THE EFFICIENCY OF USING ADVANCED PLATELET RICH FIBRIN– AUTOGENOUS BONE GRAFT MIXTURE AROUND IMMEDIATELY PLACED DENTAL IMPLANTS IN MANDIBULAR MOLAR REGION: (RANDOMIZED CONTROLLED CLINICAL TRIAL)

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ABSTRACT

Background: Immediate implants have been commonly used for the single or bi-rooted teeth. However, it was a challenge and an intriguing dilemma with respect to molar teeth, due tothe presence of multiple factors such as: multiple root morphology,achieving implant stability and bone to implant contact.The aim of this study was to assess the efficiency of using A-PRF-autograft mixture around implants placed immediately in mandibular molar region from aclinical and radiographic point of view.

Patient and methods: This study was carried out as a randomized controlled clinical trial in which twenty patients needing extraction of unrestored mandibular molars and placing of immediate implant, were selected. Patients were divided into two groups randomly; the study group where the resultant gap following the immediate insertion of a molar implant was filled with A-PRF-autograft mixtureand the control group where peri-implant gap was filled with autogenous bone graft alone.The studied variables were the degree of facial swelling, marginal bone height and the bone density around the immediately installed dental implants. The period for follow up was after six months. For statistical analysis,Mann- Whitney U test was used.

Results: The study group showed better results in the clinical and radiographic studied variables. A significant difference was seen regarding the marginal bone height.Although, regarding bone density and swelling, more acceptable results have been seen within the study group, the results showed no statistically significant difference between both groups.

Conclusion: The results assured the efficiency of using A-PRF-autograft mixturewith concurrent placement of immediate implants in the lower molar region and highlighted their promising effects on bone and soft tissue healing.

KEY WORDS: Immediate implant, mandibular molar, Advanced Platelet rich fibrin, autogenous bone.

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INTRODUCTION

Recent dental implantology aims to provide fulfilling esthetics as well as a secured osseointegration.[1] For improvements of functional and esthetical results, sufficient alveolar bone volume and architecture should be available. Preservation of alveolar bone volume is achieved by placing implants immediately after teeth extraction.[2,3]

However, extraction of molars is still a challenge due to multiple root morphology and the big socket left after extraction. Maximizing bone to implant contact (BIC) and primary stability, are both the most important aspects for the successfulness of the procedure of immediate implants in molar region.[4] Callandriello et al.[5] in his article explained that implant therapy is an attractive treatment concept for first and second molars that are commonly lost.

Placing implants in fresh extraction sockets leaves a gap between the bone and the periphery of the implant. Gaps that are less than 2mm will be resolved and new bone will beformed, whereas larger gaps may require the use of bone grafts and barrier membranes to fill the gap.[6,7]

Platelets play a critical role in inflammation and wound healing due to the presence of several growth factors and cytokines. This has led for usage of platelets as a therapeutic tool to improve tissue repair, particularly in maxillofacial and oral surgery, sports medicine and plastic surgery.[8-11]

Platelet Rich Fibrin(PRF)was developed by Choukron et al. (2001)[12]a few years later in parallel with Platelet rich plasma(PRP) to replace it in the fields of oral and maxillofacial Surgery. It is an easy method to develop fibrin gels without additives, and has been recognized as a new generation of PRP designated as PRF.

Platelet rich fibrin is an autologous grafting material that liberates during more than seven days a huge amounts of coagulation and healing molecules such as (Fibronectin, Vitronectin, Thrombospondin-1) and growth factors specially the Transforming Growth Factor, Vascular Endothelial Growth Factor (VEGF) and Platelet-Derived Growth Factors(PDGF).[13] The Advanced Platelet-Rich Fibrin was explained by Ghanaati et al. [14] and the new concept is mentioned as A-PRF; these low speed conception showed increase in growth factor release.

Therefore, there was no available data in the literature concerning the use of A-PRF mixed with autogenous bone graft around immediately placed posterior mandibular dental implants. This work was intended to solve the question of: Is mixing Advanced platelet rich fibrin with autogenous bone beneficial for accelerating bone healing around immediately placed posterior mandibular dental implants?

