Management of large perforations of the sinus mucosa with PRGF-Endoret® platelet concentrate

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The aim of the present study is to describe a new technique through which it is possible to complete the maxillary sinus lift procedure even in case of severe damage or complete removal of the sinus mucosa using the PRGF-Endoret® platelet concentrate. Eighteen patients (ratio F:M=4:5; average age: 58.2 years; DS: 8.85 years) with severe perforation (more than 10 millimetres of diameter) of the sinus mucosa during the maxillary sinus lift procedure were selected. Normally the procedure is interrupted due to impossible stabilization of the graft material inside the subantral cavity. On the contrary, our protocol foreseen the sealing of the perforation using the PRGF autologous gel membranes or the creation of a new sinus pseudo-membrane through which the graft material was covered. The PRGF-Endoret were obtained according to the protocol developed by BTI (Biotechnology Institute - Vitoria, Spain). In 14 cases out of 18 implant fixtures were concurrently inserted while in 4 cases the fixture insertion was postponed after 6 months: 37 fixtures were inserted (27 at the same time and 10 after 6 months). 2 months after surgery the CBCT showed a correct pneumatization of the maxillary sinus in 16 patients out of 18 (89% of cases), while after 12 months the radiological normalization of the maxillary sinus was present in 17 patients out of 18, bringing the healing rate to 94% of cases. Regarding implant healing, 2 out of 37 implants inserted were lost in the first month after the surgical phase, whereas 12 months after prosthesis application the other 35 implants were perfectly osteointegrated with a healing rate equal to 94.6% of the fixtures. 36 months after the surgery all the fixtures were osteointegrated (35 of 37 implants with a percentage of 94.6% of success). We may conclude that the use of PRGF allowed to complete the sinus lift even in case of severe perforation of the sinus mucosa or its total removal thanks to its capability to stabilize the graft, its antibacterial and antifungal activity and its anabolic effect and favouring bone regeneration.

It is by now well-established that the preservation of the sinus mucosa integrity is a key element to achieve a good bone regeneration during the maxillary sinus lift procedure, especially if performed via lateral wall (1-5). Its potential perforation represents an adverse event that, in case of large dimensions (6), can lead to the interruption of the procedure due to impossible stabilization of the graft material. In general, perforation is a rather common event: a meta-analysis by Al-Dajani reports an incidence equal to 23.5% (range from 4% to 40%), collected on 12 clinical trials for a total of 1600 surgical procedures (7).

Aim of the present study is to describe a new technique through which it is possible to complete the maxillary sinus lift procedure even in case of severe

Key words: sinus lift, membrane perforation, perforation sealing, PRGF-Endoret, platelet concentrates, implant integration

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0393-974X (2020)

damage or complete removal of the sinus mucosa using the PRGF-Endoret® platelet concentrate.

MATERIALS AND METHODS

For this study, 18 patients (ratio F:M=4:5; average age: 58.2 years; DS: 8.85 years) with severe perforation of the sinus mucosa during the maxillary sinus lift procedure for the insertion of implant fixtures were selected. The tearing of mucosa, which occurred randomly during the detachment phase, had to be larger than 10 millimetres in diameter (6). In 6 cases the treated sinus was the right and in 12 the left.

Normally in these cases, the procedure is interrupted due to impossible stabilization of the graft material inside the subantral cavity. On the contrary, our protocol foresaw the creation of a new sinus pseudo-membrane using autologous platelet gel membranes through which the graft material was covered. These membranes were obtained through the PRGF-Endoret® technology (acronym of Plasma Rich in Growth Factors), a particular autologous platelet concentrate obtained according to the protocol developed by BTI (Biotechnology Institute, Vitoria, Spain) (8-12).

The graft material was thus composed of heterologous bone of bovine origin (BioOss Geistlich in 0.25-1 mm granules) immersed in a gel autologous PRGF-Endoret matrix. Its peculiarity is the double formulation because it can be used both in liquid and gel form: in this way it is possible to mix the graft material with the liquid part and to be then transformed into a gel thanks to the addition of calcium chloride in appropriate concentration (20 microliters per ml of plasma). A plastic and mouldable material is thus formed to be placed in the sinus cavity without having the dispersion of heterologous bone, thanks to the adhesive capacity of the platelet gel.

