Original Article

Concentrated Growth Factors in Maxillary Sinus Floor Augmentation: A Preliminary Clinical Comparative Evaluation

Andrea Forabosco[1], Ezio Gheno[1,2], Sergio Spinato[1,3], Giovanna Garuti[1], Eleonora Forabosco[1], Ugo Consolo[1]

[1]Surgical, Medical and Dental Department of Morphological Sciences Related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio, Italy, [2]Faculty of Dentistry, School of Dental Health, BPP University, London, England, [3]Private Practice, Sassuolo, Italy

Abstract

Aims: The primary aim of this clinical study was to examine the effect of concentrated growth factors matrix (CGFm) on implant survival rate in augmented sinuses; the secondary aim was to evaluate the effect of CGFm on sinus augmentation postoperative morbidity. **Materials and Methods:** Fifty patients were selected from a pool of participants requiring maxillary sinus augmentation. Of these, 25 patients (control-group) received a corticocancellous xenograft. The other 25 patients (test group) received a mixture of 70% CGF matrix and 30% corticocancellous xenograft. Venous blood samples were drawn from each patient and immediately centrifuged. Four components were identified vertically from top to bottom: (1) An upper liquid phase constituted by serum; (2) a phase constituted by polymerized fibrin buffy coat; (3) a middle phase constituted by aggregated platelets with CGFs; and (4) a lower phase constituted by red blood cells. The middle (second and third) phases represented the CGFm and were mixed with the graft material. The survival rate was calculated and comparison was made between the 2 different groups using Kaplan–Meier analysis. Statistical significance was set at $P < 0.05$. **Results**: A 96.4% survival rate was described in the test group (with CGFm) and a 96.1% survival rate in the control group (without CGFm). No statistically significant differences were observed between the survival rates of the two groups after 1 year. **Conclusions**: The mixture of CGFm (70%) with xenograft (30%) is an alternative to xenograft material alone and is a predictable procedure resulting in less postoperative morbidity in sinus augmentation.

Keywords: Bone regeneration, concentrated growth factors, grafts, platelet-rich fibrin, sinus augmentation

Introduction

Postextraction bone resorption and pneumatization are common features in the posterior maxilla below the sinus cavity. These can determine both a quantitative reduction and qualitative worsening of bone that leads to inadequate bone dimensions for implant placement and subsequent prosthetic restoration. Boyne and James introduced maxillary sinus augmentation with lateral access to permit proper implant insertion into an atrophic maxillary posterior bone crest, approximately 40 years ago.[1] The sinus augmentation with lateral window technique has since been studied widely and presented as a safe and highly predictable regenerative treatment.[2-6]

Several materials have been utilized as graft for sinus augmentation procedures.[7]

Autogenous bone, from both intraoral and extraoral sources, was successfully used by many authors.[1,2] However, autogenous bone creates several complications including the creation of a second surgical site, consequent donor site morbidity, and long surgical times.[8] Sinus infections and rapid and unpredictable resorption can also occur when autogenous bone, obtained form iliac crest, ramus, or chin, is utilized as graft material[3,4,9] Many systematic literature reviews show that the exclusive use of autogenous bone does not improve augmented sinus implant survival rates.[3-6]

On the other hand, however, allograft, xenograft, and alloplastic materials have shown predictable and successful results.[5,10-13] Specifically, implants placed in augmented sinuses where a xenograft without autogenous bone was used revealed a survival rate of 96%.[4,5] When only autogenous bone is utilized, the survival rate falls to 92%.[4,5]

Address for correspondence: Prof. Giovanna Garuti, Via del Pozzo 71, Modena, Italy. E-mail: giovanna.garuti@unimore.it

Access this article online

Quick Response Code:

Website: www.cellsindentistry.org

DOI: 10.4103/GFSC.GFSC_6_18

How to cite this article: Forabosco A, Gheno E, Spinato S, Garuti G, Forabosco E, Consolo U. Concentrated growth factors in maxillary sinus floor augmentation: A preliminary clinical comparative evaluation. Int J Growth Factors Stem Cells Dent 2018;1:2-7.

