



## Evaluation of Alveolar Ridge Preservation Using a composite of Bioactive Glass and Platelet Rich Fibrin Alone or Combined with Melatonin in chronic periodontitis Patient

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### ABSTRACT

**Purpose:** The aim of this randomized controlled clinical trial was the evaluation of alveolar ridge preservation using a composite of bioactive glass and platelet rich fibrin either alone or combined with melatonin in chronic periodontitis patients. This aim was fulfilled through: Clinical assessment and radiographic assessment. **Subjects and Methods:** A total of thirty extraction sockets in 29 patients were randomly divided into three groups; control group treated by atraumatic extraction alone, test1 group (application of bioactive glass mixed with PRF) and test 2 group (application of bioactive glass mixed with PRF and melatonin gel). The clinical parameters recorded at baseline, 3 months and 6 months after treatment. Cone beam tomography radiographs used to measure width of socket at base line and 6months post operatively. **Results:** By clinical assessment both group II and group III showed significant increase in length and width of alveolar ridge with significant difference between the two groups in the whole study period. Radiographically; both group II and group III showed a significant increase in all parameters by time, while control group, there was a significant decrease at the end of the study period. **Conclusion:** Within the limits of this study: The composite use of bioglass, Prf & melatonin in group III reflected the best clinical, and radiographic results.

### KEYWORDS

*Bioactive glass bonegraft,  
platelet rich fibrin, periodontally  
involved teeth.*

### INTRODUCTION

Optimal restoration of dental implant requires their placement in an ideal anatomic position. However, this is not always possible, since physiological wound healing following either; tooth extraction,

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trauma, or pathology, often results in a deficiency of both hard and soft tissue. Unless augmentation procedures are carried out, placing an implant in these tissue-deficient sites would ultimately compromise the functional and aesthetic results<sup>(1)</sup>.

With the aim of minimizing the need for tissue augmentation, several authors have proposed techniques to preserve the anatomy of the alveolar ridge after tooth extraction. These procedures have collectively been termed alveolar ridge preservation (ARP) or socket preservation<sup>(2)</sup>. It is widely accepted that ridge preservation procedures following tooth extraction result in greater oro-facial bone dimension than where no ridge preservation was performed<sup>(3-5)</sup>.

Ridge preservation involves the placement of a bone graft into the socket immediately after the extraction of a tooth that cannot otherwise be preserved. This bone graft is covered by a biocompatible membrane that is subsequently covered by gum tissue. The bone graft and the membrane trigger the body's ability to heal it, bone tissue is regenerated, and the socket is repaired<sup>(6)</sup>. Numerous regenerative techniques have been shown to facilitate formation of new bone via osteoconduction and osteogenic cells that preserve the space and exclude unwanted cells from the wound<sup>(3-5)</sup>.

Bioactive glass is an osteoconductive bone substitute composed of sodium oxide, calcium oxide, phosphorus pentoxide, silicon dioxide, and silica. The formation of a biologically active hydrated calcium phosphate layer at the surface of the bioactive glass plays a key role in the formation of the bone/graft bond<sup>(7)</sup>. Bioactive hybrids glasses are materials of high interest for biomedical applications because they combine the bioactivity of ceramics, with the flexibility of the polymers<sup>(8)</sup>. These materials have the ability to chemically bond with bone and are supposed to function as small bone regenerative chambers<sup>(9)</sup>.

Bioactive glasses may have osteoconductive properties and have been tested in animal trials<sup>(10)</sup>. Studying insertion of Biphasic calcium phosphate (BCP) in fresh alveolus of dogs, a 3-month period was useful to observe new bone formation, but too short to provide information about the degradation of the material<sup>(11)</sup>.

Platelet-rich fibrin (PRF) has important properties for healing, such as angiogenesis, immune control, harnessing the circulating stem cells, and wound protection<sup>(12)</sup>. The properties of PRF are considered to promote both soft-tissue and bone regeneration and are suitable for ridge preservation. Leukocyte and platelet-rich fibrin (L-PRF), was first described by Choukroun as cited by authors<sup>(13)</sup>. It is considered as a second-generation platelet concentrate that improves healing of the both hard and soft tissues<sup>(14)</sup>.