PATIENTS ANDMETHODS

This study was carried out as an experimental, randomized controlled clinical trial. The intended sample size was 16 cases; 20% was added to the sample size from the onset of the study to abolish the expectations of drop out through the therapy protocol. Therefore, a total of twenty patients were enrolled to participate in this study. They were selected conveniently from the outpatient clinic of Oral Surgical Sciences Department, Faculty of Dentistry, Beirut Arab University, Beirut, Lebanon according to a certain inclusion criterion: patients with age fluctuating from 25 to 45 years(16 males and 4 females) requiring implant placement immediately in the mandibular molar area and teeth with unimpaired buccal plate of bone, presence of inter-radicular bone, and minimum quantity of apical bone of 4 mm to obtain initial stability. While the exclusion criteria were: patients with uncontrolled systemic conditions that might jeopardize the surgery, acute periapical abscess,and heavy smokers.

The picked sample was randomly spitted into two equal groups using the computer generated randomization table: study group in which the gaps were occupied with A-PRF-autograft mixture; and control group in which the peri-implant gaps were packed with autogenous bone graft alone. Patients were enlightened about the entire procedure, and signeda specific informed consent document. The study began after getting the approval of the Institutional Review Board (IRB) of Beirut Arab University (code:2016H-0042-D-M-0157).

Pre-operative phase

Medical and dental histories were registered; clinical and radiographic examinations were completed throughCBCT (CS 9000,Extraoral imaging system,US) for proper selection of the case and planning the proper location for implant insertion.

Operative phase

All surgeries were carried-out by the same specialist under local anesthesia using Articaine hydrochloride 4% with Adrenaline 1/100.000 (Ubistesin forte, 3M Australia).Afull thickness mucoperiostial flap was reflected,extending one tooth anterior and posterior to themolars to be extracted with one distal releasing incision. Atraumatic extraction of the roots was done using the periotome(EPTSMS, Hu Friedy, Milan, Italy). After extractions, periodontal probe was used to map the internal surfaces of the sockets for dehiscences and fenestrations before implant placement. The sockets were then curreted with (CL866-HU Friedy) then irrigated with 0.9 %normal saline solution. Autogenous bone was collectedfrom the buccal shelf area using disposable bone scrapers(Osteogenics Biomedical,Lubbock,Texas), and added to the collected bone during the drilling procedure.

Implant positions weredirected according to the manufacturer's instructions and bone leveled tapered implants(InstitutStrauman AG, Basel,Switzerland)

were placed 3-5 mm far off the apex in the inter-radicular bone.For the study group: A-PRF was prepared from the patient's own blood,through taking 20 ml of blood from the median cubital vein or cephalic vein,collected quickly into two separate tubes (each containing 10 ml) without anticoagulant and were immediately centrifuged at 1300 rpm for 8 minutes. The A-PRF was prepared according to Ghanaati et al.(2014) [(14).] The tubes were settled in the centrifuge device in a symmetrical manner (Centrifuge PRF DUO, Process for PRF, France). At the end of the centrifugation procedure, A-PRF was situated on the grid in the PRF Box (PRF box, Process for PRF, France) to produce A-PRF membranes. Serum exudate accumulated in the floor of the box was utilized to hydrate the autogenous bone graft. The membranes were cropped into small pieces and put together with the autogenous bone graft and the collected serum. The mixture was then plugged in the peri-implant gap to fill the peri-implant gap, and covered also by A-PRF membrane. Finally, interrupted sutures approximating the tissues were made using 4-0 black silksuture material **(Fig.1-7)**.

For the control group, the same surgical procedure was performed by filling the gap with autogenous bone collected from the buccal shelf of bone but without the use of the A-PRF

Fig. (1) Un-restorable mandibular right first molar indicated for extraction

Fig. (2) A full thickness flap and the extracted socket
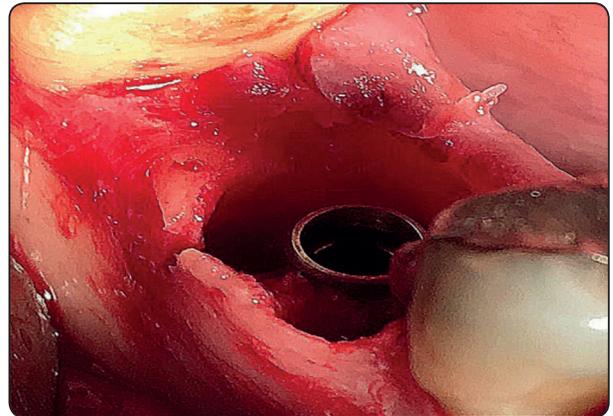

