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Review Article

The Use of Platelet-Rich Fibrin in Maxillary Sinus Augmentation: A Review of the Literature

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Abstract

The aim of this study was to review the literature on the use of Platelet-Rich Fibrin (PRF) in maxillary sinus augmentation. PRF as sole grafting material or combined with osseous graft are options in sinus augmentation, though insufficiently documented. In crestal sinus augmentation, PRF leads to acceptable outcomes close to those achieved with blood clotting. In lateral one-stage sinus augmentation, PRF alone has limited space maintenance and scaffolding effect. In lateral two-stage sinus augmentation, PRF combined to osseous graft as compared to osseous graft leads to at least similar new bone formation and to acceleration of the bone formation process. Similarly, acceleration of the bone forming process was documented with PRF as compared to osseous graft in lateral two-stage sinus augmentation. The addition of PRF to the osseous graft in lateral two-stage sinus augmentation is not justified concerning the amount of new bone, though it might be considered for earlier implant placement. There are indications of higher new bone formation and closer bone to bone substitute contact with the combined PRF/osseous graft than the osseous graft. Clear superiority of the combined PRF/osseous graft has not been proved yet. Further well designed controlled trials are required to draw firm conclusions.

Keywords: Autologous platelet concentrates; Maxillary sinus augmentation; Platelet-rich plasma; Regeneration; Osseous graft; Sinus lift

Introduction

Maxillary sinus augmentation (or sinus augmentation or sinus lift) was first introduced in the early 1980's by Boyne and James with the lateral window approach to the maxillary sinus augmentation (or lateral maxillary sinus augmentation), where autogenous osseous graft was used [1]. Then the transalveolar approach to maxillary sinus augmentation (or transcrestal approach to maxillary sinus augmentation or alveolar maxillary sinus augmentation or crestal maxillary sinus augmentation) was described by Tatum Jr[2], which was later modified by Summers [3]. Since then several modifications of the initially described techniques have been reported and various grafting materials have been tested, such as autogenous grafts (or autografts), allogenic grafts (or allografts), heterogenous grafts (or xenografts), alloplastic grafts, titanium granules, Autogenous Platelet Concentrates (APCs) and combinations of more than one grafting materials [4,5]. Moreover, sinus augmentation without any grafting material has been described both for the crestal [6] and lateral techniques [7].

Platelet concentrates are classified into four categories based on their leucocyte and fibrin content: pure platelet-rich plasma (P-PRP), leucocyte- and platelet-rich plasma (L-PRP), pure platelet-rich fibrin (P-PRF), and leucocyte- and platelet-rich fibrin (L-PRF) [8]. The various types of APCs differ in preparation protocol, content, physical and biologic characteristics. L-PRF membranes in vitro slowly release significantly larger amounts of Transforming Growth Factor β1 (TGFβ1), Platelet-Derived Growth Factor AB (PDGF-AB), Vascular Endothelial Growth Factor (VEGF) and matrix proteins (fibronectin, vitronectin and thrombospondin-1) as compared to the P-PRP gel membranes, and the release patterns differ between the two membranes [9]. The polymerization and final architecture of the fibrin matrix affect the strength and the growth factor release potential of the membrane [9]. Parameters concerning the characteristics of the centrifuge used for the preparation and the centrifugation protocol significantly affect the cells, growth factors and fibrin architecture of L-PRF [10].

PRF has been studied in both crestal [11-18] and lateral [15-17,19-34] sinus augmentation either alone [11-13,15-17,20,21,24,29,34] or in combination with other grafting materials [19,22,23,25-28,30-32].

The application of PRF in crestal sinus augmentation has been studied in prospective, [11-13,17] retrospective [16] and case report [14,15,18] studies. Several randomized controlled trials have evaluated PRF in lateral sinus augmentation [22,23,26,27,31,32].

In terms of lateral sinus augmentation, PRF has been applied in the one-stage technique (lateral one-stage sinus augmentation), where implants were placed simultaneously to the sinus augmentation, [16,17,20,21,24,28-30,33] as well as in the two-stage technique (lateral two-stage sinus augmentation), where implants were placed several months later [15,16,19,22,23,25-27,31,32].

When combined with osseous grafts in lateral sinus augmentation, PRF has been studied with allograft, [19,31] xenograft, specifically deproteinized bovine bone mineral (DBBM) [22,23,25,27,28,30,32] and alloplastic graft [26].

The outcomes of the studies on PRF use in sinus augmentation have been evaluated by the following methods.

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1. Clinically with the % of postoperative complications, the % of implant failures, and the implant stability (measured with resonance frequency analysis in implant stability quotient values, ISQ) [11-13,16,17,20-33].

