Use of Plasma Rich in Growth Factor for Schneiderian Membrane Management During Maxillary Sinus Augmentation Procedure

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The aim of this pilot study was to present a novel technique for the management of the Schneiderian membrane during maxillary sinus lift surgery using plasma rich in growth factors (PRGF). Eight maxillary sinuses were augmented in 8 patients. Two small perforations of the Schneiderian membrane occurred during the lifting procedure, which were solved using the PRGF clot before grafting the site with PRGF and anorganic bovine bone. With the exception of 1 patient who experienced pain following an acute sinus infection after 3 days of uneventful healing, the patients' postoperative quality of life was generally good. The most common complication (50% of cases) was hematoma, which disappeared after 1 week. Despite the limitations of this study concerning the sample size and the study design, the use of PRGF may be helpful in reducing complications following sinus lift surgery. More well-designed studies, with larger sample size, are needed to validate this protocol.

Key Words: sinus lift, platelet derivative, PRGF, Schneiderian membrane, sinus-lifting complication

INTRODUCTION

Implant rehabilitation of posterior edentulous maxilla could be a challenging procedure especially when residual bone height is reduced due to bone atrophy. Maxillary sinus-lifting technique is a common surgical technique to augment bone volume in atrophic posterior maxilla, to accommodate implant insertion and subsequent prosthetic rehabilitation.[1–3]

While a sinus lifting with a lateral approach was indicated in a case of less than 5–6 mm of residual bone height in the vertical dimension,[4–6] a transcrestal approach was demonstrated to be successful when at least 5 mm of bone height is available.[7,8]

When a sinus lift with lateral approach is performed, a number of complications can occur.[9] Perforation of the Schneiderian membrane is the most common complication during sinus-lifting surgery, with a mean reported incidence of 19.5% (range, 0% to 58.3%).[1,10] The perforation, if not adequately treated, could cause a chronic sinusitis and dispersion of graft material in the form of particles into the sinus cavity.[9] It has been reported that sinus membrane perforation does not necessarily indicate the need to abort the sinus augmentation surgery once the injury is repaired.[11] However, perforation management is not considered an easy and fully predictable procedure, especially when larger tears are present.[12–14]

Infection-related sequelae are other serious complications that can occur after the sinus-lift procedure. Infection of sinus and graft is one of the main causes of early failure of implants placed in the posterior maxilla after sinus surgery.[15,16] Postsurgical infection as well as the surgical

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procedure itself may often cause swelling and hematoma,[9,17] which can have a severe impact on patients' quality of life. Furthermore, postoperative nose bleeding can occur after perforation of the sinus membrane[9] and also following the detachment of the membrane from the widely vascularized sinus walls.[18,19]

Platelet concentrates have been demonstrated to be effective in oral surgery to enhance healing of both hard and soft tissues.[20–31]

The aim of this prospective study was to evaluate the effectiveness of a new technique in the management of the Schneiderian membrane during the sinus-lifting procedure to reduce intrasurgical and postsurgical complications.

Materials and Methods

The study protocol was approved by the Research Board of the IRCCS Istituto Ortopedico Galeazzi. This study was conducted following the principles embodied in the Helsinki Declaration of 1975 for biomedical research involving human subjects, as revised in 2000.[32] All patients were informed about the study protocol and signed an informed consent form before beginning the study.

Inclusion and exclusion criteria

Patients were selected from those attending the Dental Clinic of the IRCCS Istituto Ortopedico Galeazzi, Milan, Italy.

Inclusion criteria were the following:

- absence of systemic conditions that represent a relative or absolute contraindication to surgical intervention (ASA-1 or ASA-2)
- presence of atrophic edentulous posterior maxilla with a residual bone height <5 mm
- nonsmokers or mild smokers (less than 10 cigarettes per day)

Patients with acute or chronic sinusitis were excluded from the study.

Technique description

Surgery was planned through clinical and radiographic examination with the use of computerized tomography (CT) or cone-beam CT (CBCT) scans (Figure 1).