Biological fundamentals of bone-healing processes have been analyzed in the last few years by focusing on growth factor (GF) activities, extracellular matrix, and stem cells.[14,15] These studies suggested that the combined use of GFs and graft materials may improve bone healing and bone regeneration.

Platelets are a natural source of GFs including platelet-derived GF (PDGF), transforming GF (TGF)-β1 and β2 (TGF-β2), fibroblast GF (FGF), vascular endothelial GF (VEGF), and the insulin-like GF (IGF) which stimulate cell proliferation, matrix remodelling, and angiogenesis.[16] The TGF-β family includes bone morphogenetic proteins which seem to be essential in bone tissue regeneration.[14,17]

In 1998, Marx *et al*. first described the local application of platelet-rich plasma (PRP) to obtain bone regeneration in oral and maxillofacial surgery.[18] Later, Anitua also used PRP to improve bone regeneration and enhance soft-tissue healing.[19] Although these authors[18,19] have showed some clinical advantages of PRP, the precise effect of PRP on bone regeneration remains unknown.

In fact, some authors demonstrated contradictory effects of PRP inducing cell proliferation and differentiation in some cases, but opposite actions in other cases.[20]

Due to the fact that most platelet concentrates show a fibrin glue-like consistency and rapid dissolution when applied, platelet-rich fibrin (PRF) has been proposed due to its solid consistency and high concentration of platelets, leukocytes, and GFs.[21]

In 2006, concentrated GFs (CGFs) were developed and produced by centrifuging blood samples with a particular centrifuge device allowing isolation of a larger, denser, and richer in GFs fibrin matrix.[22] A preliminary investigation showed that CGFs probably have excellent regenerative capacity in sinus augmentation.[23] Nevertheless, very limited clinical data are available on the CGF use in sinus and alveolar crest bone augmentation procedures.

Therefore, the primary aim of this clinical study was to examine the effect of concentrated GFs matrix (CGFm) on augmented sinus implant survival rates; the secondary aim was to evaluate the effect of CGFm on sinus augmentation postoperative morbidity.

Materials and Methods

Subject recruitment

The 50 patients enrolled in this clinical study were selected from a pool of participants requiring maxillary sinus augmentation for posterior implant placement and were examined and treated in three private dental offices by three independent operators.

All patients were partially or totally edentulous and required either a unilateral or bilateral maxillary sinus augmentation procedure using the lateral approach and concomitant implant placement. Additional inclusion criteria were <5 mm of crestal bone height of the sinus floor as measured on the serial section of the cone-beam computed tomography (CBCT); good general health; not heavy smokers (not more than 10 cigarettes per day); absence of disease affecting bone metabolism and wound healing; absence of disease-specific to and problems within the maxillary sinus; no medication consumption for at least 3 months; and no current bisphosphonate therapy. All patients signed informed consent, in which all procedures of the study were detailed according to the 2008 Helsinki Declaration[24] and to applicable Italian Law. Contrary to public and private health centers (DM 18/3/1998 published in the Official Gazette, GU n. 122 of 28-05-1998), Italian law does not require Ethical Committee Approval for clinical work performed in private dental offices, and therefore, no ethical committee resolution is released.

Suitable free software for research purposes (Random Allocation Software v. 2-http://random-allocation-software.software.informer.com/download) was used to randomly allocate patients to either the control or test group. Consequently, of 50 patients, 25 patients (control group) received a corticocancellous heterologous porcine bone graft (OsteoBiol, Gen-Os, Tecnoss®, Italy) consisting of 0.25–1.0 mm particles moistened by saline solution and 25 patients (test-group) received a mixture of 70% CGFm (obtained as described in the protocol below) and 30% corticocancellous heterologous porcine bone graft (OsteoBiol, Gen-Os, Tecnoss®, Italy) consisting of 0.25–1.0 mm particles.