Melatonin is chemically recognized as *N*-acetyl-5-methoxytryptamine. Melatonin called hormone of night is secreted by the pineal gland, and its plasma levels concentration are 50 folds higher in night in comparison to day time. A variety of peripheral cells play a role in production of melatonin such as epithelial cells, bone marrow cells, and lymphocytes<sup>(15)</sup>. Melatonin has several functions; stimulation of the synthesis of type I collagen fibers, regulation of the body temperature, sexual development, antioxidant scavenging and detoxifying free radicals thus inhibiting the process of bone resorption through interfering with the function of osteoclasts<sup>(16)</sup>.

Preclinical studies demonstrate a direct action of melatonin in enhancing the differentiation and proliferation of bone-forming osteoblasts. In addition to increasing bone mass, melatonin also facilitates new bone growth and osteointegration, making melatonin a particularly attractive molecule for use in bone implants when used alone or in combination with other growth factors as described<sup>(17)</sup>.

According to our knowledge few studies, has been regarding the evaluation of melatonin in combination with bioactive glass and PRF in alveolar socket preservation. Thus this study was conducted, using

clinical assessment, digital radiographic analysis of cross sectional cuts of cone beam tomography and histological assessment for evaluation of alveolar ridge preservation using a composite of bioactive glass and platelet rich fibrin either alone or combined with melatonin in chronic periodontitis patients.

The aim of the present study was the evaluation of alveolar ridge preservation using a composite of bioactive glass and platelet rich fibrin either alone or combined with melatonin in chronic periodontitis patients. This aim was fulfilled through: Clinical assessment and radiographic assessment

## SUBJECTS AND METHODS

A total of 30 defects were included in this study (11 males, 18 females). The age range of participants 30-60 years; they were selected consecutively between January 2017 and May 2017. All participating patients were selected from those patients attending the outpatient clinic of the Department of Oral Medicine and Periodontology, Diagnosis and Radiology Faculty of Dental Medicine for Girls Al-Azhar University, Egypt. A randomized control clinical study was undergone on the 30 sites included in this study.

A computerized generated table was used to provide a random and equal distribution of sites into three groups. The protocol of the study was approved by Al-Azhar ethical committee. Before surgery the nature of procedure was explained for every patient and informed consent was signed by every participating patient. In this longitudinal interventional clinical attempt, all the study patients were randomly and equally assigned as following: **Group I** (control group): It included ten patients with hopeless ten teeth indicated for extraction. No socket preservation procedures were done for this group. **Group II:** (test 1) It included nine patients with ten hopeless teeth indicated for extraction. Socket preservation procedures were done using bioactive glass and PRF. **Group III:** (test 2) it included ten patients with ten hopeless teeth indicated for extraction. Socket preservation procedures were done using bioactive glass, PRF and melatonin.

**Inclusion criteria were :** Patient free from any systemic illness<sup>(18)</sup>, Patient with at least a hopeless tooth indicated for extraction for periodontal affection in the premolar-molar region ,Patients with chronic periodontitis<sup>(19)</sup>, Class I and class II sockets<sup>(20)</sup>.

**Exclusion criteria were:** Patient with poor oral hygiene, Patients with history of smoking, Pregnant or lactating women or patient receiving contraceptive pills, Patient with psychological problem.

Patients were evaluated clinically at baseline (BL), 3 months (3M) and 6 months (6M) post operatively. Wound healing index (WHI) <sup>(21)</sup> was recorded 1 and 2 weeks after surgery. The width of socket was measured using bone caliber from mid of mesial to the mid of distal sides of socket ( $W_1$ ) and from mid of buccal to the mid of lingual sides of socket ( $W_2$ ). Clinically vertical height was measured at six points: Mesio buccal line angle (L1), Mid buccal (L2), Disto buccal line angle (L3), Mesio lingual line (L4), Mid lingual (L5), Disto lingual line angle (L6).

