ORIGINAL PAPER

THE ROLE OF LEUKOCYTE- AND PLATELET-RICH FIBRIN AS A SOLE GRAFTING MATERIAL IN ALVEOLAR RIDGE PRESERVATION: A CLINICAL RADIOGRAPHIC STUDY

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ABSTRACT

Introduction: Ridge preservation is a widely used surgical technique to reduce post-extractive alveolar bone resorption; this procedure is performed with a variety of bio-materials. Leukocyte- and platelet-rich fibrin (L-PRF) is a prominent recent platelet concentrate used for ridge preservation, with a lot of controversy over the role of this bio-material.

Objectives: The aim of this study was to evaluate the role of L-PRF radiographically in reducing post-extraction dimensional changes after tooth extraction compared with unassisted bone healing.

Material and methods: Forty premolars were extracted symmetrically in a split-mouth design, and control and test sides were assigned randomly. Test extraction socket in each patient was filled with L-PRF clot and control extraction socket was unassisted, both sockets were cross-sutured. A CBCT examination was performed in two time lapses (immediately after extraction and 4 months post-extraction). Dimensional changes on both test and control sockets were analyzed, and radiographic examination was performed comparing dimensional changes of widths and heights of both sockets.

Results: The current study showed a statistically significant difference between the test group (L-PRF) over the control group (unassisted healing) in both widths and heights of the sockets.

Conclusions: After 4 months of follow-up, the use of L-PRF for the purpose of reducing post-extraction bone resorption and alveolar ridge preservation is considered beneficial, cost-effective, and recommended in a planned implant treatment.

Key words: platelet-rich fibrin, bone resorption, tooth extraction.

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INTRODUCTION

Tooth extraction is a process that is always followed by alveolar bone resorption, which continues for years. Studies showed that alveolar bone resorption during the first year is about 11-22% of alveolar bone height and 29-63% of alveolar bone width, while around two thirds of alveolar ridge is resorbed during the first three months after dental extraction [1]. At the time of implant placement, quantity and quality of the alveolar bone will determine osseointegration and longevity of implants [2]. Also the process of alveolar ridge preservation and maintaining sufficient bone will facilitate the implant treatment [3].

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Many techniques have been introduced to reduce alveolar bone resorption after extraction using different bone substitutes, including allografts, autografts, xenografts, or alloplastic materials, with resorbable or non-resorbable membranes [4, 5]. Alveolar ridge preservation is an effective process in reducing alveolar resorption both vertically and horizontally without any superiority of one technique over another [6]. Studies used different bio-materials for alveolar ridge preservation, and showed that none of them could stop the alveolar bone loss [7]. First generation, such as platelet rich plasma (PRP), and second generation, including leukocyte- and platelet-rich fibrin (L-PRF) platelet concentrates are biologically active materials, which have been well-developed to compensate for disadvantages of bone substitutes [8], and comprise a fibrin clot and a liquid component [9]. Analysis of the composition of PRF showed that it contains leukocytes, fibrin clot with platelets, cytokines, and stem cells [10]. Platelets are the dominant component of PRF, and represent cells responsible for biologic activity in PRF. Platelets play a major role in the formation of clot, they include many platelet-derived molecules that contribute to wound healing [11]. The most notable growth factors of PRF are the transforming growth factor β (TGF-β), insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) [8, 12]. Moreover, PRF contains immune cytokines, such as tumor necrosis factor α (TNF-α), and interleukin (IL)-1β, IL-6, and IL-4 [8]. TGF-β is a multipotent cytokine, the active form of TGF-β1, which is secreted by activated platelets that stimulate fibroblasts chemotaxis and collagen and fibronectin production; it induces angiogenesis [13]. Furthermore, TGF-β1 enhances osteoblasts proliferation together with osteoclasts inhibition [12]. PDGF released from platelets leads to proliferation, migration, and survival of mesenchymal cells [8]. In addition, PDGF enables angiogenesis, and activation and chemotaxis of macrophage [14]. IGF-1 is a poly-peptide hormone found in blood and released during platelet de-granulation [8]. Moreover, IGF-1 stimulates differentiation of mesenchymal cells [15], and stimulates activation of osteoblasts resulting in bone formation [14]. During tissue injury, VEGF is released by activated macrophages and platelets [12]. VEGF plays a key role in endothelial migration, proliferation, and angiogenesis-related processes [16]. EGF promotes angiogenesis and epithelialization, and is secreted by platelets, macrophages, and fibroblasts [14]. IL-1β initiates the inflammatory response at injury site by elevation of the expression of adhesion molecules on endothelial cells, in addition to stimulation of helper T-cells and chemotaxis of lymphocytes and phagocytes [17]; together with TNF-α inhibits bone formation by osteoclasts activation [16]. IL-6 is produced by lymphocytes, fibroblasts, epithelial cells, and osteoblasts following their activation [18]. IL-6 stimulate lymphocytes into plasmocytes and differentiation of T-cells [16]. Also, IL-6 is mainly produced during inflammation and re-modeling processes [19]. TNF-α is a pro-inflammatory cytokine that plays an important role during wound healing and inflammation produced by T-cells, neutrophils, and macrophages. TNF-α is regulated by IL-6 and TGF-β. This cytokine provokes re-modeling of fibroblasts and neutrophils, and also modulates the expression of pro-inflammatory cytokines [16].