Preparation of concentrated growth factors

Our protocol required that venous blood samples were obtained from the 25 patients who received the mixture of graft and CGF (test group). Blood was drawn from the patient using 2–8 sterile tubes (Vacuette 9 ml Z Serum Clot Activator, Greiner Bio-one, Austria) and immediately centrifuged (Medifuge, Silfradent srl, Forlì, Italy) for approximately 13 min. After the centrifuge process, in every tube, four components were easily identified vertically from top to bottom: (1) an upper liquid phase constituted by serum without fibrinogen and coagulation factors; (2) a phase constituted by large and dense polymerized fibrin buffy coat; (3) a middle phase constituted by aggregated platelets, white and stem cells, and containing CGFs; (4) a lower phase constituted by red blood cells[22] [Figure 1].

The first liquid phase was drawn by a pipette and then used for washing the surgical cavity immediately before graft placement.

The middle layers (the second and third phases) represented the CGFm and were easily separated from the lower phase using scissors and subsequently mixed with the graft material.

Surgical procedures

After clinical examination, a preoperative panoramic radiograph and a CBCT of the maxilla were taken for each patient.

Surgical sites were infiltrated by local anesthetic (Articaine hydrochloride – Ultracain, Sanofi-Aventis Deutschland GmbH, Frankfurt, 65926 Germany). A full-thickness flap was reflected

to expose the lateral wall of the sinus [Figure 2]. A traditional bony window osteotomy was performed [Figure 3]. The bony window was lifted, without removal, at first wall movement.

The Schneiderian membrane was then gently lifted using a broad curette. After elevation, the Schneiderian membrane was protected with an absorbable collagen membrane (OsteoBiol, Evolution, Tecnoss®, Italy).

In accordance with the random list allocation, after implant site preparation, partial sinus filling was performed using corticocancellous bone graft (OsteoBiol, Gen-Os, Tecnoss®, Italy) in 25 patients (control group). In the other 25 patients (test group), the mixture of CGFm (70%) and corticocancellous bone graft (30%) was used.

One to three implants per sinus were then placed (Immediateload SA, Lugano, Switzerland; Screw-Vent Zimmer Biomed, Carlsbad, CA, USA). In the absence of good primary stability, the implant was not placed.

After implant positioning, sinus filling was gently completed. Before soft-tissue closure, an absorbable collagen membrane (OsteoBiol, Evolution, Tecnoss®, Italy) was placed over the window, and the vestibular flap was repositioned using 4/0 sutures. All implants were submerged [Figures 4-6].

Patients were then treated with amoxicillin (Ratiopharm GmbH, Ulm, D89079 Germany), 1 g, twice a day for 6–7 days, and Synflex forte 550 mg (Recordati SpA, 20148 Milano, Italy) as analgesic after surgery. Postoperative pain and discomfort were assessed using an evaluation questionnaire immediately after surgery and 12 days later (when sutures were removed). Patients were directed to use a chlorhexidine mouthwash (0.12%), twice a day and not to brush the surgical sites for 2 weeks. Sutures were removed 10–12 days after surgery. Monthly follow-ups were scheduled to check for wound dehiscence.

The time between implant placement and exposure was approximately 4 months.

Depending on individual patient requirements, prosthetic rehabilitation was achieved using single crowns or fixed prostheses, following a delayed standard loading protocol. Clinical and radiographic evaluation with intraoral radiographs was performed at implant placement, at implant loading, and after 12 months.

At the 12-month clinical and radiographic examination, the standard of success for implant function established by Albrektsson *et al*.[25] was applied. Implants were also considered to have failed if bone loss greater than half the implant length was observed on radiographs or if the implant showed mobility.[26] Mobility was detected using the ends of two instruments, a technique commonly practiced in dentistry.