CBCT scans at baseline and at 6 months were processed using promax 3DxM mid. Planameca Finland 48kvp, 12MA. Romaxis viewer was used for analysis Two reference lines were subsequently drawn. The vertical reference line was drawn in the center of the extraction socket starting from the apical reference point. The horizontal reference line was drawn perpendicular to the vertical line at the level of highest alveolar crest. The following measurements with respect to these reference points and lines were then performed<sup>(22)</sup>: The horizontal ridge width measured at three levels (at 1 mm, 3 mm, 5 mm) below the most coronal aspect of the crest (HW-1, HW-3, HW-5) .

### Preparation of platelet-rich fibrin:

Blood samples were taken from the patient's forearm without anticoagulant in 10-ml tube and immediately centrifuged at 3000 rpm (approximately 400g according to Chokroun's calculations) for

10 minutes<sup>(23)</sup>. Within a few minutes, the absence of anticoagulant allows activation of the majority of platelets contained in the sample to trigger a coagulation cascade. A fibrin clot is then obtained in the middle of the tube, just between the red corpuscles at the bottom and acellular plasma at the top. Platelets are theoretically trapped massively in the fibrin meshes. The exudate collected at the bottom of the box may be used to hydrate graft materials, rinse the surgical site and stored as autologous grafts<sup>(24)</sup>. After removing the cover the PRF membranes were obtained from the PRF clots. With a specific tweezer the membrane was inserted in the socket. In the current study we used glass tubes and the PRF membrane is prepared immediately before its application inside the socket.

### **Surgical procedures:**

All the surgical procedures were carried out under strict aseptic conditions in the selected sites. The extraction sites were anesthetized with nerve block local anesthesia (Mepecainel 1,8 ml carpule Mepivacaine Hcl 2% Levonordefrin 1:20000). A traumatic extraction done using periotome (double ended straight end for anterior and curved end for posterior teeth). The tooth was gently luxated with periotome and carefully extracted with extraction forceps, attempting to minimize the trauma to the bone circumscribing the alveolus. After that curettage of socket using bone curette was done to remove all of granulation tissue this procedures only done for **group I**. Irrigation of socket using sterile normal saline was then performed the flap tissue was then relaxed.

**Group 2:** After complete preparation of extraction site PRF gel, it was divided into two pieces one piece was mixed with bone graft (bioactive glass) by 2 drops of plasma. The mix of PRF and graft was applied in the socket with good condensation of materials until complete filling of socket. After that the socket was filled with mix of bone graft and PRF was covered by PRF membrane (prepared from the second piece of PRF gel) which

was inserted as a saddle covering the socket. The PRF was held in place by figure eight suture across the socket entrance with resorbable suture (Egy sorb Braided Poly glycolic Acid (PGA) USP 4/0 (1,5 Metric)1\*75cm Rc 3/8c16mm TAISIER\_ME obour city Cairo-Egypt) .The suture was removed 2 weeks postoperatively.

**Group 3:** After complete preparation of extraction site, the bone e graft was mixed with PRF and melatonin gel (1ml of melatonin gel) <sup>(25)</sup>. Then the mix was applied in the socket with good condensation of materials until complete filling of socket then covered by PRF membrane. The PRF was held in place by figure eight suture across the socket entrance with resorbable suture. The suture was removed 2 weeks postoperatively.

**Postoperative instructions:** After surgery, all patients were instructed to bite on cotton with gauze for one hour. Augmentin (SKB Smith kline Beecham pharmaceuticals) antibiotic was prescribed, 1mg twice daily for five days after surgery. Ibuprofen (Brufen) (Kahira pharmaceuticals and chemical industries under licence of Abbott Laboratories-USA), was prescribed as an anti-inflammatory / analgesic drug, 600 mg twice daily for 1 to 3 days after surgery. Chlorhexidine 0.12% (kahira pharma & CHEM.IND.CO. Cairo-Egypt) mouthwash was prescribed twice daily for 3 weeks post operatively, in addition to 1 week pre operatively. The oral hygiene instructions were given, and the patients were followed up (by the same investigator) every one month after suture removal till the end of follow up.