L-PRF can be obtained by centrifugation of a patient's blood without any additives, such as calcium chloride, thrombin, or EDTA. The clot can be separated from red blood cells and platelet poor plasma (PPP). L-PRF membrane is composed of a dense, high cross-linked, fibrin network, in which platelets and leucocytes are embedded. Growth factors, particularly TGF-β, PDGF-AB, and VEGF, adhesion molecules, and pro- and anti-inflammatory cytokines are released by this biological scaffold for about 7 days [16, 20].

OBJECTIVES

The objectives of the current study was the presentation of the role of L-PRF in the alveolar ridge preservation and in reducing alveolar ridge resorption, compared with natural unassisted healing.

MATERIAL AND METHODS

Twenty patients in need of symmetrical extraction in the premolar region were considered for initial eligibility (Figure 1). Patients fulfilling inclusion criteria were invited to participate in the study. The study was performed according to the Declaration of Helsinki, and approved by a scientific committee of the Faculty of Dentistry, Damascus University. Inclusion criteria were patients ages between 18-60 years, good physical health without being medically compromised, good oral health, no contraindication for local anesthetic or minor oral surgery, and being able to understand and participate in the study. Exclusion criteria were uncontrolled periodontal diseases, patients taking drugs that could affect wound healing (i.e., immune-suppressants and corticosteroids), patients taking anticoagulants, patients with blood disorders, acute dental infections, smokers, alcoholics, and pregnant and lactating women. All patients were provided an informed consent before participation. Venous blood was collected in sterile plastic vacuum tubes without any additives and added to EBA 20 (Andreas Hettich GmbH & Co. KG, Germany) centrifuge for L-PRF preparation. Blood was immediately centrifuged at 2,700 rpm for 12 minutes (Figures 2 and 3).

Sample size was determined using G*Power version 3.1.9.7 software for sample size determination at study power of 0.80 and indication level of 0.05. Different

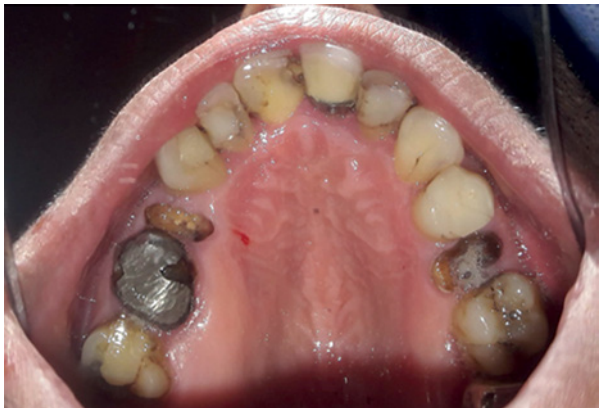

FIGURE 1. A 42 year-old patient presented with non-restorable maxillary premolars, who fulfilled inclusion criteria. The patient approved to join the study and provided an informed consent