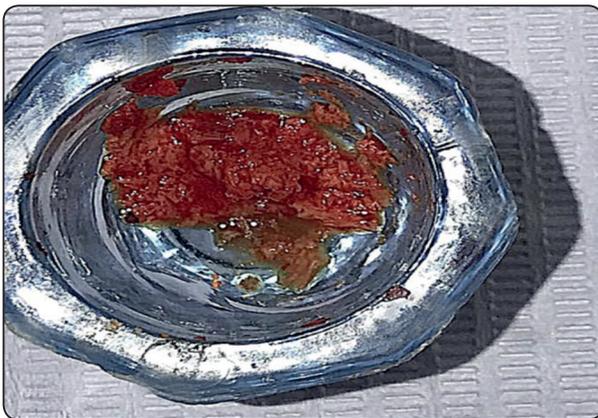Fig. (3) Immediate implant within the interradicular bone
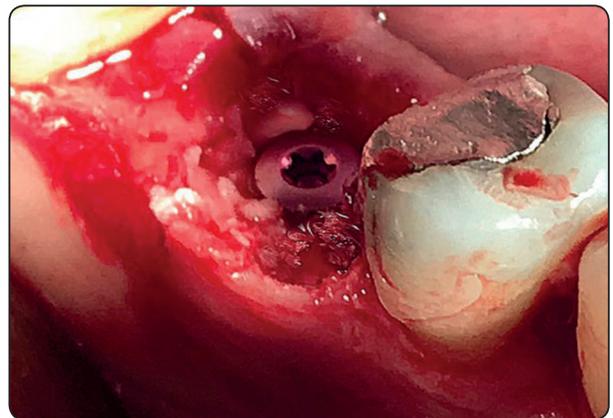

Fig. (4) Autogenous bone graft collected

Fig. (5) A-PRF- Autogenous bone mixture filling the peri-implant gap

Fig. (6) A-PRF membrane covering the surgical site

Fig. (7) Figure of eight silk suture closing the surgical site

Post-operative phase

Immediately after surgery, patients were instructed to applycold packs extra-orally every 30 minutesfor a period of 10 minutes,followed by warm saline bathe the next day.

The following medicaments were prescribed: Antibiotic (Augmentin 1g, Glaxo Smith Kline, UK) bid for 7 days, NSAID (Voltfast, Novartis International, Switzerland) 50 mgtid for 5 days and Chlorhexidine mouthwash 0.12% (Eludril, Pierre Fabre Medicament Production, France) for the next 7 days. One week after surgery, sutures were removed.

Follow-up phase

Immediate follow-up:

At the 2nd and 7th postoperative days,clinical evaluation was done to evaluate soft tissue healing by inspecting the presence or absence of inflammation, infection, the color of overlying mucosa, the presence or absence of dehiscence within the flap and the degree of facial swelling. Postoperative swelling was obtained by calculating the mean of the distance between the lateral corner of the eye and the angle of the mandible, tragus and the outer corner of the mouth, and between the tragus and soft tissue pogonion.[15] The obtained values were compared to baseline values.

Radiographically, CBCTs of cross sectional cuts were done postoperatively at the 2nd day (baseline) to calculate the distance between the implant neck and the first bone-to-implant contact in millimeters at the buccal and lingual implant sides; the marginal bone height was the mean of the two readings. CBCTs were also used to measure the bone density. Cross sectional cuts were taken and the implant length was determined, then a line was drawn in the middle and perpendicular to the implant. Another two lines buccal and lingual to the implant were

drawn each of one mm length, the mean of the two readings was recorded to give the mean bone density around the implants **(Fig.8)**.
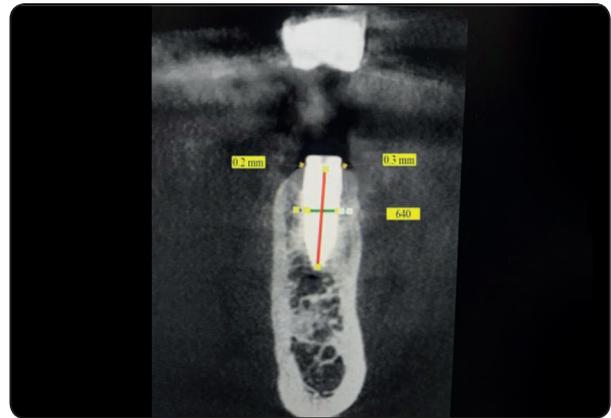