Moreover, in 14 cases out of 18 implant fixtures were

Table I. *List of the cases treated with sinus lift procedure and implant insertion.*

nr	Patient Name	Sex	Age	Medical Problems	Side	Fixture #1	Fixture #2	Fixture #3	Sinus Healing 2 m	Sinus Healing 12 m	Fixture Insertion
1	Pre N	f	45	Hypertension	Left	4x13	4x13		yes	yes	Immediate
2	Vig A	m	74	Hypertension	Left	5x13	5.5x11.5		no	no	Immediate
3	Gen W	m	65		Right	5x10	5x10		no	yes	Delayed
4	Eul I	f	76	Acute hepatitis HCV	Left	5x10	5x10	5x10	yes	yes	Delayed
5	Cal Man N	f	59	Hypertension	Left	5x11.5	5x11.5		yes	yes	Immediate
6	Min F	m	53		Left	5x13	5x13		yes	yes	Immediate
7	Fer R	f	61	Immunodepression	Right	5x11.5	5.5x11.5		yes	yes	Immediate
8	Ton M	m	62		Left	5x11.5	5x11.5		yes	yes	Delayed
9	Car F	m	64	Hypertension	Left	5x11.5	5x10		yes	yes	Immediate
10	Lon R	m	53		Left	5x10	5.5x10		yes	yes	Immediate
11	Sar E	f	56		Right	4x11.5	5x10		yes	yes	Immediate
12	Mal I	m	51		Left	5x10	5x10		yes	yes	Immediate
13	Sar A	f	54		Left	5x10	5x10		yes	yes	Immediate
14	Bel M	f	69	Hypertension	Right	5x10	5x10		yes	yes	Immediate
15	Carc A	m	49	Hypertension	Left	4x13	5x11.5	5x11.5	yes	yes	Delayed
16	Nar N	m	56		Left	5x8.5			yes	yes	Immediate
17	San I	f	53	Hypertension	Right	5x11.5	5x10		yes	yes	Immediate
18	Gal M	f	47		Right	5x8.5	5x8.5		yes	yes	Immediate
	Average Age		**58,2**	**Left Sinus**	**12**			**Healing**	**16**	**17**	
	Dev. St. Age		**8,85**	**Right Sinus**	**6**			**No**	**2**	**1**	

The measures of the implants are indicated in the middle of the table, while on the right part there is the healing of the sinuses. In yellow the lost implants and the unhealthy sinus after the surgery.

concurrently inserted (UnicCa surface BTI implants, with the particularity of ionic calcium release) while in 4 cases the fixture insertion was postponed after 6 months: 37 fixtures were therefore inserted according to the scheme shown in table I. Only in 4 patients, due to the severe bone atrophy (residual bone height less than 1 millimetre) and the consequent lack of primary stability, the implant placement was postponed: in these cases, 10 implants were placed 6 months after the sinus lift procedure and their prosthetization occurred 6 months after placement. Osteointegration was then appraised one year after the placement of the prosthesis, in other words after one year of masticatory loading, and after 3 years.

The post-surgery pharmacological protocol included a broad-spectrum antibiotic coverage (amoxicillin cps 1 gr x 3 times a day for 8 days from the day before surgery), accompanied by rinsing with 0.2% chlorhexidine-based mouthwash (1 min for 3 times a day until stitches removal for 12-14 days). For the inflammation control, granular ibuprofen 600 mg 2-3 times daily as needed was prescribed. In addition, to promote healing of sinus mucosa, ten days after surgery aerosol with hypertonic solution associated with thiamphenicol (fluimucil antibiotic 500mg/4ml) was prescribed once daily for 10 days.

Healing of the maxillary sinus was assessed clinically and through Cone Beam Computer Tomography (CBCT) by analysing the degree of sinus pneumatization after 2 and 12 months, whereas to verify the effectiveness of implant treatment the percentage of osteointegration and implant success was assessed 12 months after using provisional prosthesis and 24 months after the application of the definitive prosthesis (36 months after the implants insertion).

Table II. *Results and percentage of success.*

Results	
Total number of fixtures	37
Implant integration at 12 months	35
% Healing	94.6%
Implant integration at 36 months	35
% Healing	94.6%
Total treated sinuses	18
Healed sinuse at 2 months	16
% Healing	88.9%
Healed sinuse at 12 months	17
% Healing	94.4%

RESULTS

Results are indicated in table I and II. All patients had a post-surgery course characterized by oedema and pain controlled with common non-steroidal anti-inflammatory medicaments over the next three days, associated with nosebleeds in the same period, however without detecting graft material in the leaked blood.

Two months after surgery the radiological examination showed a correct pneumatization of the maxillary sinus in 16 patients out of 18 (89% of cases), this being expression of appropriate maxillary sinus healing process.