Statistical analysis

The sample size for one-way ANOVA with two groups, at 0.05 level and a power of 80% was calculated for each treatment group.

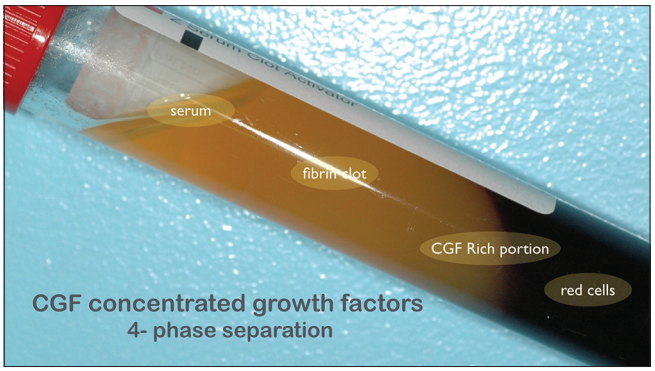

Figure 1: Blood sample after centrifugation. Four layers have been obtained

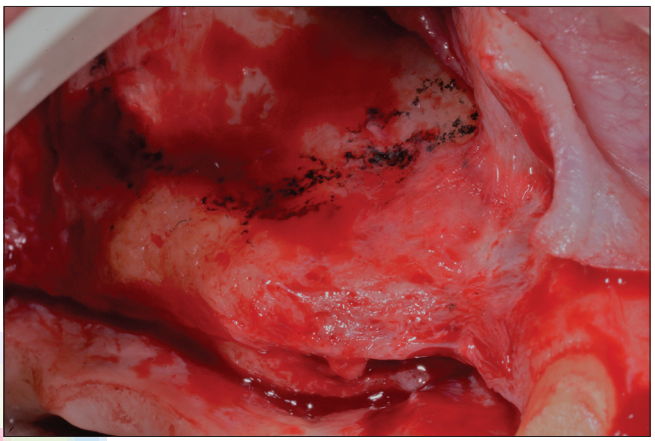

Figure 2: The full thickness flap opened

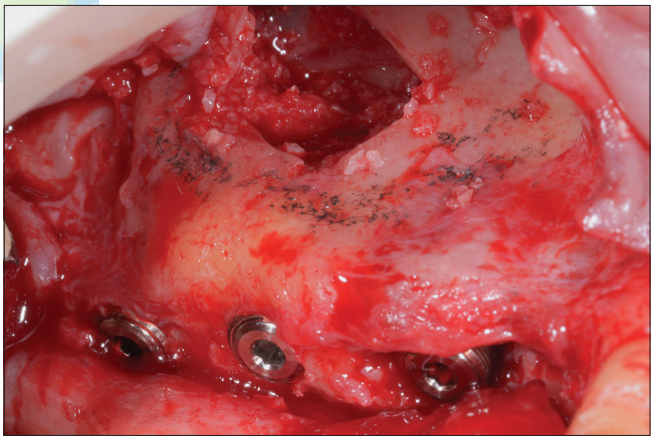

Figure 3: The initial phase of grafting procedure

Descriptive statistics concerning the patients' age, sex, and complication rates were performed considering the patient as the statistical unit of data analysis. Further analyses were carried out considering implants as the statistical units. Implant survival was expressed as the percentage of lost implants in relation to the total number of implants inserted.

The survival rate was calculated and comparison was made between the 2 different groups using Kaplan–Meier analysis.[27] Statistical significance was set at $P < 0.05$.

Results

Fifty patients, 32 females and 18 males, aged between 32 and 81 (mean age = 57.5 years) underwent unilateral (n = 45) or bilateral (n = 5) maxillary sinus augmentation with a total of 55 treated sinuses.