Fig. (8) Cross sectional cut of CBCT for immediate implant at baseline for measuring marginal bone height and bone density

Late follow-up:

Clinical evaluation: After three postoperative months, cover screws were removed andhealing abutments were inserted for two weeks. Later, implant level impressions were taken using silicone impression material(3M ESPE,USA) and implants were loaded by porcelain fused to metal crowns. Peri-implants' soft tissue healing was evaluated and implants' mobility was examined according to the clinical implant mobility scale (0-4).[16] An additional test was done to inspect the mobility by tapping the implants; a solid ring indicated that no mobility presented in contrast to the dull sound accompanied with mobile implants.[17]This test was repeated after six postoperative months.

Radiographic evaluation: CBCT scan was performed after 6 postoperative months to measureboth the marginal bone heightand the bone density around the installed implants. All calculations were compared to baseline **(Fig.9)**.
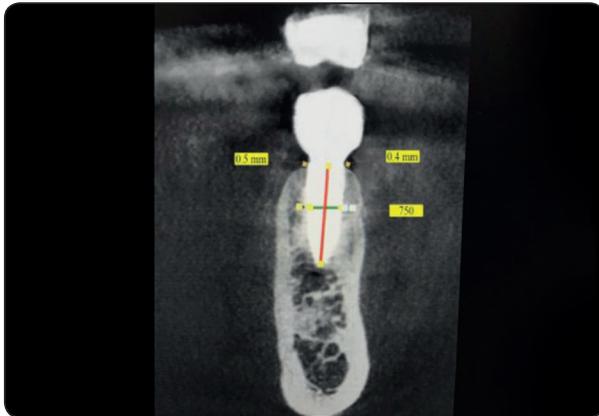
Fig. (9) Cross sectional cut of CBCT for immediate implant after 6 months for measuring marginal bone height and bone density

Statistical Analysis:

In this study, non-parametric Mann-Whitney U test was used to study changes in all the variables alternatively to the t-test.It was used to compare the differences of the studied variables for independent groups.It was usedbecause of the small sample size to compare the studied variables.Descriptive statistics were calculated as medians and converted to mean ranks. Box Plot were used to describe the obtained results.Significance level was set at 5% level. Statistical analysis was accomplished using SPSS version 24.

RESULTS

A total of 20 patients(14 males& 6 females) having mandibular molar teeth indicated for extraction, were diagnosed clinically and radiographically to ensure the presence of inter-radicular bone associated with 3-5mm of bone beyond the apex,was enrolled in the study.

The teeth involved were 16 first molars and 4 second molars. The teeth were extracted and immediately replaced by dental implants. All patients had undergone surgical procedures for immediate implant placement. For the study group ten patients had A-PRF mixed with autogenous

bone placed around the implant in the gap, whereas for the control group ten patients had autogenous bone alone in the peri-implant gap.

The results were registered as regards clinical and radiographic variables.

Clinical results

All implants showed successful osseointegration with no signs of failure (dehiscence, infection or mobility)and without any postoperative side effects.

Degree of facial swelling

The median of facial measurements at baseline was 12.81 cm in the control group and 12.61cm in the study group. By the second day, the facial swelling increased to 13.18 cm in the control group and 12.88 cm in the study group. At the 7th day, the facial swelling decreased to 12.93 cm in the control group and to 12.61 cm in the study group (**Table.1, Fig.10**).

Radiographic evaluation:

Marginal Bone Height:

The median of the marginal bone height at the second day was 0.43 in the study group and 0.51 in the control group. After 6 months the median of marginal bone height decreased to 0.35 in the study group, and to 0.21 in the control group (**Table 3, Fig, 11**).

Mann-Whitney U test revealed the results of the degree of facial swelling. At the baseline, the P-value was equal to 1.000. At the 2nd day, the P-value was equal to 0.671 while at the 7th day, the P–value was equal to 0.810. There was no statistically significant difference in the facial swelling measurements between the control and the study groups (Table.2).