## **RESULTS**

### **Clinical assessment:**

Wound healing index (WHI)<sup>(21)</sup> recorded for all patients 1 and 2 weeks after surgery showed the following criteria: Score 1 = uneventful healing with no gingival edema, erythema, suppuration, patient discomfort or flap dehiscence. Mean of change of width of the socket in bucco- lingual and mesio-distal dimension among the groups:

After 3 months, there was statistically significant difference in mean of change in both (W1) and (W2) of the three groups at (p-value=0.004, 0.003) respectively. After 6 months, group I showed the highest significant decrease in both (W1) and (W2), Meanwhile group III showed the highest statistically significantly increase in both (W1) and (W2) at (p-value=0.004,0.003) respectively. Group II showed significant increase in (W1) while no significant increase in (W2).**Table (1)**

Clinically vertical height was measured at six points: Mesio buccal line angle (L1), Mid buccal (L2), Disto buccal line angle (L3), Mesio lingual line angle (L4), Mid lingual (L5), Disto lingual line angle (L6).Mean of change in measurements of

(L1, L2) and (L3) among the three groups. After 3 months, there was statistically significant difference in mean of change in (L1), (L2) and (L3) among the three groups at (p-value=0.002, 0.004and 0.002) respectively. After 6 months, group I showed the highest significant decrease in L1, L2 and L3, Meanwhile group III showed the highest significant increase in L1 and L3 at (p-value= 0.001, 0.002) respectively. Moreover, group II showed higher increase in L2 than group III at (p-value=0.004).

**Table (2)**

**Table (1): Comparison of means and (SD) of change of (W1) and (W2) among the three groups at different time intervals using Wilcoxon signed-rank test.**

		Group I		Group II		Group III		P-value
		Mean	SD	Mean	SD	Mean	SD	
W1 (B-L)	Base line – 3 months	-2.00	0.70	0.78	0.75	1.00	0.95	0.004*
	Base line - 6 months	-2.80	0.83	1.64	1.46	1.42	0.93	0.004*
W2 (M-D)	Base line – 3 months	-1.30	1.20	0.00	0.00	0.35	0.47	0.003*
	Base line - 6 months	-2.70	2.17	0.00	0.00	0.36	0.48	0.003*

**Table (2): Comparison of means and (SD) of change of (L1, L2) and (L3) among the three groups at different time intervals using Wilcoxon signed-rank test.**

		Group I		Group II		Group III		P-value
		Mean	SD	Mean	SD	Mean	SD	
L1	Base line – 3 months	-1.20	0.45	0.71	1.49	1.714	2.06	0.002*
	Base line - 6 months	-2.20	0.84	0.86	1.46	2.29	1.70	0.001*
L2	Base line – 3 months	-1.20	0.45	1.57	1.90	1.43	1.39	0.004*
	Base line - 6 months	-2.20	0.84	2.00	2.31	1.85	1.35	0.004*
L3	Base line-3months	-1.40	0.54	0.86	1.21	1.57	0.53	0.002*
	BaseLine-6months	2.40	0.89	1.29	1.49	2.29	1.25	0.002*

Mean of change in Measurements of (L4, L5) and (L6) among the three groups. After 3 months, there was statistically significant difference in mean of change in (L4), (L5) and (6) among the three groups at (p-value=0.003, 0.004and 0.00) respectively. After 6 months, group I showed the highest significant decrease in L4, L5 and L6, Meanwhile group III showed the highest significant increase in L4, L5 and L6 at (p-value=0.002, 0.004 and 0.00) respectively. Moreover, group II showed increase in L4, L5 and L6 at (p-value=0.002, 0.004

and 0.00). **Table (3)** .

**Radiographic assessment:**

The horizontal ridge width measured (at 1 mm, 3 mm, 5 mm) below the most coronal aspect of the crest (HW-1, HW-3, HW-5).Mean of change among the groups: At 6 months, statistically significant difference was revealed among the three groups. In favor of group III showed the highest increase in (HW-1), (HW-3) and (HW-5) at (p-value= 0.003, 0.004and 0.004).**Table (4)**

**Table (3): Comparison of Mean & SD of change of (L4), (L5) and (L6) among the groups at different time intervals using Wilcoxon signed-rank test.**