2. Radiographically [11-13,16,17,20-25,27-35] by using panorex, [13,20-25,27,30,33,35] periapicals, [11,12,21,30] Computed Tomography (CT), [13,16,21,23,24,31,34] Cone Beam Computed Tomography (CBCT) [17,28,29,32] and three-dimensional Volumetric Computed Tomography (VCT) [20,21] and by measuring bone height gain, [11,12,13,16,17,20,21,24,25,28-31,33,34] bone density [22-24,27,31,34] and bone volume [24,31,32].

3. Histologically and histomorphometrically [19,20,23,25-27,31,32]by assessing the % of newly formed bone, [19,20,22,23,25-27,31,32,35] the % of residual bone substitute, [25-27,32] the % of soft tissues [25-27,32] and the contact length between newly formed bone and bone substitute [22].

In terms of the use of PRF in sinus augmentation, central questions are: "Is PRF as sole grafting material successful in crestal and lateral sinus augmentation?", "Is PRF as sole grafting material superior to blood clotting alone in crestal and lateral sinus augmentation?", "Is the addition of PRF to osseous graft beneficial in lateral sinus augmentation?", "When PRF is used as sole grafting material in lateral sinus augmentation, is it preferable to place the implants simultaneously or at a later time?" The present review provides answers to these questions. Therefore, the aim of the present study was to thoroughly review the literature on the use of PRF in sinus augmentation.

Crestal approach to sinus augmentation

In terms of the crestal approach to (or crestal) sinus augmentation, PRF has been used: (1) as a membrane (PRF membrane) to cover the Schneiderian (or sinus) membrane, [11-13,16,17] where the use of one, two, [13,36] three [11] or more [11,12,16,17] membranes has been reported and (2) as a filling material in PRF clot (or plug) form [12]. For the crestal sinus augmentation, PRF has been studied as a sole grafting material without being combined with other materials.

In one of the first of these prospective studies, the crestal sinus augmentation with PRF membranes, where the subsinus bone height immediately after implant placement was 6.5±1.7 mm, led to endosinus bone height gain of 3.2±1.5 mm and to the formation of a new distinct bone structure bordering the sinus floor at 12 months, as assessed by digitized non-standardized periapical radiographs. It was suggested that PRF membranes used as a sole grafting material in the crestal sinus augmentation can create a space for bone formation beyond the sinus floor and lead to predictable endosinus bone gain [11].

Then, a prospective study evaluated radiographically the crestal sinus augmentation in cases with mean preoperative bone height of 6.6 mm by using PRF membranes or PRF plugs for grafting. Six different implant systems were used. The mean gain in bone height was 3.4 mm, as assessed with periapicals. The authors concluded that this technique is safe and highly successful at sites with bone height 5-8 mm [12].

Later, another prospective study evaluated radiographically (with panorex and CT) crestal sinus augmentation with PRF membranes as grafting material used in cases with preoperative bone height <5 mm. Two types of implants were tested: Hydroxyapatite (HA) and Sandblasted Acid-etched (SA) implants. At one year, the bone height gain was 4.38 and 4.00 mm in the SA and HA groups, respectively [13].

A recent single cohort prospective study evaluated radiographically the use of L-PRF membrane in the crestal sinus augmentation in sites with bone height of 6.2±1.5 mm and found that at six months the bone height gain was 3.4±1.2 mm, as assessed by CBCT [17].

A very recent systematic review [37] concluded that the existing evidence is not strong enough to make firm conclusions on the beneficial effects of the sole use of platelet concentrates in sinus augmentation. Though, their analysis on the sole use of platelet concentrates included studies both on crestal and lateral one-stage sinus augmentation without subclassifying them.

The existing data indicate that the application of PRF as sole grafting material in crestal sinus augmentation can lead to an average of 3 mm gain in bone height. Though, there are no controlled clinical studies comparing PRF alone to blood clot alone and/or to osseous grafts. When blood clot alone was compared to DBBM in crestal sinus augmentation, it was found that the bone height gain was 1.7+2 mm for the former and 4.1+2.4 mm for the latter, their difference was statistically significant and the osseous graft almost doubled the probability of bone gain ≥2 mm [6]. Results on the sole use of PRF in crestal sinus augmentation should be interpreted with caution until randomized controlled trials comparing PRF to other techniques are published. The available data show PRF might be considered as a viable option for crestal sinus augmentation but do not allow to draw conclusions on whether PRF is equivalent to other techniques. Taking into consideration that the addition of an osseous graft to the osteotome-mediated sinus augmentation improves the outcomes [6] it is imperative to have well designed controlled trials for solid conclusions on PRF. The high content in growth factors together with the gelatinous consistency that helps to gently press the sinus membrane and raise it make PRF a promising grafting material for crestal sinus augmentation, especially in cases where the desired sinus lift is small.