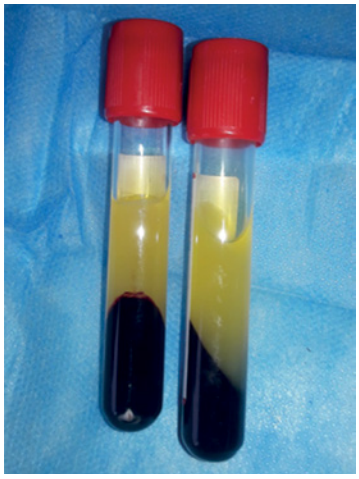

FIGURE 2. Two 4 ml vacuum clot activation tubes prepared for socket fill

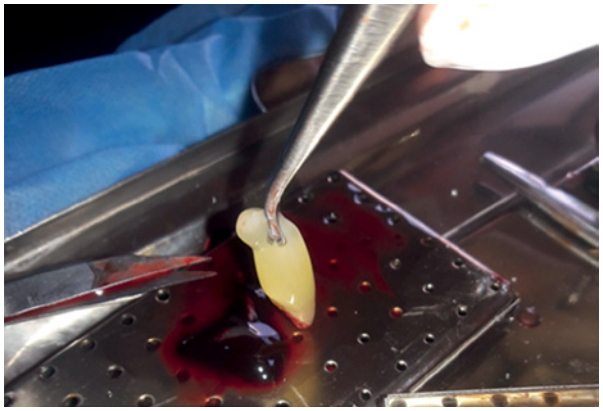

FIGURE 3. Red blood cells carefully separated from leukocyte- and platelet-rich fibrin clot, which was trimmed and packed carefully within the test socket

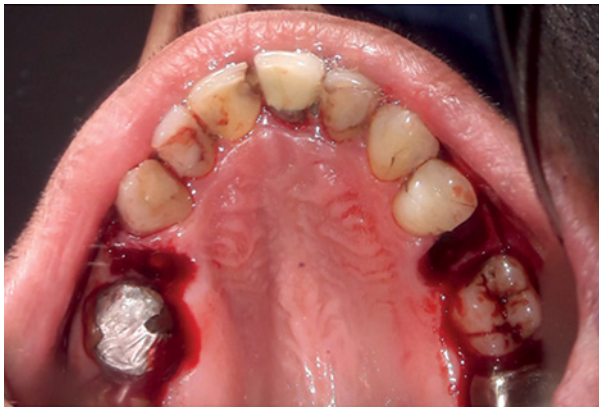

FIGURE 4. Flap-less atraumatic extractions performed under local anesthesia and under sterile conditions

studies in the literature included different sample sizes, but many of similar split-mouth randomized trials of about 20 patients were found in Castro [21], and Temmerman [22].

Forty flap-less tooth extractions were performed in sterile environment and under local anesthesia (Figure 4); sockets were carefully cleaned after extraction, randomized using coin flipping, and allocated into test or control groups by filling one extraction socket with L-PRF and the other socket remaining empty. Both test and control extraction sockets were sutured with crossed suture using (Mersilk 3/0, Ethicon™, Johnson & Johnson®) to stabilize the L-PRF clot on the test socket and the coagulum on the control socket (Figure 5). All patients were scheduled for follow-up and suture removal after one week of the extraction.

Radiographic study was performed by taking 2 cone-beam computed topographies (CBCT) for every patient; the first scan was done immediately after extraction (T1), while the second scan was performed 4 months

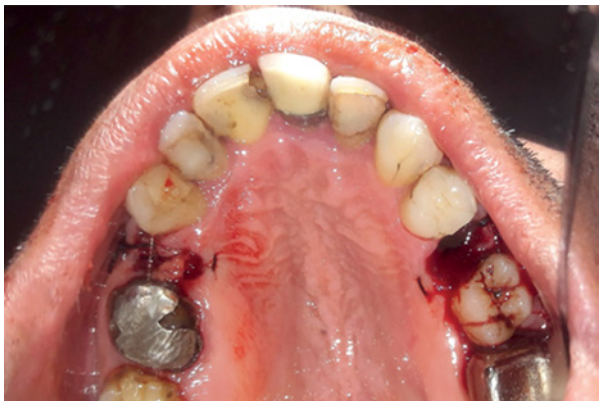

FIGURE 5. Final solution after extraction and application of leukocyte-and platelet-rich fibrin clot in the test socket. The control socket was unassisted. Both the sockets were cross-sutured

post-extraction (T2) as a pre-implant surgery scan using CS 9600 unit (Carestream Dental LLC, USA), with voxel size 75 µm and scan time 5.5 seconds. CBCT scans were