TABLE (1) Descriptive statistics of Degree of facial swelling

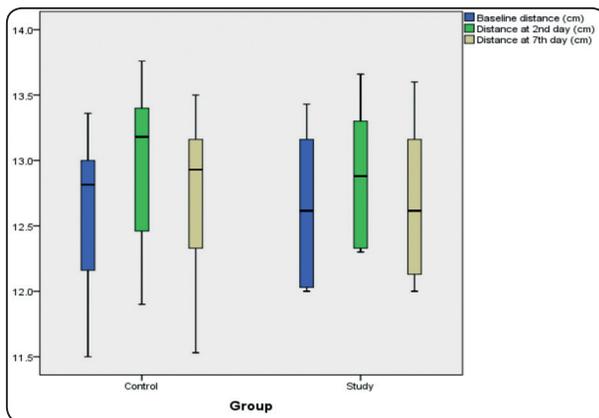| Group		Facial measurement at Baseline (cm)	Facial Swelling at 2nd day (cm)	Facial Swelling at 7th day (cm)
Control	N	10	10	10
	Median	12.8150	13.1800	12.9300
Study	N	10	10	10
	Median	12.6150	12.8800	12.6150
Total	N	20	20	20
	Median	12.7650	13.0600	12.8150

Fig. (10) Box Plot graph showing the variations of facial swelling measurements across baseline, 2nd and 7th postoperative days.

TABLE (2) Test Statistics of the degree of facial swelling

	Baseline facial measurement (cm)	Facial swelling at 2nd day (cm)	Facial swelling at 7th day (cm)
Mann-Whitney U	50.000	44.000	46.500
Wilcoxon W	105.000	99.000	101.500
Z	.000	-.454	-.265
Asymp. Sig. (2-tailed)	1.000	.650	.791
Exact Sig. [2*(1-tailed Sig.)]	1.000[b]	.684[b]	.796[b]
Exact Sig. (2-tailed)	1.000	.671	.810
Exact Sig. (1-tailed)	.508	.335	.405
Point Probability	.015	.014	.014

a. Grouping Variable: Group b. Not corrected for ties.

TABLE (3) Descriptive statistics of marginal bone height

Group		Marginal bone height at 2nd day (baseline)	Marginal bone height at 6months postoperatively
Study	N	10	10
	Median	.4350	.3500
control	N	10	10
	Median	.5150	.2050
Total	N	20	20
	Median	.4500	.2950

Mann-Whitney U test revealed that p-value was equal to 0.342 at the second postoperative day. After six postoperative months, the P-value became 0.003. The decrease in the crestal bone was more pronounced in the control group than that in the study group with a statistically significant decrease after 6 postoperative months (Table.4).

TABLE (4) Test Statisticsof marginal bone height

	Marginal bone height at 2nd day postoperatively (mm)	Marginal bone height at 6 months postoperatively
Mann-Whitney U	37.000	13.000
Wilcoxon W	92.000	68.000
Z	-.985	-2.818
Asymp. Sig. (2-tailed)	.324	.005
Exact Sig. [2*(1-tailed Sig.)]	.353[b]	.004[b]
Exact Sig. (2-tailed)	.342	.003
Exact Sig. (1-tailed)	.171	.002
Point Probability	.009	.000

a. Grouping Variable: Groupb. Not corrected for ties. p<0.05 =significant difference
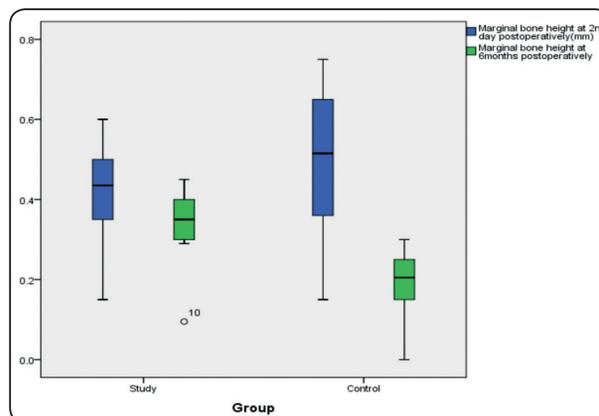

Fig. (11) Box Plot graph showing variation of the median of marginal bone height at 2nd day and after 6 months comparing control group to the study group.

Bone Density:

Mann-Whitney U test revealed that the median of bone density at the second day was equal to 635.2 in the control group and was 581 in the study group. After 6 postoperative months the bone density increased to 802.5 in the control group and to 827.5 in the study group **(Table 5,Fig.11)**.

TABLE (5) Descriptive statistics of bone density (voxel).