After 12 months the radiological normalization of the maxillary sinus was present in 17 patients out of 18, bringing the healing rate to 94% of cases.

In regards to implant healing, 2 out of 37 implants inserted were lost in the first month after the surgical phase, whereas 12 months after prosthesis application the other 35 implants were perfectly osteointegrated with a healing rate equal to 94.6% of the fixtures. Three years after all the fixtures were osteointegrated (35 of 37 implants with a percentage of 94.6% of success).

DISCUSSION

The maxillary sinus lift procedure requires the maintenance of the absolute integrity of the sinus mucosa in order to create a submucosal (subantral) space to accommodate the graft material that, soaked by the patient's blood clot, is progressively invaded by new blood vessels and by multipotent cells which ensure a progressive deposition of new bone tissue. In this process, the stability of the clot and the integrity of the sinus membrane are important factors: the presence of perforations, especially of large dimension (diameter greater than 10 mm) represents a negative prognostic element, as it can also determine the dispersion of the graft material in the maxillary sinus with the possible appearance of *ex vacuo* sinusitis due to obstruction of the sinus ostium.

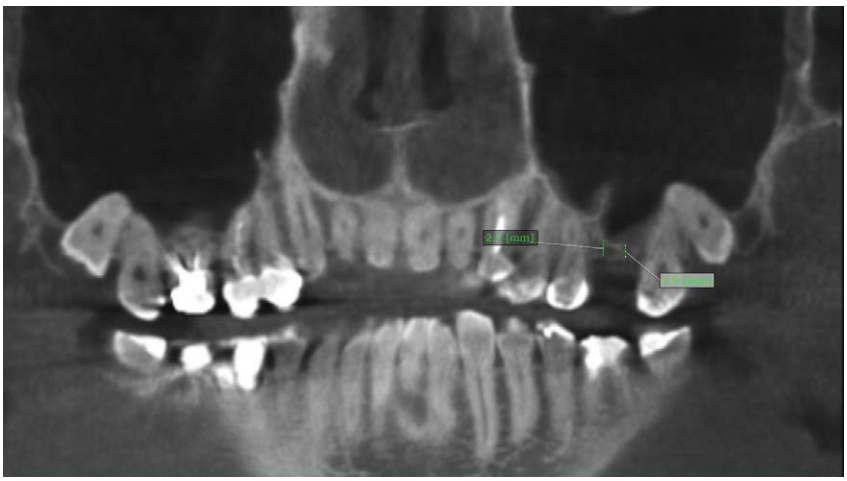

Fig. 1. *Initial CBCT panoramic view with the measures of the residual bone.*

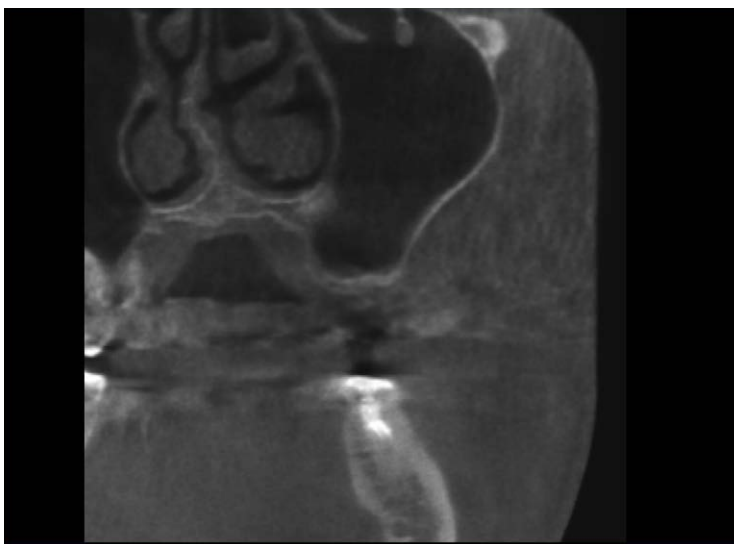

Fig. 2. *Initial CBCT section at 2.6 level shows a very resorbed bone.*

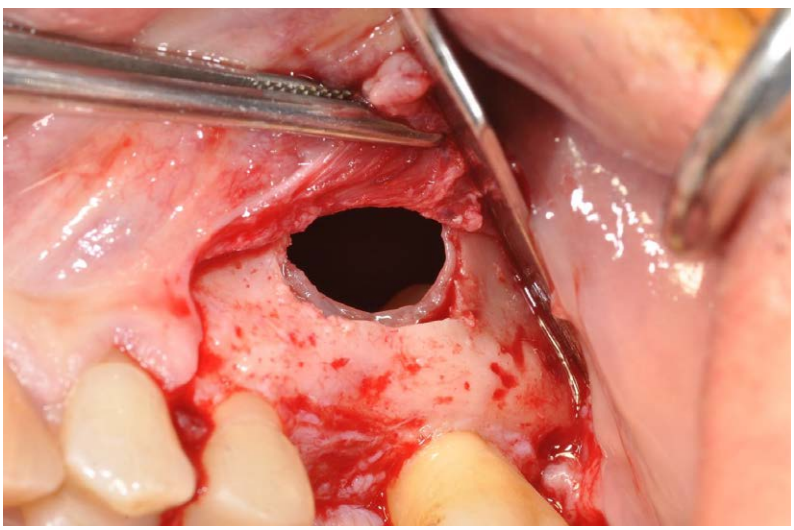

Fig. 3. *Large perforations during sinus lift procedure.*

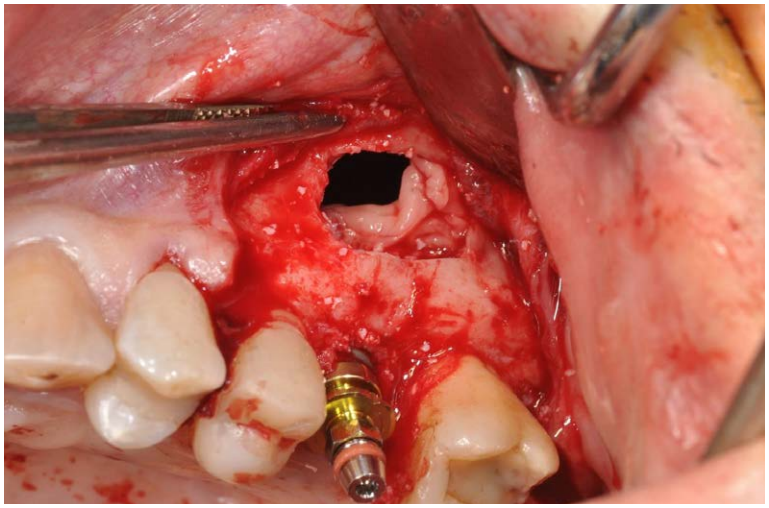

Fig. 4. *PRGF-Endoret membrane to cover the graft material (autologous PRGF gel mixed with heterologous bone). Fixture BTI interna plus UnicCa surface (diameter 5 mm, length 8.5 mm).*

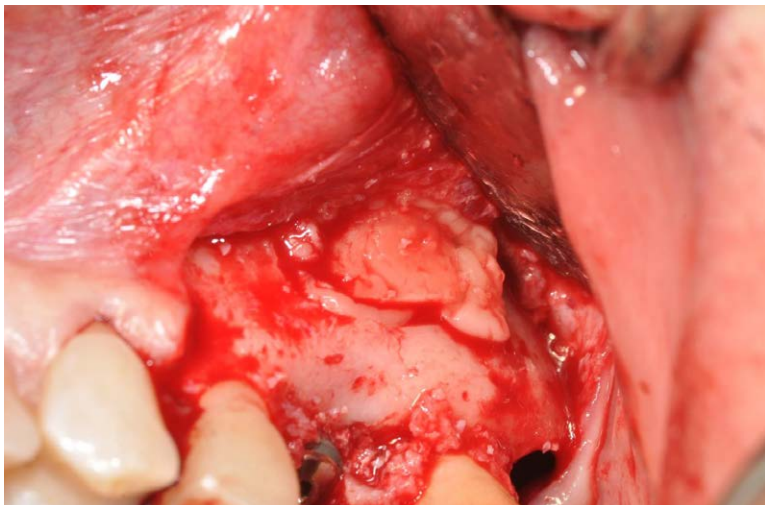

Fig. 5. *Bone block repositioning to cover the bone window. Note the leak of the PRGF gel membrane to recreate a sinus psudomucosa.*