PRGF preparation

Forty milliliters of peripheral blood of all patients was collected using citrated tubes to prepare the platelet concentrate, according to the manufacturer's instruction (PRGF System IV, BTI Biotechnology Institute, Vitoria, Alava, Spain). The platelet concentrate is obtained by a 1-step centrifugation process (580*g* for 8 minutes). The supernatant is then separated into 2 fractions, taking care not to collect the leukocyte-rich layer: the deeper half is plasma very rich in growth factors (PVRGF), and the upper half is plasma rich in growth factors (PRGF). Each fraction is activated with calcium chloride a few minutes before use.

Surgical protocol

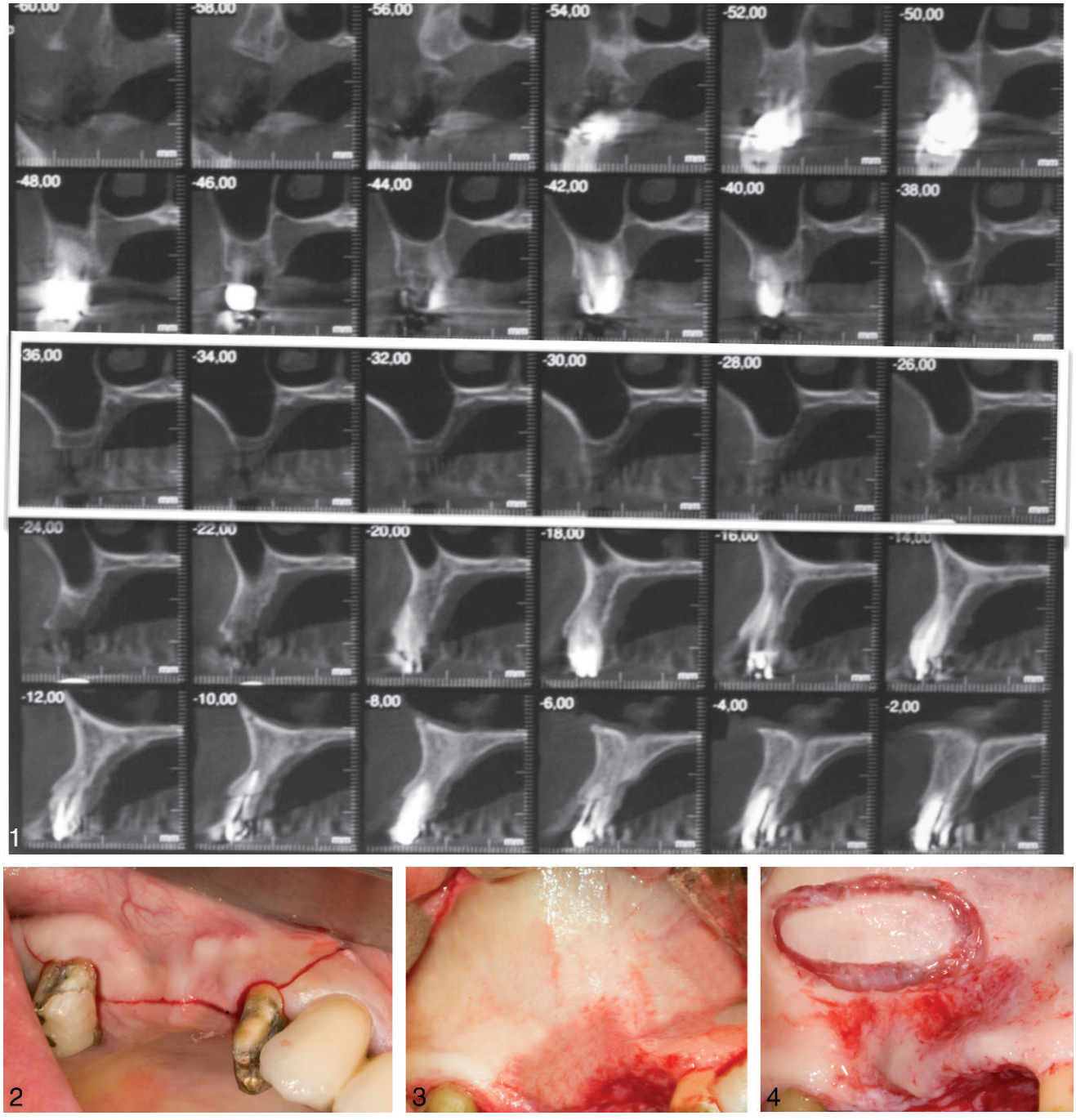
Local anesthesia was administered with the use of articaine 4% and epinephrine 1:100 000.