Lateral approach to sinus augmentation

In terms of the lateral sinus augmentation, PRF has been used:

1. To fill the area below the raised sinus membrane either as a sole grafting material or in combination to osseous grafts, [26,27,29-32]

2. As a barrier membrane to cover the lateral osteotomy window, [38]

3. As a membrane to cover the perforated sinus membrane [39] and (4) in combination of more than one of the above [16,17,19-25,28,33,34].

Lateral one-stage sinus augmentation

PRF as sole grafting material in lateral one-stage sinus augmentation: Several studies in humans [17,20,21,24,29,33] and one experimental study [40] have evaluated PRF as sole grafting material in lateral one-stage sinus augmentation. The experimental study explored PRF alone in lateral one-stage sinus augmentation

in dogs, where one implant was placed per sinus so that the implant was introduced into the sinus by 6 mm [40]. At six months, the level of the sinus was not maintained as compared to immediately postoperatively (with CT), the sinus membrane had fallen down onto the implant, bone-like tissue had formed around the implants and the part of the implants introduced into the sinus was not fully covered with bone. The membrane collapse was mainly attributed to the following. PRF did not maintain the space created long enough for new bone to form since it rapidly resorbs [8,10,41]. Moreover, the air pressure in the sinus helped the membrane to fall and reduced the space initially created. Finally, the limited number of implants (one) per sinus did not create sufficient tenting effect. More implants per sinus site would help the tenting effect. The authors concluded that in lateral one-stage sinus augmentation with PRF alone predicting the height of the new bone that would form was not possible, especially around the implants [40].

In humans, the use of PRF as sole grafting material in the lateral one-stage sinus augmentation was initially assessed in two case series, where PRF membranes covered the sinus membrane and the lateral osteotomy window, PRF clots filled the sinus cavity and implants (of more than one implant systems) were placed simultaneously [20,21]. The preoperative bone height was 2.9±0.9 mm in the first [20] and 1.8±0.5 mm in the second [21] study. At 6 months, the radiographic gain in bone height was 10.1±0.9 mm [20] and 10.4±1.2 mm, [21] respectively. The final level of the sinus floor was in continuation with the implant apical end [20,21]. At 6 months, all implants were clinically stable and all biopsies showed well organized and vital bone [20].It was suggested that PRF as sole grafting material is an option for lateral one-stage sinus augmentation [20].

A prospective study evaluated PRF clots as sole grafting material in lateral one-stage sinus augmentation in nine sinuses with bone height 4.28±1.00 mm and bone width 7.46±1.15 mm. At six months, the new bone had height 7.5 mm, volume 0.70±0.31 mL and density 323±156.2 Hounsfield units (HU), as assessed by CT [24].

In a single cohort prospective study six cases of lateral one-stage sinus augmentation, where the bone height was 4.6±1.8 mm, were managed with L-PRF membrane alone for sinus membrane coverage, sinus grafting and lateral osteotomy window coverage. At six months, the bone height gain was 5.4±1.5 mm, as assessed by CBCT [17]. Though, the number of cases was very limited which affects the interpretation of the results.

A recent split-mouth trial compared with CBCT PRF as a sole grafting material to no grafting in lateral one-stage sinus augmentation in non-smokers with bone height 4-8mm [29]. For both groups, preoperative bone height was similar, same type 11.5 mm long implants were placed and lateral osteotomy window was covered by collagen membrane. At six months, there was statistically significant bone height gain for both groups (4.86 and 3.61 mm for PRF and ungrafted group, respectively), the bone height gain and bone density were statistically significantly higher for the PRF as compared to the ungrafted group (by 1.42 mm and 52.85 units, respectively). The authors concluded that for the lateral one-stage sinus augmentation in cases of bone height ≥4 mm, grafting with PRF alone had beneficial effects in terms of bone height gain and bone density increase as compared to non-grafting [29].

The effect of collagen plugs used as carriers for injectable PRF (i-PRF) (or i-PRF–soaked collagen plugs) in lateral one-stage sinus augmentation was evaluated with panoramic radiography in a recent retrospective pilot study [33]. Bone height gain of 6.3±1.3mm was reported at 6 months. Though, these positive results should be interpreted with caution due to the small number of cases studied and the radiographic technique selected for the evaluation.