		Group I		Group II		Group III		P-value
		Mean	SD	Mean	SD	Mean	SD	
L4	Base line – 3 months	- 2.0000	1.00	0.71	0.48	0.85	1.57	0.003*
	Base line - 6 months	-2.20	1.30	1.00	0.48	1.28	1.52	0.002*
L5	Base line – 3 months	-2.00	1.00	1.14	1.34	1.71	2.36	0.004*
	Base line - 6 months	-2.20	1.30	1.57	1.27	1.86	2.41	0.004*
L6	Base line – 3 months	-1.60	1.14	0.71	0.49	1.43	2.69	0.00*
	Base line - 6 months	-1.80	1.09	1.43	0.98	1.57	2.82	0.00*

**Table (4): Comparison of Mean & SD of change in horizontal ridge width (HW) at 1mm, 3mm and 5mm from the crest among the groups using Wilcoxon signed-rank test**

		Change (Base Line –6 months.)			
		Mean	SD	Kruskal-Wallis H	p-value
HW_1	G I	-1.18	0.44	8.684	0.003*
	G II	0.31	0.26		
	G III	2.34	2.31		
HW-3	G I	-1.26	1.39	8.4	0.004*
	G II	0.27	0.09		
	G III	1.58	1.22		
HW-5	G I	-1.14	1.02	8.221	0.004*
	G II	0.41	0.33		
	G III	1.55	1.64		

## DISCUSSION

During the healing phase following tooth extraction, dimensional loss of bone height and bone width is a natural occurrence. The remodeling of alveolar bone at the extraction site always decreases ridge volume and deforms the ridge configuration, which consequently impairs placement of dental implants in the ideal positions. To achieve a predictable esthetic and functional restoration, it is important to preserve the dimension of alveolar ridge width and height after tooth extraction. Thus, socket preservation plays a very crucial role<sup>(26)</sup>.

Various bone-grafting and bone substitute materials have been used for ridge preservation procedures. The resorbable viable bone graft and synthetic bone substitutes has been utilized in orthopedic and other surgical specialties for almost 30 years<sup>(27)</sup>. In recent studies, it is pointed out that, platelet-rich fibrin (PRF) which is derived autogenously from the own blood of the individuals, increase regeneration and accelerate the healing of the wound, due to the consisting various growing factors<sup>(28)</sup>. Recently, the investigation and applications of melatonin in the hard tissues, bone and tooth have received great attention. Melatonin has been investigated relative to bone remodeling<sup>(29)</sup> osteoporosis<sup>(30,31)</sup>, osseointegration of dental implants<sup>(32)</sup>, and dentine formation<sup>(33)</sup>.

This randomized control clinical study was undergone on 29 patients with 30 sites for extraction of hopeless teeth in the lower premolar molar region. All of the subjects were free from any systemic illness and none of them had taken any medication<sup>(18)</sup>. Smokers were excluded from this study, as it was found that tissues exposed to tobacco respond by expressing elevated levels of cytokines in those tissues presumably as a part of injury response mechanism<sup>(34)</sup>.

Lactating or pregnant females were excluded as well since it was proven that circulating levels of cytokines are affected by pregnancy<sup>(35)</sup>.

Bioglass have been used as a grafting material in the socket in the current study. Healing of extraction sockets filled with bioactive glass has been reported in different animal model studies<sup>(36)</sup>. The use of bioglass is in accordance with a study conducted by author who used bioglass for ridge augmentation and socket preservation and concluded that the bioactive glass was able to maintain the alveolar ridge width and height in the augmentation cases<sup>(37)</sup>. Moreover, in a clinical trial to evaluate the effect of bioactive glass scaffold for the preservation of alveolar bone following tooth extraction, it was found that bioactive glass scaffolds appeared to enhance the recruitment of stem cells from the grafted sockets. They concluded that bioglass scaffolds appeared to preserve alveolar bone following extraction and allow for a more active bone modeling and remodeling process<sup>(38)</sup>.

PRF was used in the current study for many benefits as it contain many growth factors, including the PDGF, TGF- $\beta$ , IGF, EGF, fibroblast growth factor, and bone morphogenic protein. PRF allows a significant postoperative protection of the surgical site and seems to accelerate the integration, maturation, and remodeling, while enhancing bone graft density. PRF was applied in two ways; mixed with bone graft and as a membrane covering the graft material. This in accordance with several studies that used PRF in socket preservation procedures<sup>(27-36)</sup>. In the current study, PRF was mixed with the graft material this in accordance with, Nacopoulos et al. who compared healing properties of PRF in combination with a ceramic synthetic material composed of hydroxyapatite and beta tricalcium phosphate (b-TCP) in an animal model and found that PRF addition to the ceramic material significantly increased the formation of new bone, providing a better substrate for bone regeneration<sup>(39)</sup>.