A trapezoidal flap was elevated after 1 horizontal incision in the middle portion of the edentulous mucosa of the posterior maxilla and 2 vestibular vertical incisions extending apically to the mucogingival junction (Figure 2). A periosteal incision was performed when needed to reduce tensile stresses to the flap. After the elevation of the full-thickness mucoperiosteal flap, the lateral sinus wall was exposed and its extension detected referring to CT scans (Figure 3).

An ellittic window in the sinus wall was created with the use of a piezoelectric device through abrasion of bone wall (Figure 4). Subsequently, the initial detachment of the Schneiderian membrane started from the mesial wall and then from the distal one using specific sinus membrane elevators. After the initial detachment, the PRGF clot was placed above the membrane surface and the procedure continued until the membrane was detached as needed (Figure 5).

Then, the Schneiderian membrane was elevated (Figure 6) so that the roof of the newly created bone cavity consisted of the PRGF clot, firmly adherent to the lifted membrane (Figures 7 and 8).

Deproteinized bovine bone matrix was used to fill the cavity. It was combined with activated liquid fraction of PRGF to have a handling mixture in which the bovine bone is incorporated[22] (Figure 9). After filling the cavity, a PRGF membrane was positioned to cover and protect the window created in the sinus wall (Figure 10).

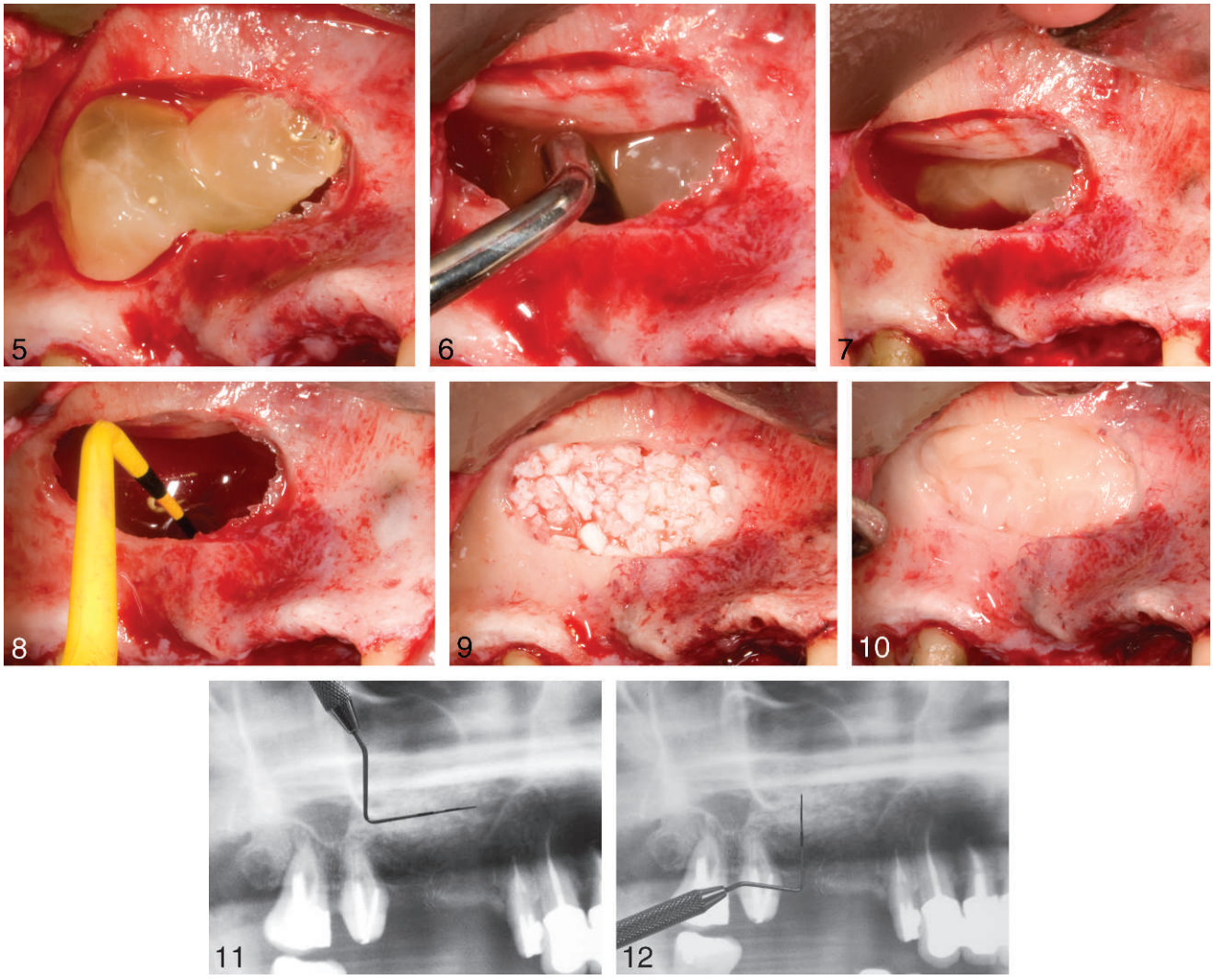


Figures 1–4. Figure 1. Computerized tomography scans showing low residual bone height in the atrophic posterior maxilla. **Figure 2.** Trapezoidal flap design. **Figure 3.** Mucoperiosteal flap reflection. **Figure 4.** An ellittic window was created in the sinus wall through the piezoelectric device.