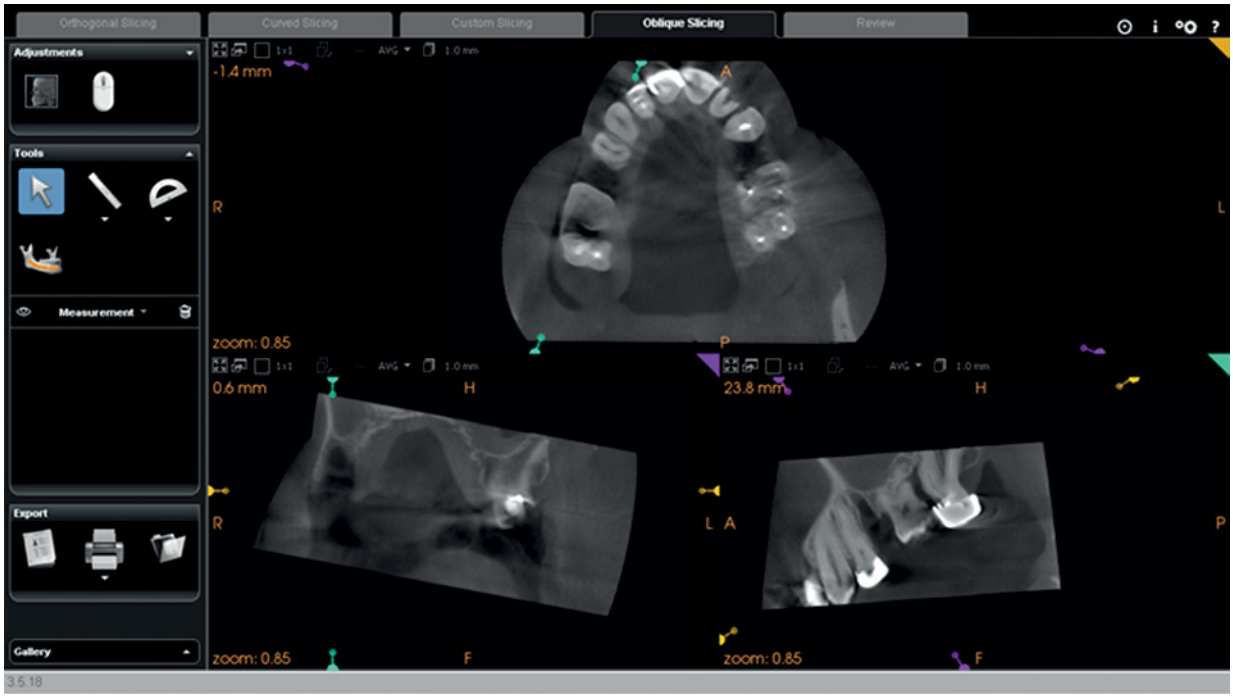

FIGURE 6. Standardization of cone-beam computed topographies planes

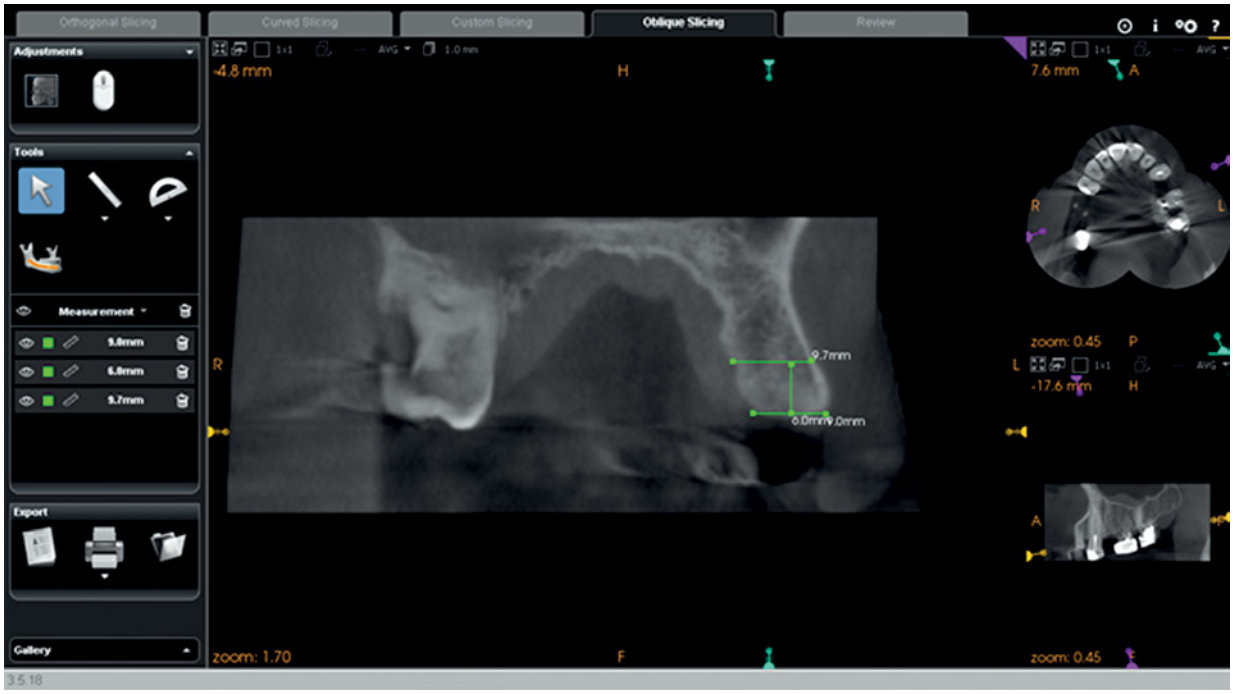

FIGURE 7. Calculating the width of the socket in T1 by measuring the width of the alveolar crest and 6 mm subcrestally

studied in appropriate viewing conditions; all scans were viewed in a dimly lit, quiet room, using a medical grade diagnostic display (Eonis 22" Dental, Barco, Belgium). All scans were viewed and observed by the researcher (MA) who is an oral and maxillofacial resident with more than 5 years of experience in viewing CBCTs, and previously scored 0.78 using Cohen's