The available data in humans show that PRF as sole grafting material is an option in the lateral one-stage sinus augmentation but do not allow comparisons to osseous grafts or to non-grafting. Randomized controlled trials comparing PRF alone to other techniques are required to fully evaluate the effect of PRF as sole grafting material in the lateral one-stage sinus augmentation. There is no doubt that the high regenerative potential of PRF is advantageous. It seems that the clinician's main concern is whether PRF alone can maintain the space created for regeneration long enough for the bone formation to occur. It takes long for new bone to form whereas PRF resorbs quickly [8,10,41]. This entails the risk of partial sinus membrane collapse and reduction of the space available for regeneration resulting in less sinus augmentation than initially anticipated. The attempted lift of the sinus membrane is greater with the lateral than crestal approach to sinus augmentation. Therefore, PRF grafting should raise the sinus membrane more in the lateral than crestal approach and maintain it there for long. When DBBM was compared to non-grafting in a randomized controlled trial on lateral one-stage sinus augmentation, it was found at six months that both techniques were considered reliable but DBBM was statistically significantly superior in bone height gain (8.59 ± 0.74 vs 4.85 ± 0.5 mm) and bone density, as assessed with CBCT [42]. This finding raises more concerns on the space-making and space-maintaining ability of PRF alone in the lateral one stage sinus augmentation.

PRF combined with osseous graft in lateral one-stage sinus augmentation: A case series study evaluated with CBCT the combination of PRF (in clots) and DBBM in lateral one-stage sinus augmentation in sites with bone height 4-5 mm [28]. PRF membrane covered the lateral osteotomy window and the sinus membrane in case of perforation. At six months, the bone height gain was 10.12 mm. The outcome was not affected by sinus membrane perforation. The authors concluded that the lateral one-stage sinus augmentation using a combination of DBBM and PRF clot as grafting material and PRF membrane as barrier membrane seems to be effective and predictable in augmenting posterior maxillary sites of 4-5 mm bone height [28]. Another case series of similar design, where the bone height was 3-5 mm, showed that at 12 months the bone height gain was 7 mm, as assessed by periapical and panoramic radiographs [30].

An experimental study compared histologically the combination of PRF and DBBM to the combination of commercial fibrin and DBBM in lateral one-stage sinus augmentation and found that at six months the combined PRF/DBBM graft led to statistically significantly higher bone formation and bone-implant contact than the combination of commercial fibrin and DBBM [43].

It seems that the combination of PRF and DBBM is a viable option for lateral one-stage sinus augmentation, though the available data is insufficient to draw safe conclusions. Randomized controlled trials are lacking. Moreover, there is no information on other types of

osseous grafts. One might speculate that the combination of PRF and DBBM over PRF alone might be advantageous in space maintenance, since DBBM resorbs slowly. Though, there are no direct comparisons between PRF with and without DBBM.

Lateral two-stage sinus augmentation

PRF alone compared to osseous graft in lateral two-stage sinus augmentation:A randomized controlled trial compared clinically, radiographically and histomorphometrically in non-smokers titanium-prepared PRF (T-PRF) and allograft in lateral two-stage sinus augmentation in sites with bone height <5 mm [31]. For both groups, collagen membrane covered the lateral osteotomy window. After sinus augmentation, at four and six months in the T-PRF and allograft groups, respectively, CT and bone biopsies were performed and implants were placed. At three months after implantation implant stability was assessed. The two groups did not statistically significantly differ in the % of newly formed bone, as assessed histomorphometrically, and in implant stability, as measured in ISQ values. Though, for the T-PRF as compared histomorphometrically to the allograft group the % of newly formed bone was non-statistically significantly lower and the % of cancellous bone ratio was non-statistically significantly higher. The allograft group had statistically significantly better bone volume (by 53%), bone density (by 86%) and bone height (by 69%) compared to the T-PRF group, as assessed by CT. It seems that T-PRF alone was successful in lateral two-stage sinus augmentation. The T-PRF outcome at four months as compared to the allograft outcome at six months was histomorphometrically similar and radiographically statistically significantly inferior in bone volume, height and density [31]. Bone formation was accelerated in the T-PRF group as compared histomorphometrically to the allograft group.

Comparison between DBBM and PRF as grafting materials in lateral two-stage sinus augmentation in sites with bone height <4 mm, where the lateral osteotomy window was covered by collagen and PRF membrane respectively, showed at three months statistically significantly higher augmented bone height and bone density for the DBBM than PRF group, as assessed by CT [34].