Afterward, the flap was repositioned in order to stabilize the soft tissue and allow a complete closure of the flap itself. Liquid PRGF was gently injected through a needle in the wound after flap closure with the aim of speeding up the primary healing.

Patients were instructed not to do anything that would abruptly raise or lower pressure in the sinus cavity for 10 days postsurgery, such as sneeze with mouth closed, blow the nose, fly on an airplane, suck through a straw, go swimming, do diving, blow up balloons, or play a wind instrument.

Furthermore, patients were instructed to avoid



Figures 5–12. Figure 5. Plasma rich in growth factors (PRGF) clot was placed over the window, adherent to the Schneiderian membrane. **Figure 6.** Sinus membrane was lifted through the use of an appropriate instrument. The presence of the PRGF clot protected the membrane itself during such a maneuver. **Figure 7.** After complete lifting, the PRGF clot remains strictly adherent to the lifted sinus membrane. **Figure 8.** Evaluation of the depth and height of the newly created cavity. **Figure 9.** The cavity is filled with deproteinized bovine bone matrix (big granules) mixed with PRGF liquid. **Figure 10.** The fibrin membrane is placed close to the window, protecting the bone graft and with the aim of enhancing soft-tissue healing. **Figure 11.** Postsurgical radiographic control. Width evaluation. **Figure 12.** Postsurgical radiographic control. Height evaluation.

vigorous mouth rinsing, hard and hot food, strenuous exertion, smoking, and touching the gums for at least 3 days following surgery.

Ice packs were provided after surgery. Moreover, patients were instructed to gently rinse with a 0.2% chlorhexidine digluconate solution twice a day for 10 days for plaque control. All patients were prescribed nonsteroidal analgesics for pain relief and swelling control to be self-administered. Antibiotic therapy with amoxicillin 1 g twice a day for 6 days was prescribed to all patients.