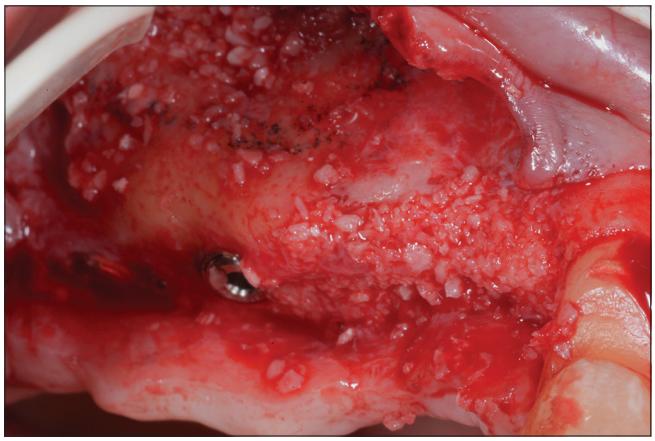

Figure 4: The mixture of concentrated growth factors and xenograft placed in sinus

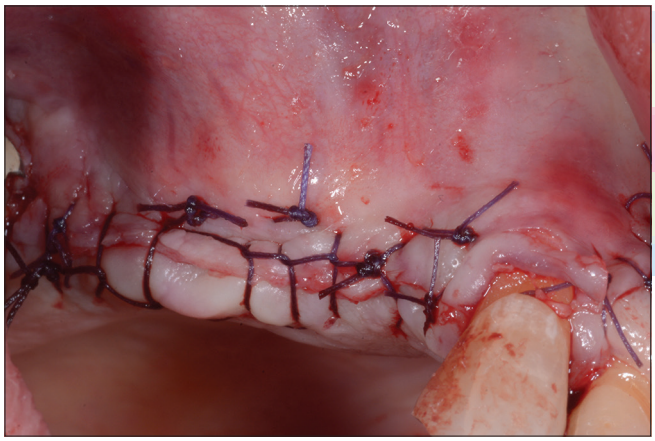

Figure 5: Final sutures

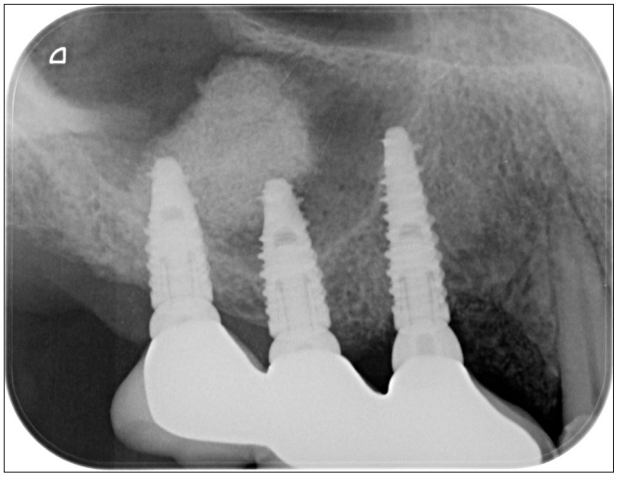

Figure 6: The radiographic outcome immediately after the surgery

A total of 106 implants were placed in augmented sinuses [Table 1].

Regarding the control and test groups:

1. In the 25 patients (17 females and 8 males) of the control group (without CGFm), 27 sinuses were augmented and 51 implants were placed
2. In the 25 patients (15 females and 10 males) of the test group (with CGFm), 28 sinuses were augmented and 55 implants were placed.

During the 1-year follow-up, four implants were lost, resulting in a survival rate of 96.2%.

All four implants were lost before loading at the reopening appointment due to lack of osseointegration.

In both groups, two implants were lost, resulting in a 96.4% survival rate in the test group (with CGFm) and a 96.1% survival rate in the control group (without CGFm). However, no statistically significant differences were observed between the survival rates of the two groups [Table 2].

Immediately and 12 days after surgery, no pain and discomfort were reported in the test group.

Primary wound closure was obtained in all surgeries with no complaint registered or adverse effect observed during the follow-up in the test group.