An experimental study in sheep compared histologically and histomorphometrically PRF membrane grafting to the combination of DMMB and autograft in a ratio 1:1 in lateral two-stage sinus augmentation at three, six and nine months [44]. Collagen membranes covered the lateral osteotomy window in both treatment groups. At three months, there was new bone formation for the combined DMMB/autograft group only. At six months, there was new bone formation in both groups. At nine months, the new bone could no more be distinguished from the pristine bone in the combined DMMB/autograft group, whereas new bone formation was in process in the PRF group. PRF remnants were found both at six and nine months. These experimental results indicated that the regeneration potential of PRF membrane was slower than that of the combined DBBM/autograft as grafting material for lateral two-stage maxillary sinus augmentation [44].

Histologic and histomorphometric data in animals [44] and humans [31] show that PRF as sole grafting material in lateral two-stage sinus augmentation leads to significant new bone formation. Moreover, radiographic data in humans show that PRF as sole grafting material in lateral two-stage sinus augmentation leads to significant increase in bone height and volume [31]. Therefore, the sole use of PRF for grafting is a viable option in lateral two-stage sinus augmentation. Data from a randomized controlled trial on lateral two-stage sinus augmentation show that PRF as compared to osseous graft accelerates the process of new bone formation and achieves earlier bone formation, though the increase achieved is statistically significantly less in height and volume [31]. It seems that in lateral two-stage sinus augmentation, with PRF alone, as compared to osseous graft, bone is formed sooner but the augmented sinus is shorter and smaller. This means that the sufficient scaffolding effect of PRF in lateral two-stage sinus augmentation is questioned. It should be taken into consideration that these results were achieved with T-PRF, which is a modification of PRF [31]. We assume that PRF acts in a similar way to T-PRF. Though, conclusions on PRF can not be drawn without testing it. In order to draw conclusions on the sole use of PRF in lateral two-stage sinus augmentation there is need for randomized controlled trials on PRF as compared to non-grafting and to osseous grafts.

PRF and osseous graft compared to osseous graft alone in lateral two-stage sinus augmentation: The addition of PRF to an osseous graft as compared to the osseous graft alone in the lateral two-stage sinus augmentation has been studied in randomized controlled trials [22,23,26,27,32] and retrospective studies [19,25]. The combination of PRF to an osseous graft as compared to the osseous graft alone in the lateral two-stage sinus augmentation has been tested for allografts, [19] xenografts [22,23,25,27,32] and alloplastic grafts [26].

Choukroun et al. [19] first addressed the possible beneficial effect of the addition of PRF to osseous grafts in lateral two-stage sinus augmentation. In a preliminary retrospective study, they compared histologically and histomorphometrically PRF combined with freeze-dried bone allograft (FDBA) to FDBA alone. The histomorphometric results of the combined PRF/FDBA group after four months of healing appeared equivalent to those of the FDBA group after eight months of healing. Moreover, the % of newly formed bone was the same for both groups. The addition of PRF to FDBA accelerated the healing process, achieved earlier tissue maturation and therefore led to a reduction of healing time (by half) prior to implant placement. These results were encouranging and promising for successful earlier implantation after lateral two-stage sinus augmentation. Though, the very limited number of cases analyzed in this study underlined that further investigation was required to draw conclusions. Choukroun et al. [45] suggested that the role of PRF in the combined PRF/osseous graft material is that of a matrix that allows neo-angiogenesis, stem cell retention and migration of osteoprogenitor cells.

Zhang et al. [22] in a randomized controlled trial compared histologically and histomorphometrically the combination of DBBM and L-PRF to that of DBBM alone for the purpose of lateral two-stage sinus augmentation, in sites with bone height <5mm. The lateral osteotomy window was covered by L-PRF membrane for the combined graft group, whereas it was left with no membrane in the DBBM group. At six months, the combined L-PRF/DBBM graft group as compared to the DBBM group presented non-statistically significantly higher % of newly formed bone (by 1.4 times), non-statistically significantly lower % of residual bone substitute (by 1.5 times) and non-statistically significantly higher % of contact length

between newly formed bone and bone substitute. The authors of this study concluded that the addition of L-PRF to DBBM in lateral two-stage sinus augmentation in sites with bone height <5mm did not statistically significantly affect the six-month outcome achieved with DBBM alone, as assessed histomorphometrically. This study showed that the combination of L-PRF and DBBM is effective in lateral two-stage sinus augmentation reaching to histomorphometric outcomes similar to those of DBBM alone. Though the absence of statistically significant benefit with the addition of L-PRF to the xenograft, there was a non-statistically significant trend for better histomorphometric results as expressed with more bone formation, less residual bone substitute and closer contact between new bone and bone substitute [22].