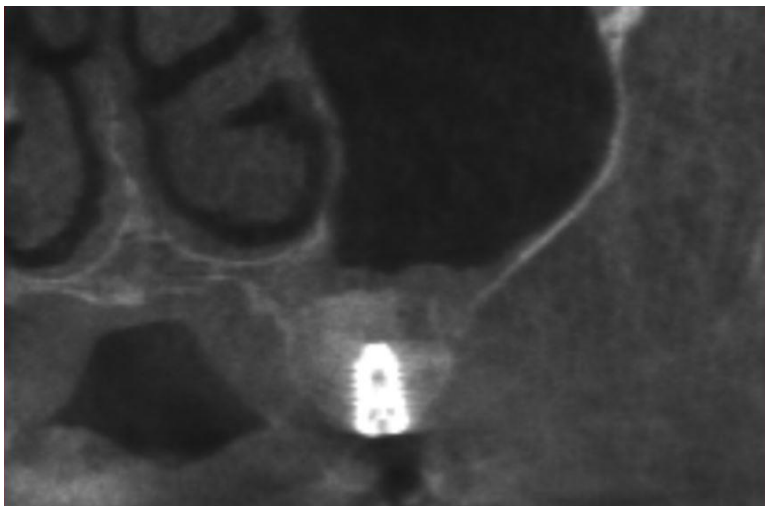

Fig. 6. *CBCT control after 2 months: the sinus appears healthy and the bone is stable around the implant.*