Parameter evaluation

Occurrence of complications during surgery (such as perforation of Schneiderian membrane) was recorded.

A designed questionnaire, used in previously published studies,[33–35] was administered to all subjects to evaluate postoperative functional limitations (eg, in chewing, talking, sleeping, daily routine, and missed work), as well as pain and the presence of other symptoms (swelling, bleeding, nausea, bad taste/breath). For pain assessment, a

10-cm graduated visual analog scale (VAS) was adopted, where 0 = *no pain* and 100 = *unbearable pain*. For other symptoms and functional limitations, the answers were based on a 5-point Likert-type scale, ranging from 1 (*none*) to 5 (*very much*). Finally, patients were asked if they had taken any analgesics on each postoperative day. Patients received the questionnaire to fill in daily starting on the day of surgery for a week. Questionnaires were returned postage paid.

A dental panoramic radiograph was taken immediately after sinus surgery (Figures 11 and 12). A CT or CBCT scan was taken 6 months later soon before implant placement to assess the stability of bone graft and bone volume.

Results of Case Series

A total of 8 sinuses in 8 patients (4 women and 4 men) were treated following the previously described protocol. The mean age of the patients was 54 ± 8.2 years, ranging from 41 to 65 years. One patient was a smoker (mean 10 cigarettes/d). All patients were systemically healthy and did not present with sinusal chronic or acute pathologies at the time of surgery.

The mean residual bone height was 2.4 ± 0.9 mm, ranging from 1 to 4 mm.

Two Schneiderian membrane perforations less than 5 mm occurred during surgeries.

Four patients did not experience any complications during the healing phase. Three patients showed hematoma localized under the orbit. One patient experienced acute sinusitis, due to influenza virus infection, after 3 days of uneventful healing, which caused a sharp pain. The subject then underwent successful pharmacological treatment for the acute inflammation. Two weeks after surgery, a complete healing was observed.

In general, patients' normal activities (mouth opening, chewing, speaking, and sleeping) were not impaired. Three patients experienced difficulty in eating some types of food for the first 2 days after surgery. A mean of 1.86 days of work per subject were missed due to surgical intervention. Swelling was present in all patients only on the first day. With the exception of the patient who experienced the acute sinusitis, pain levels were low even in the first days postsurgery. Excluding the previously cited patient, the VAS score decreased from 11.25 ± 5.8 on day 1 to 4.0 ± 5.9 on day 2 and to 1.7 ± 3.2 on the third day. A complete absence of pain was reported by all patients since day 4.

All postoperative radiographs demonstrated full incorporation of bone graft under the new floor of the sinus cavity, without dispersion of granules into the sinus lumen.

Discussion

Maxillary sinus floor augmentation with the lateral approach is an important treatment option for the prosthetic rehabilitation of the atrophic posterior maxilla. The application of bone graft creates the condition to increase bone volume after the healing period, allowing implant positioning after an adequate healing period.[36]

Platelet concentrates have been used in sinus surgery with the aims of shortening healing time, enhancing hard- and soft-tissue healing, and improving bone quality, even if conflicting results have been reported.[21,37,38]

PRGF belongs to a recent generation of autologous platelet concentrates. After activation with calcium chloride or autologous thrombin, platelets locally release a number of growth factors and bioactive proteins, modulating and enhancing healing processes.[39,40]

Different PRGF formulations are available and have different therapeutic indications.[40]

The liquid PRGF (PVRGF) can be used to bioactivate the surface of dental implants[41] and to enhance soft-tissue healing. The scaffold-like PRGF, with a gel consistency, has the potential to promote bone regeneration when associated with other osteoconductive materials. Furthermore, it may act as a glue for granular bone substitutes, preventing their dispersion and improving graft-handling properties and adaption to filling bone defects. Elastic fibrin can be use to seal peri-implant defects in postextraction sites and, in general, as a natural barrier membrane in all guided bone regeneration procedures.[22,23]

PRGF mechanical and biological properties were considered in planning and performing the herein described protocol.