Primary wound closure was also obtained in all surgeries in the control group. However, immediately after surgery, intense

Table 1: Information about placed implants

	No CGF (control group)	With CGF (test group)
Number of patients who received 1 implant	9	9
Number of patients who received 2 implants	11	10
Number of patients who received 3 implants	3	3
Number of patients who received 5 implants (bilateral sinus augmentation)	1	1
Number of patients who received 6 implants (bilateral sinus augmentation)	1	2
Total	51	55

CGF: Concentrated growth factor

Table 2: Number of implants lost and survival rates

Group	Number of implants placed	Number of implants lost	Survival rates (%)
With CGF (test group)	55	2	96.4*
No CGF (control group)	51	2	96.1**
Total	106	4	96.2

No statistically significant differences (P>0.05) between * and **. CGF: Concentrated growth factor

pain was recorded in two patients. Postoperative relevant swelling occurred in 10 (out of 25) patients and headaches were reported by 4 patients.

Discussion

Important systematic reviews highlighted that autogenous bone alone does not improve the survival rate of implants placed in augmented sinuses.[3-6] Furthermore, some of these reviews[4,5] emphasized the disappointing 82% implant survival rate when autogenous block graft was used.

A slightly higher survival rate between 88% and 92% was described when the particulate autogenous bone was employed.[3,4] On the contrary, a survival rate of 96% from 10,000 examined implants was reported in two reviews[3,4] in sinus augmentations when xenograft was used without the autogenous bone.

In perfect agreement with the latter data, in this present clinical study, the total implant survival rate was 96.2% after 12 months loading: specifically, a 96.1% survival rate was reported in the control group, in which xenograft alone was used, while a 96.4% survival rate was described in the test group, in which a mixture of CGFm and xenograft was utilized.

Moreover, very similar outcomes were also obtained in an investigation, in which autologous fibrin-rich blocks with CGFs without grafting materials were used in the sinus augmentation by lateral window approach.[28] To confirm this, a recent study has demonstrated that both PRF and CGF preparations contain significant amounts of GFs capable of stimulating periosteal cell proliferation,[29] suggesting that PRF and CGF preparations act not only as a scaffolding material but also as a reservoir to deliver certain GFs at the site of application.[30]

The development of PRF significantly simplified the preparation procedure of platelet-concentrated biomaterials and facilitated their clinical application in bone regeneration procedures. In fact, in our protocol, after the centrifuge process, the four components are easily identified and isolated vertically from top to bottom of the tube: (1) an upper liquid phase constituted by serum without fibrinogen and coagulation factors; (2) a phase constituted by large and dense polymerized fibrin buffy coat; (3) a middle phase constituted by aggregated platelets, white and stem cells, and containing CGFs; and (4) a lower phase constituted by red blood cells.[22]

In the present clinical investigation, the second and third phases which are constituted by a fibrin-rich layer and by aggregated platelets containing CGFs were used, and we refer to these two middle layers as the CGFm. The consistency and malleability of this matrix simplified sinus filling during sinus augmentation procedures and allowed us to use only a limited amount (30%) of expensive grafting materials, thus very significantly reducing costs.

It is possible to promote not only hard tissue but also soft-tissue healing by means of platelet concentrates. Previous studies demonstrated that platelets stimulate angiogenesis, cell proliferation, and matrix remodelling.[16,22] Indeed, blood derivatives contain a wide range of biological elements (cells, GFs, cytokines, and scaffold-forming elements which play key roles in wound healing.[31]

Anti-inflammatory and analgesic effects of CGFm are well-known.[21] In this preliminary investigation, an additional positive effect of CGFm use on soft-tissue healing was recorded, in agreement with other authors.[30,32] We observed that patients treated with CGFm in sinus augmentation procedures reported less postoperative pain, swelling, and morbidity.