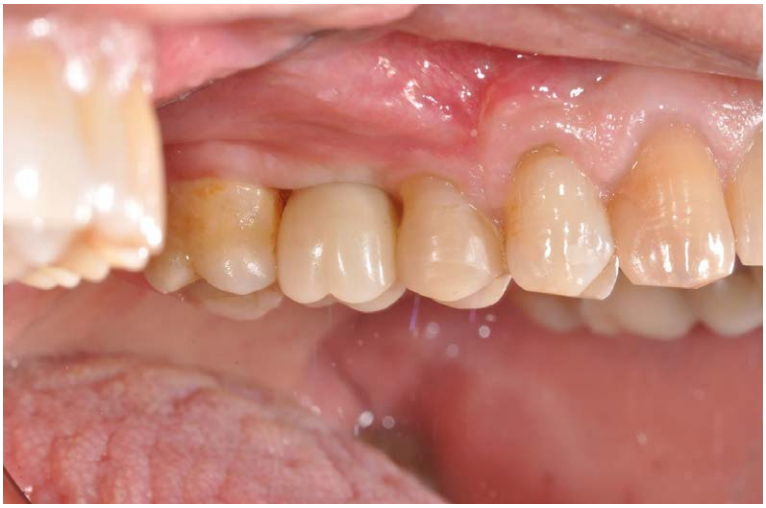

Fig. 7. *Provisional crown after 6 months.*

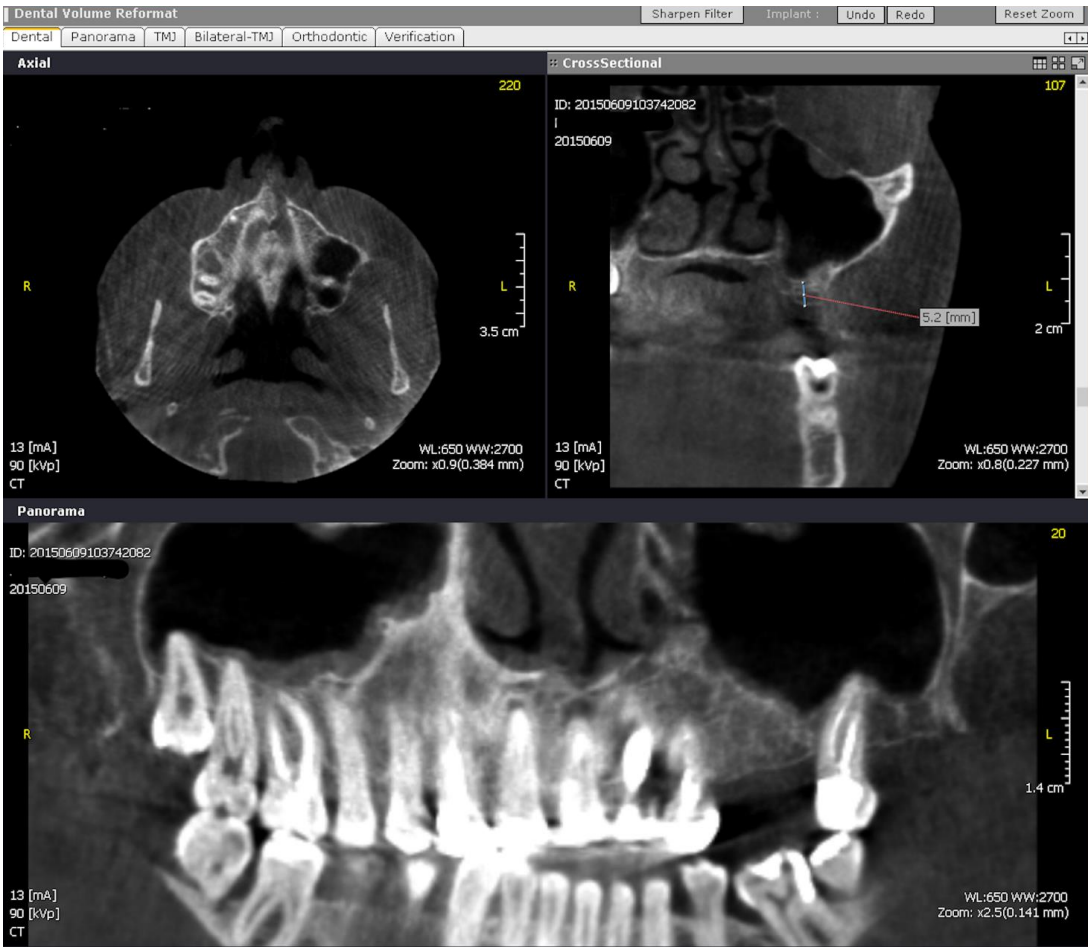

Fig. 8. *Another case of sinus lift procedure with implant insertion and apicoectomy of 2.7.*

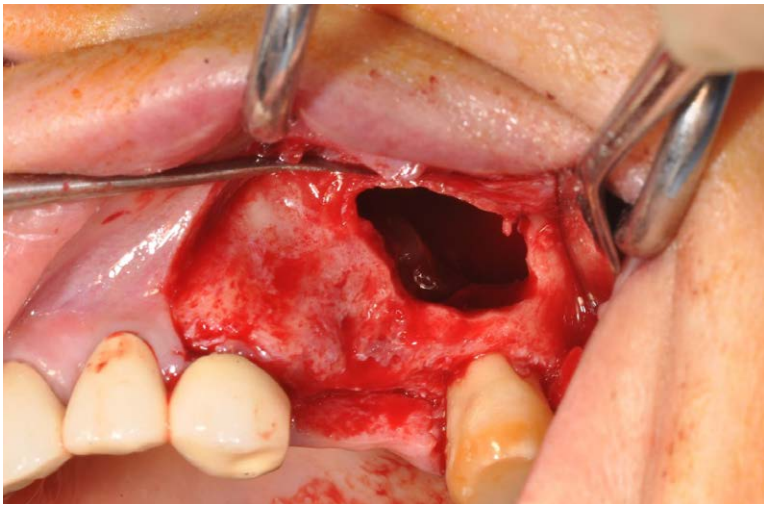

Fig. 9. *Large perforation of the sinus mucosa after apicoectomy of 2.7.*

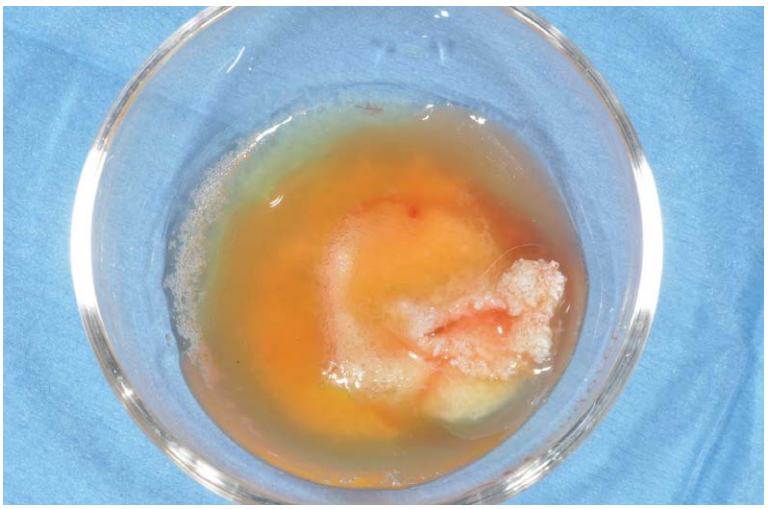

Fig. 10. *Graft material: PRGF mixed with heterologous bovine bone after the gelification process.*