κ coefficient. Standardization of T1 and T2 CBCT was done by matching reproducible reference lines in both CBCTs, which was performed by linking horizontal plane to the cemento-enamel junction of adjacent teeth, while sagittal plane was linked to the root canals of adjacent teeth (Figure 6). Radiographic study was done using CS 3D imaging version 3.5.18 software. Dimensional changes of the socket's width

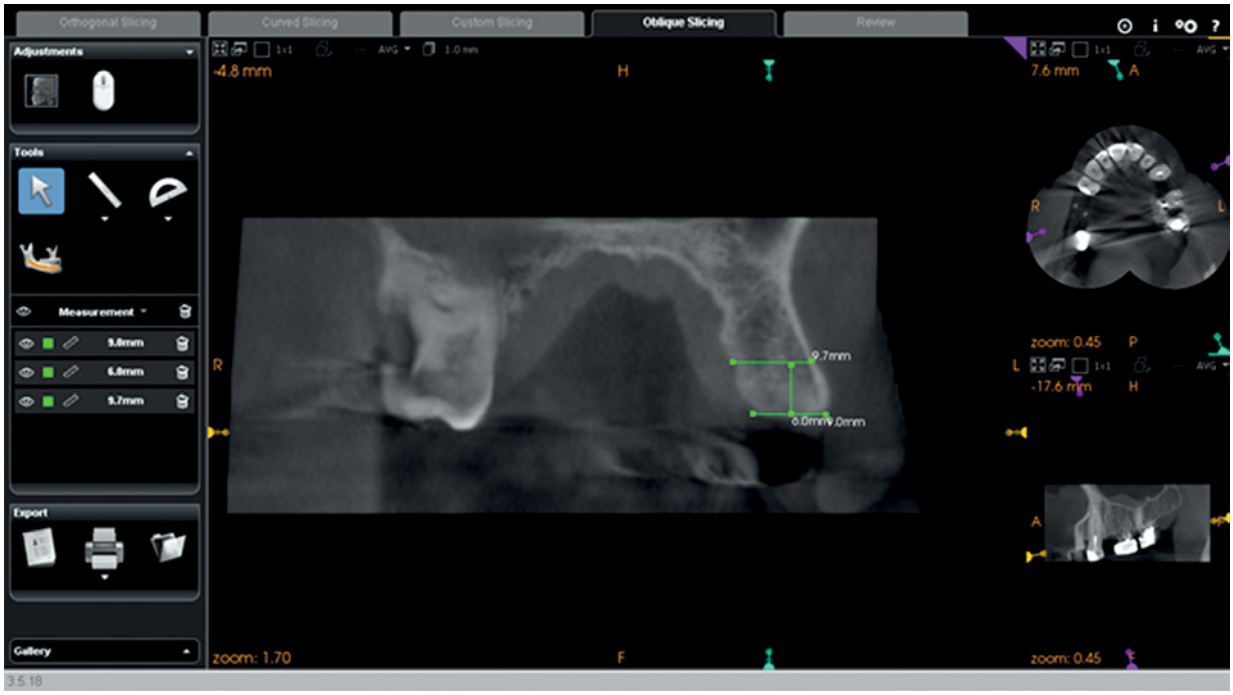

FIGURE 8. Calculating the width of the socket in T2 by measuring the width of the alveolar crest and 6 mm sub-crestally. The difference between T1 and T2 was studied for each patient