Soon after, another randomized controlled trial by Tatullo et al. [23] evaluated clinically and histologically the addition of PRF to DBBM in the lateral two-stage sinus augmentation in non-smokers with bone height < 5mm. For the combined graft group, two masses of amorphous PRF were placed at the sinus base, then PRF clots mixed with DBBM were placed in the subsinus cavity and two PRF membranes were placed over the lateral osteotomy window below the bone window cover. For the DBBM group, the subsinus cavity was filled with graft. For each treatment group, there were three subgroups based on implant placement time, specifically early (at 106 days post sinus augmentation), intermediate (at 120 days) and late (at 150 days) implantation protocol. Primary implant stability (in ISQ values) was similar for both treatment groups at all implant placement times. Histologic evaluation of bone samples from the PRF/DBBM sites at 106 days post-augmentation, revealed "lamellar bone tissue with acellular osteocyte lacunae and an intensely-eosinophilic bone matrix mixed with fragments of lamellar bone tissue with inhabited osteocyte lacunae and a slightly-eosinophilic bone matrix". Thus, there was "lamellar bone tissue with an interposed stroma that appeared relaxed and richly vascularized". Histologic evaluation of bone samples from the DBBM sites at 106 days post-augmentation, revealed "trabeculae of lamellar bone tissue with inhabited osteocyte lacunae, immersed in a dense poorly-cellular fibrous stroma, in which were included fragments of lamellar bone with empty osteocyte lacunae and with an intensely-eosinophilic bone matrix". Histologic evaluation of bone samples from the PRF/DBBM sites at 120 days post-augmentation, showed "lamellar bone tissue with inhabited osteocyte lacunae, delimited by osteoblasts. The interposed stroma was relaxed and richly vascularized by capillary vessels." Histologic evaluation of bone samples from the PRF/DBBM sites at 150 days post-augmentation, showed "the presence of trabeculae of mature lamellar bone in a relaxed and richly vascularized stroma." It seems that the addition of PRF to DBBM accelerated the healing process and therefore reduced the healing time, favoring bone formation. The histologic and histomorphometric data showed that the PRF enhanced the production of new bone as early as 3.5 months post-augmentation surgery. The increased neoangiogenesis seen in the samples from the combined graft group provided ample blood supply to the newly-formed bone. This reduced the non-vital bone areas as compared to the DBBM group [23].

Later, a randomized controlled trial by Nizam et al. [27] evaluated radiographically, histologically and histometrically in non-smokers the addition of PRF to DBBM in lateral two-stage sinus augmentation in sites with bone height <5 mm. At the lateral osteotomy window in both treatment groups, collagen membrane covered the repositioned osseous wall. At six months, there was no qualitative difference in histologic analyses between the treatment groups. Newly formed bone was in direct contact with the residual grafting material in all samples. The % of newly formed bone, residual bone graft, bone graft in contact with the newly formed bone and soft tissue were similar for both groups. At six months, the radiographic subsinus bone height was similar for both groups. PRF combined with DBBM was successful in lateral two-stage maxillary sinus augmentation. The addition of PRF to DBBM did not significantly improve the amount of regenerated bone or the amount of the xenograft integrated into the newly formed bone, as assessed at six months. Though, the similarity in bone substitute volume per tissue volume at six months for both groups showed that the addition of PRF to DBBM did not significantly affect the resorption of DBBM up to the sixth month [27].

A relatively recent randomized controlled trial by Pichotano et al. [32] evaluated in non-smokers (with bone height <4 mm) the possible impact of the addition of L-PRF to DBBM for early implant placement after lateral sinus augmentation. Sinus augmentation was performed either with DBBM alone or combined L-PRF/DBBM, where PRF membrane fragments were mixed with DBBM. Collagen membrane covered all lateral osteotomy windows. Then implants of same type, length and diameter were placed at four and eight months postoperatively for the L-PRF/DBBM and DBBM group, respectively. Each site was subjected to CBCT prior to sinus augmentation, immediately after it and prior to implantation (four and eight months postoperatively for the L-PRF/DBBM and DBBM group, respectively). Both procedures were effective for sinus augmentation. Graft volume did not significantly differ between groups at any time point (prior to sinus lift, immediately after it, at implantation), as evaluated by CBCT. For both groups, graft volume was significantly reduced at implantation as compared to immediately post-augmentation. At implantation, ISQ values were significantly higher for DBBM than L-PRF/DBBM group, whereas at implant loading they were similar for both groups. At implantation, the histologic and histometric analysis showed that the L-PRF/DBBM group as compared to DBBM group presented significantly higher % of newly formed bone and significantly lower % of residual graft. These findings suggested that augmenting the sinus with the combined L-PRF/DBBM graft led to higher new bone formation at four months as compared to that achieved by DBBM alone at eight months. Thus, the composite L-PRF/DBBM graft allowed early implant placement, at four months post sinus augmentation. The authors of the study suggested that the significantly lower % of residual graft at implantation for the combined than the DBBM graft might imply earlier maturation of the graft which might affect the healing time [32].