First, the elasticity of the PRGF clot, as well as its tight adhesion to the sinus membrane, may allow a safer and more atraumatic management of the membrane itself during the detachment phase.

Then, the occurrence of membrane tears and perforations may decrease due to a reinforcement of the membrane, especially in case of thinner ones. Finally, the lateral compression of the clot underneath the membrane decreased the forces favoring detachment due to the hydraulic pressure caused by the clot itself. After completion of the lifting procedure, the PRGF clot remains attached to the sinus membrane, further protecting the membrane itself during the filling of the cavity. PRGF supernatant properties were used in preparing the bone graft by mixing the liquid with the particulated bone graft. Hence, the obtained clot facilitated the manipulation of the graft, allowing a safer approach. This was because granules of the bone substitute were amalgamated with the gel, preventing their escape into the sinus in case of accidental membrane perforation. In addition, the PRGF was expected to stabilize the graft quickly. PRGF is hypothesized to work as a space maker among granules, accelerating fibrin formation, vascular ingrowth, and osteogenic cell migration into the graft and contemporarily avoiding excessive compression of bone graft material during placement. Furthermore, the mixture of clot and bone granules could reduce the risk of perforations caused by the sharpness of the granules themselves.

Biological interactions of PRGF with soft and hard tissues must also be considered to support the use of platelet derivatives in the sinus-lifting procedure.

First, PRGF releases a number of factors that are involved in the promotion of tissue regeneration, such as fibrinogen, fibronectin, platelet-derived growth factor, transforming growth factor-β, vascular endothelial growth factors, and others.[42] Then, the concentrate has a marked anti-inflammatory action by the suppression of proinflammatory chemokines such as IL-1[43,44] and also has an antimicrobial effect.[45] These characteristics, together with the hemostatic properties and high biocompatibility, contributed to the observed reduction of postsurgical discomfort, favorably affecting the patients' quality of life.[35]

The proposed technique was elaborated considering the above described characteristics of platelet concentrates. The small number of patients in the present study did not allow a comparison with the prevalence of such sinus membrane perforations as described in the scientific literature (average 19.5%, ranging from 0% to 58%[1,10]). The small tears that occurred were successfully managed by approximating the PRGF clot to the sinus membrane. Finally, hemostatic properties of PRGF also could be involved in determining the absence of nose bleeding in patients, which may be caused by the lesion of posterior lateral nasal arteries perforating the nasal wall laterally, often occurring during membrane detachment from the mesial/nasal wall.[19]

Conclusions

In this case series, a description of a new technique for sinus membrane management with the aid of platelet-derived concentrates was presented. Despite the limitation of the study design (the small number of cases), the patients' quality of life postsurgery was minimally affected, and the occurrence of postsurgical adverse sequelae was extremely low.

Randomized controlled clinical trials with a larger sample size are needed to validate this technique.

Abbreviations

CBCT: cone beam computerized tomography
CT: computerized tomography
PRGF: plasma rich in growth factors
PVRGF: plasma very rich in growth factors
VAS: visual analog scale

References

1. 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;35:216–240.

2. Wallace SS, Froum SJ. Effect of maxillary sinus augmentation on the survival of endosseous dental implants: a systematic review. *Ann Periodontol*. 2003;8:328–343.

3. 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;24:565–577.

4. Del Fabbro M, Rosano G, Taschieri S. Implant survival rates after maxillary sinus augmentation. *Eur J Oral Sci*. 2008;116:497–506.

5. Manso MC, Wassal T. A 10-year longitudinal study of 160 implants simultaneously installed in severely atrophic posterior maxillas grafted with autogenous bone and a synthetic bioactive resorbable graft. *Implant Dent*. 2010;19:351–360.