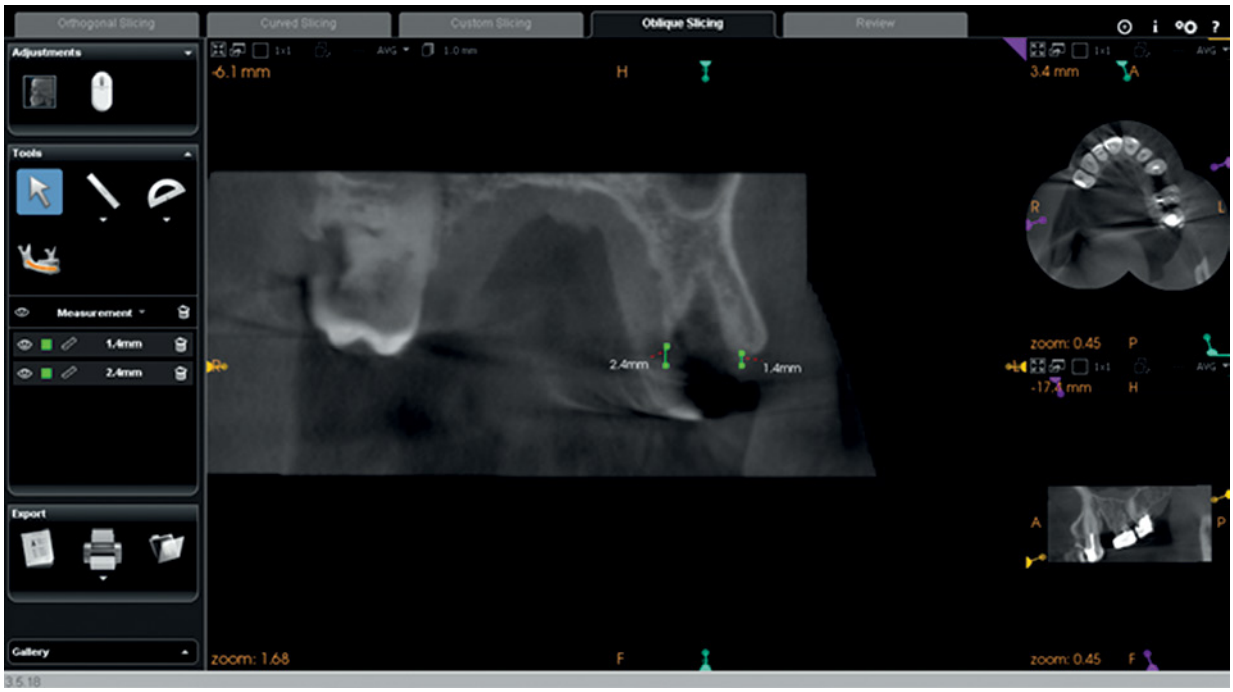

FIGURE 9. Calculating the height of the socket in T1 by measuring the distance between the pre-established reference line and the alveolar crest both buccally and lingually

were determined by calculating the width of the socket at the alveolar crest and 6 millimeters sub-crestal in T1, and then compared with the same technique of measurements in T2 (Figures 7 and 8).

Dimensional changes of the socket's height were defined by calculating the distance between the crest of the socket and the pre-established reference line on both the buccal and lingual plates in T1 and T2 (Figures 9 and 10). For statistical study, SPSS version 24 was applied to investigate dimensional changes in both the groups (L-PRF and test groups) 4 months post-treatment.