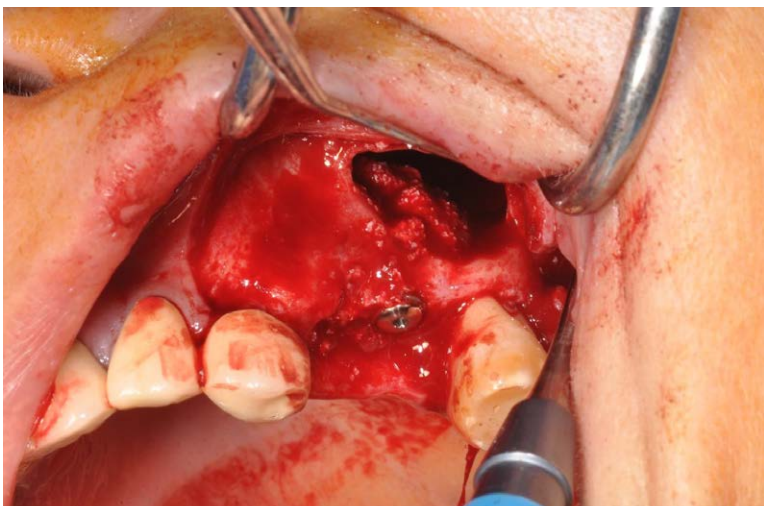

Fig. 11. *Positioning of the graft material into the sinus.*

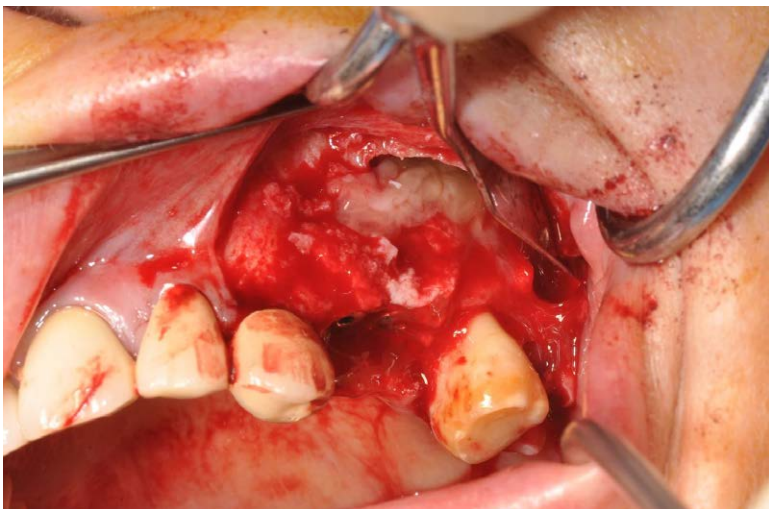

Fig. 12. *Covering the graft material with PRGF gel membrane to recreate a pseudomucosa.*

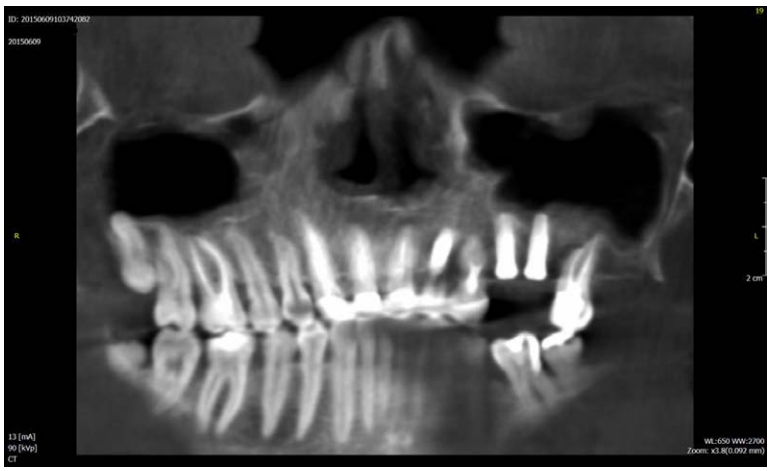

Fig. 13. *CBCT control after 12 months: the sinus appears healthy.*

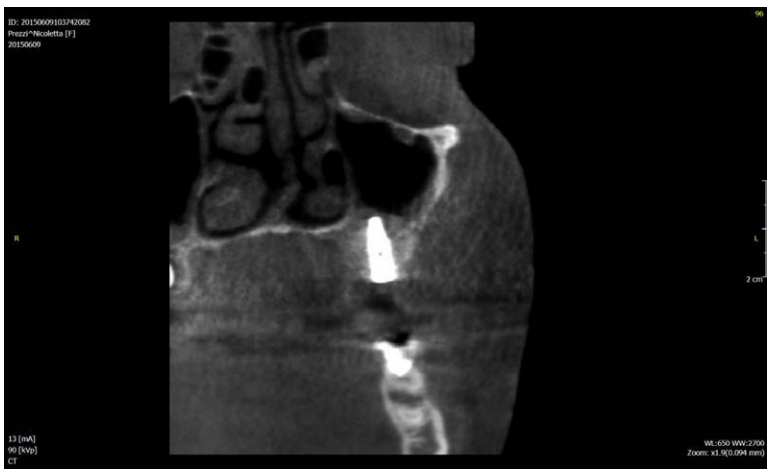

Fig. 14. *CBCT control after 12 months: cross section at 2.6 level. The sinus appears ventilate.*