Group		Density of bone at 2nd day	Density of bone at 6month
Control	N	10	10
	Median	635.2500	802.5000
Study	N	10	10
	Median	581.0000	827.5000
Total	N	20	20
	Median	613.7500	810.0000

Statistically, the P-value was equal to 0.481 considering bone density at the 2nd postoperative day and 0.684 after six postoperative months. There was no significant difference comparing the two groups **(Table.6)**.

TABLE (6) Test Statistics of bone density

	Density of bone at 2nd day	Density of bone at 6month
Mann-Whitney U	40.000	44.500
Wilcoxon W	95.000	99.500
Z	-.756-	-.417-
Asymp. Sig. (2-tailed)	.450	.677
Exact Sig. [2*(1-tailed Sig.)]	.481[b]	.684[b]

a. Grouping Variable: Group b. Not corrected for ties.
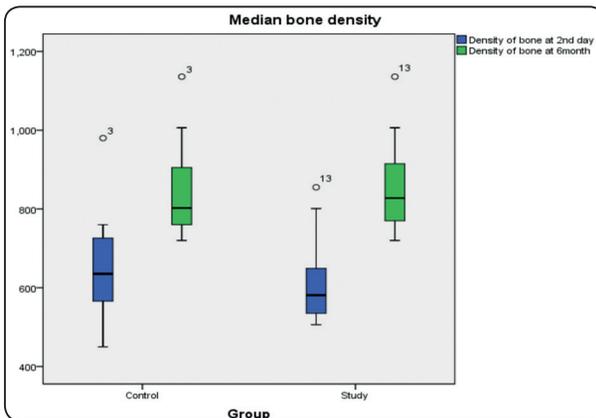
P value<0.05=significant difference

Fig. (12) Box plot showing variation of bone density median comparing the two groups.

DISCUSSION

Immediate implant in lower molar region is challenging due to the anatomical limitations such as inferior alveolar nerve and insufficient available bone for implant stability.[18]In addition to that, molars are multi-rooted that makes the extraction sockets wider than the implant diameter, which results in a gap between the cervical region of the implant and the bone.[19]This gap which is greater than 2mm in width is better to be filled using a slow resorbing graft material.[20]Platelet rich fibrin fragments mixed with the bone graft serve as a biological connector between bone particles.[21]

In the current study, there was no drop-out from the selected sample and thismay be attributed to the well-educated level of the selected patients and their commitment to their treatment in addition to the availability of the social media which makes the follow up communication with the patients easier. Therefore,twenty patients,14 males and 6 females were included to participate in this study.Their ages fluctuated from 27 to 42 years with mean age of 31.64 years.

Advanced Platelet rich fibrin is an autologous healing biomaterial.Its protocol is simple and non-expensive, with single centrifugation without any additives. It was described by Ghanaati et al. 2014[14] who explained PRFas a strong natural fibrin matrix containing almost all the platelets and growth factorswith high concentrations.

Full thickness mucoperiostealflap elevation with vertical releasing incisions was used in this work to allow for better visualization and better handling of the different surgical steps and healing in accordance to Koo et al. (2008) [22] and Kim & Kim (2014) [23].

The teeth were loosened using a curved periotome for their atraumatic extraction,and then they were sectionedand each root was removed alone inorder to preserve the inter-radicular bone, this was in parallel with Zafiropolous et al. (2010).[24]

Implant placement in theroot socket lead to a non-ideal restorative position and mechanical overload of the implant. The resulting shape of the restoration rendered a difficulty in oral hygiene, which increased the risk for peri-implantitis. To avoid these problems, immediate implants were placed in the inter-radicular bone in matching the recommendations ofTallarico et al.(2017)[18] and Deporter&Ketabi(2017).[20]The primary stability was acquired by engaging 3 to 5 mm of bone exceeding the root apex.[25]

The resulting gaps were filled with bone, this was in parallel with Spinato et al.(2012)[26],who recommended the use of regenerative material when the gap was > 1.5-3mm.

Advanced platelet rich fibrin clots were pressed into membranes to preventdrying up or destruction of leukocytes found in the PRF clots and to avoid shrinkage of the fibrin matrix architecture.[27] A-PRF membranes were cut, mixed with the autogenous bone harvestedparticles,and used as membranes to cover the graft and the implant in harmony with Kökdere et al.(2015)[28], who found that PRF kept the autogenous particulate bone together with more new bone formation and osteoblasts'presence when it was mixed with autogenous particulate bone grafts.The flaps were repositioned to their pre-surgical levels and sutured with silk utilizing a figure of eight suture technique.