A retrospective study in non-smokers compared clinically, radiographically and histologically the addition of PRF to DBBM in lateral two-stage sinus augmentation in sites with bone height <5 mm [25]. For the combined graft group, PRF membrane covered the sinus membrane, DBBM/PRF mixed in 1:2 ratios filled the subsinus cavity and PRF membrane covered the lateral osteotomy window. Collagen membrane covered the lateral osteotomy window in the DBBM group. At six months (implantation time), the two groups did

not statistically significantly differ histologically in the % of areas of newly formed bone, residual bone-substitute and connective tissue. For both groups, the bone-substitute remnants were surrounded by mineralized trabecular structures of newly formed bone and connective tissue consisting of fibroblasts, collagen fibers, and blood vessels. Vascularity and inflammation level were similar for both groups. These findings indicated similar rate and amount of new bone formation at six months for both groups. Moreover, at 24 months after implant loading the radiographic sinus floor level was above the original sinus height for both groups, as assessed in panoramic radiographs. Based on the histologic findings, it was suggested that the combined DBBM/PRF graft together with PRF membrane might be a successful alternative to the combination of DBBM and collagen membrane for the lateral two-stage sinus augmentation in non-smokers.

A randomized controlled clinical trial by Comert et al. [26] compared histologically and histomorhometrically PRF combined with β-tricalcium phosphate (β-TCP), PRP combined with β-TCP and β-TCP alone in lateral two-stage sinus augmentation in sites with bone height up to 7 mm. Collagen membrane covered all lateral osteotomy windows. At six months, all groups showed similar composition and distribution of histologic structures since the % of new bone formation, residual graft particle area and soft tissue area did not statistically significantly differ among groups. Osteoblast, osteoclast, osteocyte, and capillary vessel contents were similar among groups. PRF/β-TCP group presented significantly lower osteoprogenitor cell content and significantly higher inflammatory cell content as compared to the other groups. These findings suggested that the addition of either PRF or PRP to β-TCP did not further enhance new bone formation in lateral two-stage sinus augmentation [26].

Randomized controlled trials [22,23,26,27,32] and retrospective studies [19,25] have showed that the combination of PRF to osseous grafts is effective in lateral two-stage sinus augmentation. It seems that it is an alternative option to osseous grafting alone for lateral two-stage sinus augmentation[19,22,23,25-27,32]. Based on histologic evaluation, the final outcome of the lateral two-stage sinus augmentation is similar for the combined PRF/osseous graft material and the osseous graft alone in most studies[22,25-27]. However, superior histologic outcome in terms of bone formation has been reported for the combined PRF/osseous graft over the osseous graft alone in two randomized controlled trials [22,32] with one study reaching statistical significance [32] and the other not reaching it [22]. Therefore, the addition of PRF to osseous graft did not significantly quantitatively enhance new bone formation in lateral two-stage sinus augmentation in all the studies, except for one [32]. Moreover, there are non-statistically significant indications that the addition of PRF to the osseous graft leads to longer contact length between new bone and bone substitute [22]. The % of residual bone substitute was reduced by the addition of PRF to the graft in two studies, [22,32] where statistical significance was reached in only one of them [32]. Accelerated healing of the bone formation process was histologically found in two randomized controlled trials [23,32] and one retrospective study [19] on lateral two-stage sinus augmentation, which might be beneficial for earlier implant placement. Overall, the prevailing data show that the addition of PRF to osseous graft in lateral two-stage sinus augmentation does not enhance the amount of new bone formed with osseous graft alone but it seems that it accelerates the process of bone formation leading to mature bone earlier.

PRF membrane coverage of the lateral osteotomy window: PRF membrane and collagen membrane have been compared as barrier membranes to cover the lateral osteotomy window in a randomized controlled trial involving sinuses (of bone height <5 mm) augmented with a combination of autograft and DBBM at ratio 1:1 [38]. At five months (implantation time), the groups did not statistically significantly differ in the % of vital bone formation and residual bone-substitute, as assessed histomorphometrically. Thus, this study showed that for the combined autograft/DBBM sinus augmentation the coverage of the lateral osteotomy window with either PRF or collagen membrane led to similar amount of vital bone formation and residual bone-substitute [38].