This effect is motivated by the fact that several GFs are present in platelets, including PDGF; FGF; TGF-β1 and β2 (TGF-β2); IGF; and VEGF.[31]

However, the future clinical studies should be performed using visual analog scales or visual rating scales for a better description of patient-reported postoperative symptoms.

Conclusions

Within the limits of this study, the following conclusions can be drawn: (1) The mixture of CGFm (70%) with xenograft (30%) acts as an alternative to xenograft material alone and behaves predictably in sinus augmentation procedures and (2) The use of CGFm determines less postoperative morbidity in sinus augmentation procedures.

Nevertheless, long-term clinical, histological, and histomorphometric studies on CGFm are required to confirm or refute these findings. Particularly, the future studies with only CGFm in augmented sinuses should be carried out.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Boyne PJ, James RA. Grafting of the maxillary sinus floor with autogenous marrow and bone. J Oral Surg 1980;38:613-6.
2. Block MS, Kent JN, Kallukaran FU, Thunthy K, Weinberg R. Bone maintenance 5 to 10 years after sinus grafting. J Oral Maxillofac Surg 1998;56:706-14.
3. Wallace SS, Froum SJ. Effect of maxillary sinus augmentation on the survival of endosseous dental implants. A systematic review. Ann Periodontol 2003;8:328-43.
4. Del Fabbro M, Testori T, Francetti L, Weinstein R. Systematic review of survival rates for implants placed in the grafted maxillary sinus. Int J Periodontics Restorative Dent 2004;24:565-77.
5. Aghaloo TL, Moy PK. Which hard tissue augmentation techniques are the most successful in furnishing bony support for implant placement? Int J Oral Maxillofac Implants 2007;22 Suppl:49-70.
6. Pjetursson BE, Tan WC, Zwahlen M, Lang NP. A systematic review of the success of sinus floor elevation and survival of implants inserted in combination with sinus floor elevation. J Clin Periodontol 2008;35:216-40.
7. Wallace SS. Indicazioni cliniche dei differenti tipi di materiali da innesto. In: Testori T, editor. La Chirurgia Del Seno Mascellare e le