A non-functional healing period was recommended in order to give better survival rate as Branemark stated in his 2stageprotocol.[29]This occlusal load-free healing period was achieved by submerging the implant below the soft tissue and allowing the surgical site to heal without placement of any direct load on the implant.

Immediately postoperatively, ice packs were given to the patients,they were applied extra-orally for 10 minutes every 30 minutes in a way to control the postoperative suspected edema.This was in agreement with Abdelkarim et al. (2015).[30]Warm fomentations replaced the cold ones for the following 3 days. Postoperative antibiotics and anti-inflammatory were prescribed to the patients for 7 days. This was in harmony with Lang et al. (2012).[31]

The immediate clinical follow up at 2nd and 7th post-operative days showed an uneventful healing with healthy non-inflamed marginal areas. The degree of facial swelling was also evaluated at the same periods of time for both groups.Results showed no statistical significant difference throughout baseline,2nd,and 7th postoperative days between both groups. The median of facial measurement was slightly higher in the control group than that in the study group at 2nd day and it resolute faster in the study group than that in the control group after 7th postoperative days. Results showed that A-PRF

decreased swelling and helped in faster resolution of postoperative edema but with no significant difference. The results were in accordance with Asutay et al. (2017)[32]who studied the effect of PRF on morbidities after lower third molar surgery. Also it was in congruent with Arenaz-Bua et al.[33] who reported no statistically significant difference in swelling between study and control groups when using platelet concentrates in impacted mandibular third molars surgeries.

In this study, the dose delivered to each patient concerning CBCTs was up to a point of maximum permitted dose according to the national council on radiation protection and measurements (NCRP).[34]

The marginal bone height was measured by CBCT cross sectional cuts.Its defined as the distance between the implant neck and the first bone to implant contact that was measured buccally and lingually at the second day after implant insertion(baseline) and after 6 months postoperatively. Mann-Whitney U test was done to compare the results of the two groups during the same interval of time. Results were significant, with a pronounced decrease observed more in the control group. This was in congruent with Boora et al.(2015)[35] who analyzed the effect of PRF on the peri-implant tissue response following one-stage implant placement with non-functional immediate provisionalization in maxillary anterior region where they found that that there was a statistically significant lesser mean value for the study than the control measured at insertion of implant (baseline),1 months and at 3 months.

Moreover, these results were in harmony with Zaki et al.[36] who studied the effect of PRF mixed with allogenic bone graft around immediate implants. Results showed less marginal bone loss in the study group with a statistically significant difference.

Regarding bone density; although CBCT is an inaccurate method for detection of the bone density, it was used for its availability and less radiation dose in comparison with the CT scan. It gives an idea

about the progression of healing in terms of grey scale. Results showed improvement in the bone density from baseline immediately after implant placement and the gaps were freshly grafted and 6 months postoperatively where the gaps appear to be fulfilled withdenser bone. Although the inter-group variation was in favor for the study group due to varieties of growth factors present in A-PRF, the outcomes were not statistically significant; this could be associated with the small sample size and the short term of evaluation.The bone density results are in harmony with Zhang et al.(2012)[37] who carried out sinus floor elevations, grafted PRF-Bio-Oss mixture in the study group and Bio-Oss alone in the control group. After 6 postoperative months,they found that the percentage of new bone formation in the study group was about 1.4 times more than that controls with no significant difference.

Moreover, these results are in harmony with Kalashet al.[38]who studied the efficiency of PRF mixed with xenograft in the peri-implant gap of immediately placed implants in the maxillary region on the bone density. They found that there was no significant difference between the two groups although there were improvements in bone density comparing radiographs at baseline and after 9 months follow up.

CONCLUSION

In this study, it can be concluded that immediate implant placement with A-PRF- autogenous bone mixture in the lower molar region may be a predictable surgical procedure with successful prognosis. Faster bone formation with denser bone occurred in the study groups where autologous bone graft were mixed with A-PRF. Autologous bone remains as the gold standard of materials used to optimize the mandibular bone regeneration. This technique allows adequate acceleration of bone healing with a decrease in crestal bone loss. It enhances the increaseinbone volume with faster soft tissue healing and less postoperative swelling.

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