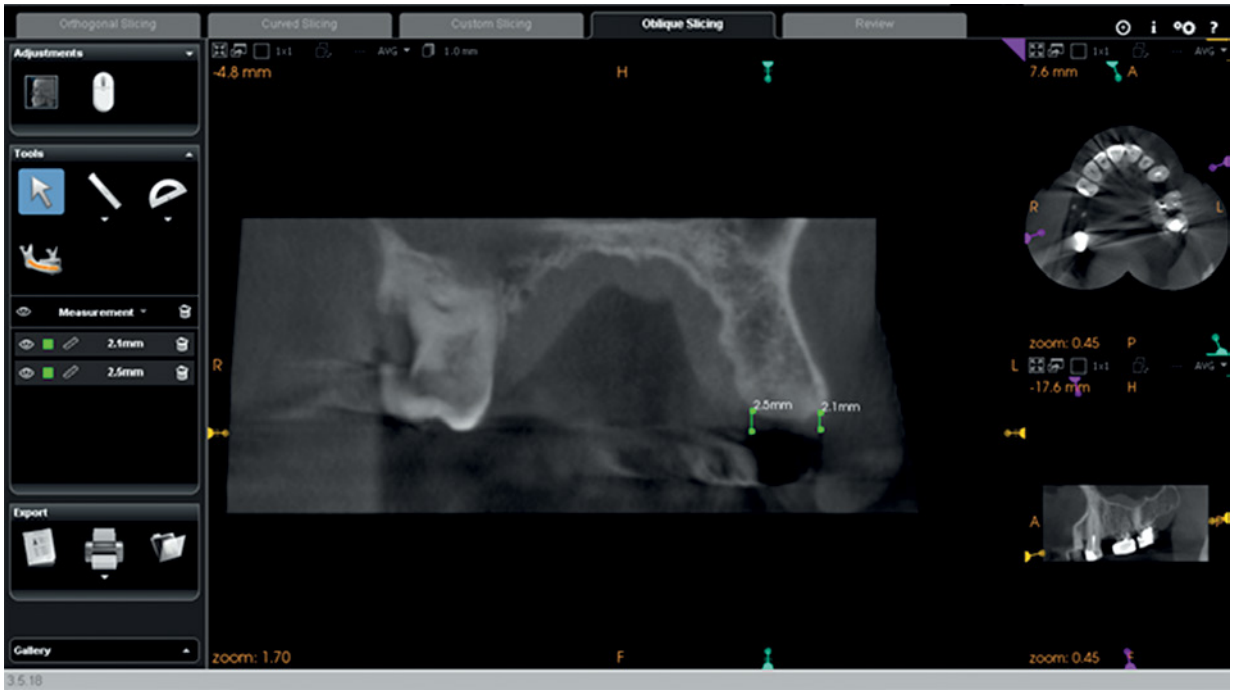

FIGURE 10. Calculating the height of the socket in T2 by measuring the distance between the pre-established reference line and the alveolar crest both buccally and lingually. The difference between T1 and T2 was studied for each patient

RESULTS

Statistical differences were estimated at the indication level of 0.05; therefore, any *p*-value above the indication level of 0.05 was considered statistically insignificant difference, while any *p*-value value below the indication level of 0.05 was considered statistically important difference, a real difference that could be attributed to different studied characteristics between the two sides of the comparison in the applicable statistical test (statistically important difference).

To emphasize the effect of L-PRF in reducing vertical bone resorption on the buccal plate between the study group and the control group, the test value was found 3.313 ($p = 0.004$). Therefore, there was a statistically significant difference between the two groups of the study sample, where statistically significant difference was in favor of the L-PRF group, in which the average value of vertical bone resorption at the crest of buccal bone was 0.46 mm in the test group, and 1.65 mm in the control group (Table 1).

For the resorption on the lingual plate between the study group and the control group, the test value was 2.318 ($p = 0.032$). Thus, there was a statistically significant difference between the two groups of the study sample, with statistically significant difference in favor of the L-PRF group, in which the average value of vertical bone resorption at the crest of lingual bone was 0.52 mm in the test group, and 1.92 mm in the control group (Table 1).

To reveal the effect of L-PRF in reducing horizontal bone resorption at the crest of the alveolar bone between the study and the control groups, the test value was 1.798 ($p = 0.089$). Therefore, there was no statistically significant difference between the two groups of the study sample, in which the average value of horizontal bone resorption (width of the socket) at the crest of alveolar bone was 1.31 mm in the test group, and 2.17 mm in the control group (Table 2).

TABLE 1. Results of statistical test for the height of the socket

Comparison	No. of patients	Average	SD	*t*-test	Degree of freedom	*p*-value	Decision
Buccally							
L-PRF	10	0.46	0.291	3.313	18	0.004	Significant differences
Control	10	1.65	1.098				
Lingually							
L-PRF	10	0.52	0.316	2.318	18	0.032	Significant differences
Control	10	1.92	1.884				

TABLE 2. Results of statistical test for the width of the socket

Comparison	No. of patients	Average	SD	*t*-test	Degree of freedom	*p*-value	Decision
At alveolar bone crest							
L-PRF	10	1.31	1.291	1.798	18	0.089	No significant differences
Control	10	2.17	0.787				
6 mm sub-crestally							
L-PRF	10	0.29	0.561	4.233	18	0.001	Significant differences
Control	10	1.22	0.410				

For the resorption in the width of alveolar bone 6 mm sub-crestally between the study group and the control group, the test value was found 4.233 ($p = 0.001$). Thus, there was a statistically significant difference between the two groups of the study sample, where statistically significant difference was in favor of the (L-PRF) group, in which the average value of horizontal bone resorption (width of the socket) at 6 mm sub-crestally was 0.29 mm in the test group, and 1.22 mm in the control group (Table 2).