Alternative Terapeutiche. 1st ed. Viterbo: Promoden; 2005. p. 170-82.
8. Chiapasco M, Casentini P, Zaniboni M. Bone augmentation procedures in implant dentistry. Int J Oral Maxillofac Implants 2009;24 Suppl:237-59.
9. Kahnberg KE, Vannas-Löfqvist L. Sinus lift procedure using a 2-stage surgical technique: I. Clinical and radiographic report up to 5 years. Int J Oral Maxillofac Implants 2008;23:876-84.
10. Froum SJ, Wallace SS, Elian N, Cho SC, Tarnow DP. Comparison of mineralized cancellous bone allograft (Puros) and anorganic bovine bone matrix (Bio-oss) for sinus augmentation: Histomorphometry at 26 to 32 weeks after grafting. Int J Periodontics Restorative Dent 2006;26:543-51.
11. Soardi CM, Spinato S, Zaffe D, Wang HL. Atrophic maxillary floor augmentation by mineralized human bone allograft in sinuses of different size: An histologic and histomorphometric analysis. Clin Oral Implants Res 2011;22:560-6.
12. Orsini G, Scarano A, Piattelli M, Piccirilli M, Caputi S, Piattelli A, *et al.* Histologic and ultrastructural analysis of regenerated bone in maxillary sinus augmentation using a porcine bone-derived biomaterial. J Periodontol 2006;77:1984-90.
13. Galindo-Moreno P, Avila G, Fernández-Barbero JE, Mesa F, O'Valle-Ravassa F, Wang HL, *et al.* Clinical and histologic comparison of two different composite grafts for sinus augmentation: A pilot clinical trial. Clin Oral Implants Res 2008;19:755-9.
14. Lynch SE, Buser D, Hernandez RA, Weber HP, Stich H, Fox CH, *et al.* Effects of the platelet-derived growth factor/insulin-like growth factor-I combination on bone regeneration around titanium dental implants. Results of a pilot study in beagle dogs. J Periodontol 1991;62:710-6.
15. Jakse N, Tangl S, Gilli R, Berghold A, Lorenzoni M, Eskici A, *et al.* Influence of PRP on autogenous sinus grafts. An experimental study on sheep. Clin Oral Implants Res 2003;14:578-83.
16. Intini G. The use of platelet-rich plasma in bone reconstruction therapy. Biomaterials 2009;30:4956-66.
17. Roberts AB, Sporn MB. Physiological actions and clinical applications of transforming growth factor-beta (TGF-beta). Growth Factors 1993;8:1-9.
18. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR, *et al.* Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:638-46.
19. Anitua E. Plasma rich in growth factors: Preliminary results of use in the preparation of future sites for implants. Int J Oral Maxillofac Implants 1999;14:529-35.
20. Dohan Ehrenfest DM, de Peppo GM, Doglioli P, Sammartino G. Slow release of growth factors and thrombospondin-1 in choukroun's platelet-rich fibrin (PRF): A gold standard to achieve for all surgical platelet concentrates technologies. Growth Factors 2009;27:63-9.
21. Choukroun J, Diss A, Simonpieri A, Girard MO, Schoeffler C, Dohan SL, *et al.* Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part IV: Clinical effects on tissue healing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:e56-60.
22. Rodella LF, Favero G, Boninsegna R, Buffoli B, Labanca M, Scarì G, *et al.* Growth factors, CD34 positive cells, and fibrin network analysis in concentrated growth factors fraction. Microsc Res Tech 2011;74:772-7.
23. Sohn DS, Moon JW, Moon YS, Park JS, Jung HS. The use of concentrated growth factors (CGF) for sinus augmentation. J Oral Implant 2009;38:25-38.
24. Puri KS, Suresh KR, Gogtay NJ, Thatte UM. Declaration of Helsinki, 2008: Implications for stakeholders in research. J Postgrad Med 2009;55:131-4.
25. Albrektsson T, Zarb G, Worthington P, Eriksson AR. The long-term efficacy of currently used dental implants: A review and proposed criteria of success. Int J Oral Maxillofac Implants 1986;1:11-25.
26. Misch CE, Perel ML, Wang HL, Sammartino G, Galindo-Moreno P, Trisi P, *et al.* Implant success, survival, and failure: The International Congress of Oral Implantologists (ICOI) Pisa Consensus Conference. Implant Dent 2008;17:5-15.
27. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
28. Sohn DS, Heo JU, Kwak DH, Kim DE, Kim JM, Moon JW, *et al.* Bone regeneration in the maxillary sinus using an autologous fibrin-rich block with concentrated growth factors alone. Implant Dent 2011;20:389-95.
29. Masuki H, Okudera T, Watanebe T, Suzuki M, Nishiyama K, Okudera H, *et al.* Growth factor and pro-inflammatory cytokine contents in platelet-rich plasma (PRP), plasma rich in growth factors (PRGF), advanced platelet-rich fibrin (A-PRF), and concentrated growth factors (CGF). Int J Implant Dent 2016;2:19.
30. Forabosco A, Spinato S, Garuti G, Forabosco E, Consolo U. I fattori di crescita piastrinici e i concentrated growth factors. Doctor Os 2017;28:604-8.
31. Mendes BB, Gómez-Florit M, Babo PS, Domingues RM, Reis RL, Gomes ME, *et al.* Blood derivatives awaken in regenerative medicine strategies to modulate wound healing. Adv Drug Deliv Rev 2017. pii: S0169-409X(17)30321-6.
32. Inchingolo F, Cantore S, Dipalma G, Georgakopoulos I, Almasri M, Gheno E, *et al.* Platelet rich fibrin in the management of medication-related osteonecrosis of the jaw: A clinical and histopathological evaluation. J Biol Regul Homeost Agents 2017;31:811-6.