Placement of a PRF membrane on top of a collagen membrane covering the lateral osteotomy window has also been suggested [36].

PRF membrane coverage of the sinus membrane: An experimental study on the repair of the perforated maxillary sinus membrane found histologically in rabbits that there were no statistically significant differences between collagen and PRF membranes in the healing of the perforated sinus membrane [46].

For the lateral two-stage sinus augmentation with xenograft, the sinus lift outcome was retrospectively compared between a group of sinuses with non-perforated sinus membrane and a group of sinuses with perforated and PRF-managed membranes [39]. All lateral osteotomy windows were covered by collagen membrane. At six to eight months, the subsinus bone height gain did not statistically significantly differ between groups, as assessed with CBCT (11.18±1.2 mm for the non-perforated and 10.12±1.4 mm for the perforated group) and possible vasculogenesis was observed in both groups. Therefore, in case the sinus membrane gets perforated and then covered with PRF, the outcome of the lateral two-stage sinus augmentation is not negatively affected in terms of bone height gain [39].

Therefore, PRF membrane may be considered as an alternative option to collagen membrane in the management of sinus membrane perforations. The easiness in manipulation and the enhancement of healing make PRF a suitable material for this purpose. It has been suggested to cover the perforated sinus membrane with PRF membrane in case the perforation has a small diameter (<5 mm) [36]. The preventive use of PRF to reduce the risk of membrane perforation has been suggested as well [21].

Conclusion

It seems that using PRF alone in crestal sinus augmentation, using PRF alone or combined with osseous graft in lateral sinus augmentation are treatment options, though documentation is not sufficient. Among all PRF applications in sinus augmentation, the combination of PRF with osseous graft as compared to osseous graft in lateral two-stage sinus augmentation has been mostly documented.

In terms of crestal sinus augmentation, where limited augmentation is required, it seems that PRF can lead to acceptable outcomes close to those achieved with blood clotting alone, though direct comparisons are lacking. In terms of lateral one-stage sinus

augmentation, PRF as sole grafting material has limited space maintenance and scaffolding effect which is compensated by the tenting effect of the implants. Selecting PRF alone for lateral one-stage sinus augmentation raises several questions, since there are no comparisons to other techniques. On the other hand, grafting the sinus with PRF alone and placing the implants at a later time might lead to unsufficient increase of the dimensions of the sinus for the proper placement of the desired implants. With PRF-mediated lateral two-stage sinus augmentation the bone height gain is not predictable at all, since the tenting effect of the implants is missing and PRF has high resorption rate. It seems that the use of PRF alone should not be considered in the two-stage approach. Moreover, the dimensions of the sinus and the extent of the desired sinus lift might play a role in the decision to graft with PRF alone. A large sinus requiring major lift seems to be less successfully managed with PRF alone.

In terms of lateral two-stage sinus augmentation, the combination of PRF to osseous graft as compared to osseous graft alone leads to at least similar new bone formation and to acceleration of the bone formation process. Similarly, acceleration of the bone forming process was documented when PRF was used alone as compared to osseous graft in lateral two-stage sinus augmentation. The addition of PRF to the osseous graft in lateral two-stage sinus augmentation is not justified concerning the amount of new bone, though it might be considered in cases where placing the implants earlier is important. In cases where the implant placement can be postponed until new bone is formed and new bone gets mature undisturbed, the addition of PRF to the osseous graft in lateral sinus augmentation is not justified. Whenever acceleration of the healing process of the bone is a priority then adding PRF to the osseous graft might make a difference. Anyhow, achieving the desired bone formation at an earlier time is challenging for lateral two-stage sinus augmentation. Grafting with osseous graft alone and waiting for the proper time for new bone to form and mature prior to implantation might prove equivalent to adding PRF in lateral sinus augmentation. At this point it should be taken into consideration that there are indications that more new bone is formed with the combined PRF/osseous graft material as compared to osseous graft alone in lateral two-stage sinus augmentation. If this is so, then the combined graft would be superior to the osseous graft since it would lead to more new bone at an earlier time. Moreover, there are indications of closer contact between the new bone and the bone substitute for the PRF-containing graft over the PRF-free graft, which might prove to be advantageous for PRF. Further well designed controlled trials are required to draw firm conclusions. Future studies should focus on specific APCs not differing in preparation method and content, which might affect their potential. Finally, the PRF membrane is a successful method to manage the perforated sinus membrane and cover the lateral osteotomy window. In conclusion, it seems that PRF is a promising regenerative agent when combined with osseous graft in lateral two-stage sinus augmentation. Though, clear superiority of the combined PRF/osseous graft material has not been proved yet.

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