DISCUSSION

Many external and internal changes of the socket take place after extraction, for this reason, maintaining suitable alveolar ridge volume is mandatory for successful implant treatment [23]. The process of alveolar ridge preservation includes many techniques aimed to reduce soft and hard tissue dimensional changes after extraction [6]. A recent study hypothesized that L-PRF membranes may have the capacity to stop the catabolic process caused by osteoclastic activity [24]. The use of PRF matrices in many studies has showed promising results regarding the ridge preservation [25]. A recent systematic review compared using L-PRF with natural healing in extraction sockets, and showed decreased alveolar ridge re-modeling and reduced post-operative pain in L-PRF group [26]. Another study revealed that even though the new generations of PRF failed to reduce dimensional changes in multiple extractions, they showed significant radiographic superiority for socket fill [21]. Temmerman *et al.* [22] reported that, in horizontal dimension, the mean change at 1 mm sub-crestal was 1.4 mm for L-PRF group, and 5.0 mm for control group.

In the present study, symmetrical extraction was performed in premolars region with application of L-PRF clot compared with unassisted healing in a split-mouth design. Patients who participated in this study were planned to receive implant therapy.

The measurements of width and height of the socket were measured immediately after the extraction, and follow-up analyses were performed 4 months post-treatment.

In the CBCT analysis, significant statistical differences in favor of the L-PRF group were found in the reduction of vertical bone resorption (height of the socket) both buccally and lingually, except at the crest of the socket (Table 1).

The conducted study showed the mean vertical loss of buccal bone of 0.46 mm in the L-PRF group, while the control group showed the mean of 1.65 mm of vertical buccal bone loss. The mean vertical loss of lingual bone was 0.52 mm in the L-PRF group, while the control group showed the mean of 1.92 mm of vertical lingual bone loss.

Evaluation of dimensional changes in the width of the alveolar bone showed the mean horizontal bone loss at the crest of the socket in the L-PRF group of 1.31 mm, while the control group showed the mean value of 2.17 mm of horizontal crestal bone loss. The mean horizontal bone loss 6 mm sub-crestally was 0.29 mm in the L-PRF group, while the control group showed the mean value of 1.22 mm of horizontal bone loss.

A recent study evaluating post-extraction dimensional changes using CBCT analysis showed that mean loss of alveolar bone height was 1.79 mm for PRF group, and 1.98 mm for non-PRF group. The same study demonstrated that mean loss of alveolar bone width was 1.49 mm for PRF group, and 1.85 mm for non-PRF group [27]. Results of previously conducted studies [21, 22] are considered close to the results of the present study. This coincidence may be attributed to the employment of PRF matrices, which stimulate the cells to differentiate faster and to produce new bony tissue that lead to a reduction of transverse atrophy in alveolar bone with continued release of five most important growth factors for up to 14 days [28].

A very recent study performed on alveolar ridge preservation using L-PRF compared with unassisted healing showed that L-PRF group had a higher concentration of growth factor, but such an increased concentration did not translate into clinical differences. The results of this study were based on a difference in the width of the socket only without considering the height of the socket [29].

Another split-mouth randomized controlled trial concluded that no differences were found in three dimensional alveolar ridge preservation between L-PRF group and normal healing group. This study was performed on upper third molars only, and can be assumed that the role of L-PRF could vary when applied into areas of low-bone quality [30].

A distinct case report performed alveolar ridge preservation using L-PRF compared with natural heal-

ing, and found that there was a histological difference between grafted site compared with non-grafted one, with the grafted site showing better bone quality. In this study, biopsies were taken from premolar regions [31].

In the current study, the most noted disadvantages were the need of specialized centrifuge in the dental facility, and the prolonged time of preparation compared with traditional ready-made bone granules.

CONCLUSIONS

On the present study, the L-PRF group showed significant superiority of alveolar ridge preservation both horizontally and vertically compared with unassisted socket healing.

CONFLICT OF INTEREST

The authors declare no potential conflict of interests with respect to the authorship and/or publication of this article.

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