Melatonin have been used, in this study as it is an important mediator in bone formation and stimulation of osteoblast differentiation<sup>(40)</sup>. Study

evaluated the effect of the topical application of melatonin on osteointegration of dental implants in Beagle dogs fourteen days after their insertion. After two weeks treatment period, melatonin significantly increased the perimeter of bone, inter-thread bone and density of bone that in direct contact with the treated implants when compared with control implants. They concluded that topical application of melatonin may act as a biomimetic agent in the placement of endo-osseous dental implants<sup>(41)</sup>. This is in accordance with *in vivo* studies which reported links between melatonin and bone metabolism<sup>(40)</sup>.

In the current study wound healing index (WHI)<sup>(21)</sup> recorded for all patients 1 and 2 weeks after surgery showed uneventful healing with no gingival edema, erythema, suppuration, patient discomfort or flap dehiscence this may be related to that all patients run on antibiotic regimen post operatively to control postoperative infection. In the present study, by comparing MD & BL width clinically among the three groups (I,II,III) at 3 months, there was statistically high significant difference in mean of change in both dimensions among the three groups at (p-value=0.004, 0.003) respectively. After 6 months, group I showed the highest significant decrease in both, meanwhile group III showed the highest statistically significantly increase in both dimensions at (p-value=0.004,0.003) respectively. Group II showed significant increase in B-L width while no significant increase in M-D width.

Authers reported a significant change in bucco lingual width concurrent with our study<sup>(42)</sup>. Contrary to our results this study<sup>(43)</sup> reported a significant reduction of the horizontal dimension in  $\beta$ -TCP grafted group nine months after socket preservation. Through the study period it was found that, after three months group II and group III showed a significant increase in vertical height of socket of respectively compared to group I at (p-value=0.002, 0.004) respectively, Group III showed the highest increase in vertical height at six months. This in accordance with other study<sup>(44)</sup> who performed a 6-month clinical study who tested freeze dried

bone allograft and collagen membrane for socket preservation versus non grafted socket for implant site development. He found that test group showed a vertical gain of 1.3 mm versus a loss of 0.9 mm for the control group. This results is in contrast with auther<sup>(27)</sup> who comparing the clinical parameters between Group I (PRF) and Group II ( $\beta$ -TCP-CI) after six months found a significant decrease in mid-buccal crestal height in Group I (PRF) and bucco lingual/palatal width of both the groups. Similar results were reported by other clinical studies.

By comparing the radiographic linear measurements, through the whole study period, the horizontal ridge width showed statistically significant difference among the three groups. Both group II and group III showed significant increase in horizontal ridge width at 1,3,5mm from the crest (p-value= 0.003, 0.004 and 0.004) but group III was higher than group II. The amount of gain in group III was 2.3mm, 1.58mm and 1.55 respectively. Group I showed significant decrease in horizontal ridge width at 1,3,5 mm. The amount of loss in group I was -1.18,-1.26 and -1.14 respectively The significant decrease in ridge width in control group in the radiograph is in agreement with the study demonstrated a ridge width reduction at the level 1 mm below the crest (-3.3mm) for control sites<sup>(22)</sup>.

In a study using different treatment modalities for ridge preservation; b-tricalcium-phosphate-particles with polylactid coating (b-TCP), demineralized bovine bone mineral with 10% collagen covered with a collagen matrix (DBBM-C/CM), DBBM-C covered with an autogenous soft-tissue graft (DBBM-C/PG), it was found that after 6months the width of ridge radiographically was -3.3mm for(b-TCP),- 1.2 for (DBBM-C/CM) and -1.4for (DBBM-C/PG).In conclusion Group II and group III showed significant gain in the width and height of the alveolar bone, compared to group I The composite use of bioglass, Prf & melatonin in group III reflected the best clinical and radiographic findings.



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