0.029*	0.915	0.017*
Bone Density	526.76±36.12	594.90±39.01	7.047	0.038*	0.842	0.005*
Group B						
Bone Height	10.98±3.53	3.93±1.07	2.317	<0.001**		
Bone Width	8.47±2.58	6.15±2.12	7.332	0.008*		
Bone Density	517.84±40.61	533.40±37.53	7.028	0.097		

*Statistically significant: (P < 0.05)
**High statistically significant: (P < 0.01).

3.3. Histological Evaluation

All biopsies showed newly formed bone, residual graft material, and well vascularized uninflamed connective tissue. No necrosis or foreign body reactions were detected. Residual graft granules were in contact with active osteoblasts forming osteoid and new woven bone, demonstrating persistent osteogenesis.

In group A, figure 4 of specimens presented at periphery a thick layer of newly formed compact bone characterized by Haversian system composed of concentric layers of bone lamellae encircling centrally placed Haversian canals. The rest of the specimen was filled by fibrous connective tissue composed of collagen fibers and fibroblast cells. At the next layer to the newly formed bone, the collagen fibers were less dense, mixed with remnants of residual bone graft in all specimens.

While in group B, figure 4 of specimens filled with regular areas of bone calcification of compact type with well-formed Haversian system composed of concentric bone lamellae enclosing central Haversian canals. There was a very small area of loose fibrous tissue composed of fine collagen fibers, fibroblast cells and blood vessels containing red blood cells. All specimens presented showed complete maturation of bone with little amount of residual graft in some cases. Accordingly, complete bone maturation occurred later in group B than group A.

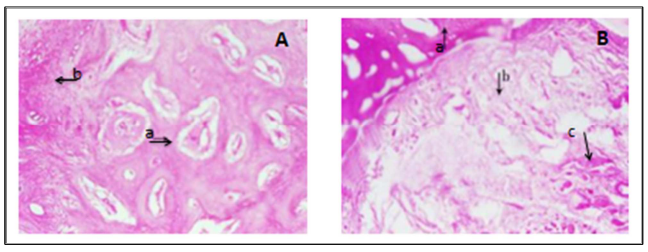

Figure 4. *(A) Microscopic photographic for group I at 6month, arrow (a) pointed to mature spongy bone, arrow (b) pointed to thin area of loose fibrous connective tissue areas. (B) Microscopic photographic for group II at 6month, arrow (a) pointed to thick layer of newly formed compact bone trabeculae with Haverssian canal, arrow (b) pointed to fine fibrous connective tissue and followed by dense fibrous connective tissue at the center, arrow (c) pointed to residual bone graft (100 X).*

4. Discussion

Tooth extraction due to endodontic, traumatic or untreatable periodontal problem is a traumatic procedure that immediately resulting in destruction of surrounding hard and soft tissues [20]. Generally, remodeling of the alveolar bone after tooth extraction yields reduced dimensions in the vertical and horizontal directions of the alveolar ridge up to 40% to 60% respectively after 3 months [21] Ridge preservation is a procedure undertaken following an extraction, which is designed to minimize alveolar ridge resorption and maximize bone formation within the socket.

Different surgical techniques and regenerative materials have been used for preservation of socket including, a traumatic tooth extraction, immediate implant placement, using bone grafting, osteogenic material or absorbable or non-absorbable membrane. In addition, no single biomaterial is optimum for socket preservation. Instead, surgeons should consider the advantages and disadvantages of each alternative in a given clinical situation to improve the clinical outcomes [22].

The present study aimed to evaluate clinically and radiographically the potentiality of melatonin addition to beta-tri calcium phosphate in preservation of the alveolar ridge and reducing the bone dimensional changes following tooth extraction in sites planned for delayed implant placement.

Beta tricalcium phosphate was selected for socket preservation because medical grade β-TCP seems to be an acceptable graft material for extraction socket bone regeneration as it is completely resorbable and allows new trabecular bone arrangement in a limited 3-6 month period, [23] and selection of melatonin because tooth extraction is a traumatic surgical procedure resulting in production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) contributes to manifestation of inflammation and/or infection at the site of extraction. Indeed, placement of melatonin in the extraction sockets of dogs normalizes the levels of lipid peroxides, nitrates, and nitrites raised in reaction to tooth extraction, in addition to its anti-inflammatory, immune-modulatory and osteogenic efficacy [24].

Cone beam computed tomography was used for radiographic analysis of the quality and quantity of preserved sockets, as CBCT scan is a highly accurate tool in linear measurements in the axial and cross sectional image planes at

different areas of the maxillofacial region. And one of the major uses of CBCT is the presurgical implant planning such as the linear measurement of alveolar bone height and width in addition to its accuracy, reproducibility, lower patient radiation dose and faster scanning time [25].

Clinical vertical and horizontal bone changes in the form of bucco-lingual width, relative socket depth, mid-buccal and mid-palatal/lingunl crestal heights exhibited noticeable preservation of the extraction socket and reduction of the degree of alveolar bone loss in β-TCP-melatonin group when compared to β-TCP group after 6months. These results are in agreement with different clinical studies concluded that, the use of combined regenerative therapies rendered more favorable vertical and horizontal socket preservation [26-28].

Quantity and quality of bone formation in the form of radiographic linear measurement of bone height, width and density exhibited noticeable preservation of the extraction socket and reduction of the degree of alveolar bone loss in β-TCP-melatonin group when compared to β-TCP group after complete healing of the extraction socket at 6 months. These results are in agreement with different radiographic studies concluded that, alveolar ridge preservation by different combined grafting materials consistently rendered more favorable [29-31], with the exception of two studies; In the trial by Araujo et al 2015, [32] the non-grafted sockets exhibited slightly better results in terms of radiographic bone height as compared to the grafted sockets; however, these differences were not clinically or statistically significant. In the study by Jung et al 2013, [33] the application of an alloplast (β-TCP with a polylactide–co-glycolide coating) without membrane, rendered significantly inferior results as compared to the control group.

Regarding bone density scores increased in both groups with superiority for group A than group B. Therefore, there was highly statistically significant difference between both groups at 6 month intervals, although both group did not show any statistically significant difference at baseline. This was in the same line with our results of histological evaluation for bone specimens at 6 months. That showed earlier bone maturation with complete bone formation in group I than group II. This is in accordance with Pandey et al [34] who deduced that the topical application of melatonin may act as a biomimetic agent in the placement of endo-osseous dental implants.

In the same side, Srinath et al [35] reported that melatonin acts on prostaglandin E2, thereby inhibiting the differentiation of osteoclasts induced by cell-to-cell contact between osteoblasts and osteoclasts. As well as its action at the level of osteoclasts lacuna, via its antioxidant properties, neutralizes the reactive species, thus inhibiting bone resorption.

5. Conclusion

From the results of the study, it can be concluded that a mixture of β-TCP with Melatonin has a highly regenerative effect compared with β-TCP bone graft alone. Where clinical, radiographic, and histological assessment observed addition of Melatonin to β-TCP bone graft leaded to decrease bone resorption and increase bone density with more bone maturation. It leaded to preserve on 3- D volume of alveolar ridge after tooth extraction with increased bone density.

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Conflicts of Interest

There are no conflicts of interest.

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