6. Hatano N, Shimizu Y, Ooya K. A clinical long-term radiographic evaluation of graft height changes after maxillary

sinus floor augmentation with a 2:1 autogenous bone/xenograft mixture and simultaneous placement of dental implants. *Clin Oral Implants Res*. 2004;15:339–345.

7. Tan WC, Lang NP, Zwahlen M, Pjetursson BE. A systematic review of the success of sinus floor elevation and survival of implants inserted in combination with sinus floor elevation. Part II: transalveolar technique. *J Clin Periodontol*. 2008;35:241–254.

8. Del Fabbro M, Corbella S, Weinstein T, Ceresoli V, Taschieri S. Implant survival rates after osteotome-mediated maxillary sinus augmentation: a systematic review. *Clin Implant Dent Relat Res*. 2012;14(suppl 1):e159–e168.

9. Katranji A, Fotek P, Wang HL. Sinus augmentation complications: etiology and treatment. *Implant Dent*. 2008;17: 339–349.

10. Schwartz-Arad D, Herzberg R, Dolev E. The prevalence of surgical complications of the sinus graft procedure and their impact on implant survival. *J Periodontol*. 2004;75:511–516.

11. Fugazzotto PA, Vlassis J. A simplified classification and repair system for sinus membrane perforations. *J Periodontol*. 2003; 74:1534–1541.

12. Chan HL, Wang HL. Sinus pathology and anatomy in relation to complications in lateral window sinus augmentation. *Implant Dent*. 2011;20:406–412.

13. Hernandez-Alfaro F, Torradeflot MM, Marti C. Prevalence and management of Schneiderian membrane perforations during sinus-lift procedures. *Clin Oral Implants Res*. 2008;19:91–98.

14. Testori T, Wallace SS, Del Fabbro M, et al. Repair of large sinus membrane perforations using stabilized collagen barrier membranes: surgical techniques with histologic and radiographic evidence of success. *Int J Periodontics Restorative Dent*. 2008;28:9–17.

15. Peleg M, Mazor Z, Garg AK. Augmentation grafting of the maxillary sinus and simultaneous implant placement in patients with 3 to 5 mm of residual alveolar bone height. *Int J Oral Maxillofac Implants*. 1999;14:549–556.

16. Cho-Lee GY, Naval-Gias L, Castrejon-Castrejon S, et al. A 12-year retrospective analytic study of the implant survival rate in 177 consecutive maxillary sinus augmentation procedures. *Int J Oral Maxillofac Implants*. 2010;25:1019–1027.

17. Levin L, Herzberg R, Dolev E, Schwartz-Arad D. Smoking and complications of onlay bone grafts and sinus lift operations. *Int J Oral Maxillofac Implants*. 2004;19:369–373.

18. Rosano G, Taschieri S, Gaudy JF, Weinstein T, Del Fabbro M. Maxillary sinus vascular anatomy and its relation to sinus lift surgery. *Clin Oral Implants Res*. 2011;22:711–715.

19. Rosano G, Taschieri S, Gaudy JF, Lesmes D, Del Fabbro M. Maxillary sinus septa: a cadaveric study. *J Oral Maxillofac Surg*. 2010; 68:1360–1364.

20. Del Fabbro M, Bortolin M, Taschieri S. Is autologous platelet concentrate beneficial for post-extraction socket healing? A systematic review. *Int J Oral Maxillofac Surg*. 2011;40:891–900.

21. Del Fabbro M, Bortolin M, Taschieri S, Weinstein RL. Effect of autologous growth factors in maxillary sinus augmentation: a systematic review. *Clin Implant Dent Relat Res*. 2011 [published online March 31, 2011].

22. Anitua E, Prado R, Orive G. A lateral approach for sinus elevation using PRGF technology. *Clin Implant Dent Relat Res*. 2009; 11(suppl 1):e23–e31.

23. Anitua E, Prado R, Orive G. Bilateral sinus elevation evaluating plasma rich in growth factors technology: a report of five cases. *Clin Implant Dent Relat Res*. 2012;14:51–60.

24. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: growth factor enhancement for bone grafts. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;85:638–646.

25. Gruber R, Varga F, Fischer MB, Watzek G. Platelets stimulate proliferation of bone cells: involvement of platelet-derived growth factor, microparticles and membranes. *Clin Oral Implants Res*. 2002; 13:529–535.

26. Giannobile WV. Periodontal tissue engineering by growth factors. *Bone*. 1996;19:23S–37S.

27. Lind M. Growth factor stimulation of bone healing: effects on osteoblasts, osteomies, and implants fixation. *Acta Orthop Scand Suppl*. 1998;283:2–37.

28. Carlson NE, Roach RB Jr. Platelet-rich plasma: clinical applications in dentistry. *J Am Dent Assoc*. 2002;133:1383–1386.

29. Del Fabbro M, Bortolin M, Taschieri S, Weinstein R. Is platelet concentrate advantageous for the surgical treatment of periodontal diseases? A systematic review and meta-analysis. *J Periodontol*. 2011;82:1100–1111.

30. Betoni-Junior W, Dechichi P, Zanetta-Barbosa D, Esteves J, Magalhaes A. Evaluation of the bone healing process utilizing platelet-rich plasma activated by thrombin and calcium chloride: a histologic study in rabbit. *J Oral Implantol*. 2010 [published online November 1, 2010].

31. Rutkowski JL, Johnson DA, Radio NM, Fennell JW. Platelet rich plasma to facilitate wound healing following tooth extraction. *J Oral Implantol*. 2010;36:11–23.

32. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2000;284:3043–3045.

33. Shugars DA, Benson K, White RP Jr, Simpson KN, Bader JD. Developing a measure of patient perceptions of short-term outcomes of third molar surgery. *J Oral Maxillofac Surg*. 1996;54: 1402–1408.

34. Tsesis I, Shoshani Y, Givol N, Yahalom R, Fuss Z, Taicher S. Comparison of quality of life after surgical endodontic treatment using two techniques: a prospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2005;99:367–371.

35. Del Fabbro M, Taschieri S, Weinstein R. Quality of life after microscopic periradicular surgery using two different incision techniques: a randomized clinical study. *Int Endod J*. 2009;42:360–367.

36. Garg AK. Augmentation grafting of the maxillary sinus for placement of dental implants: anatomy, physiology, and procedures. *Implant Dent*. 1999;8:36–46.

37. Boyapati L, Wang HL. The role of platelet-rich plasma in sinus augmentation: a critical review. *Implant Dent*. 2006;15:160–170.

38. Arora NS, Ramanayake T, Ren YF, Romanos GE. Platelet-rich plasma in sinus augmentation procedures: a systematic literature review: Part II. *Implant Dent*. 2010;19:145–157.

39. Anitua E, Sanchez M, Nurden AT, Nurden P, Orive G, Andia I. New insights into and novel applications for platelet-rich fibrin therapies. *Trends Biotechnol*. 2006;24:227–234.

40. Anitua E, Sanchez M, Orive G, Andia I. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. *Biomaterials*. 2007;28:4551–4560.

41. Anitua EA. Enhancement of osseointegration by generating a dynamic implant surface. *J Oral Implantol*. 2006;32:72–76.

42. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost*. 2004;91:4–15.

43. El-Sharkawy H, Kantarci A, Deady J, et al. Platelet-rich plasma: growth factors and pro- and anti-inflammatory properties. *J Periodontol*. 2007;78:661–669.

44. Woodall J Jr, Tucci M, Mishra A, Asfour A, Benghuzzi H. Cellular effects of platelet rich plasma interleukin1 release from prp treated macrophages. *Biomed Sci Instrum*. 2008;44:489–494.

45. Bielecki TM, Gazdzik TS, Arendt J, Szczepanski T, Krol W, Wielkoszynski T. Antibacterial effect of autologous platelet gel enriched with growth factors and other active substances: an in vitro study. *J Bone Joint Surg Br*. 2007;89:417–420.