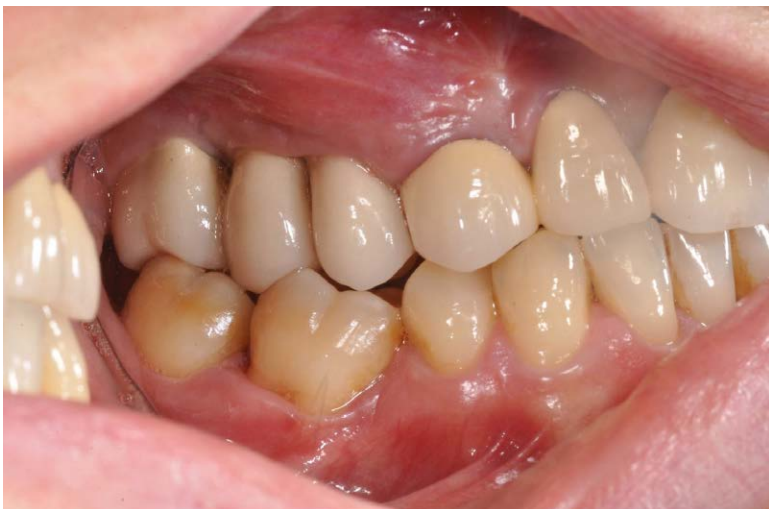

Fig. 15. *Definitive implant-supported single crowns after 4 years of masticatory load.*

The perforation of the sinus membrane is a rather common event and, if large, can determine the interruption of the surgical procedure. Hernandez-Alfaro et al. (6) classified the perforations in 3 degrees according to the diameter of the perforation: our study evaluated patients with level 3 perforation, in other words with diameter up to 10 millimetre or with total damage and removal of sinus mucosa.

Over the years several authors have developed different techniques to close the sinus membrane perforation using collagen or resorbable membranes, connective matrices, fibrin glue or suturing the flaps of the sinus mucosa (13), however, in case of large perforations the only possibility was the interruption of the procedure (14).

Our work shows instead that the use of PRGF-Endoret®, a particular platelet concentrate used both in liquid and gel form, allows to terminate the procedure even in case of large perforations or total removal of the sinus mucosa.

In fact, using PRGF gel membranes it was made possible sealing the large perforations of the sinus mucosa thanks to the adhesive capabilities of the autologous fibrin contained in the platelet concentrate. Moreover, it allowed the adhesion of the graft material to the native bone avoiding its dispersion into the sinus in case of total removal of mucosa. Additionally, the release of platelet growth factors promotes the transformation in osteoblastic direction of the clot: indeed, thanks to the degranulation of platelets there is a release of several growth factors (GFs) which are key elements of any healing process (15-18); therefore, if the heterologous material acts as a space maintainer, the autologous component provides those biological elements necessary for tissue regeneration: indeed, the macrophage degradation of the fibrin network ensures the preservation and progressive release of Growth Factors, released early from platelets, for a period of about 20 days (19, 20). In this way, the growth factors thus released extend their anabolic effect over time, amplifying the healing processes: the interaction with the factors released from the surrounding bone tissue directs the maturation of the clot in an osteorigenerative direction.

In addition to the biological advantage on healing, there is also a practical advantage: the gelification of plasma has made it possible to incorporate the graft material, making it easily manipulated within the defect to be treated and avoiding dispersion in the sinus cavity (21).

In case of complete removal of the Schneiderian membrane due to extreme laceration or due to purulent sinusitis, the graft material (heterologous bone mixed with PRGF autologous gel) has been covered with PRGF-Endoret membranes to further protect it: in this way, the regrowth above the graft of the damaged or removed sinus membrane is

encouraged.

Lastly, it should be considered that platelet concentrates have a strong antibacterial effect due to the increased concentration of those plasma molecules that normally constitute the humoral immunity: antibacterial molecules and immunoglobulins inhibit bacterial growth in the grafted material despite the absence of a protective sinus mucosa (22, 23). All these factors promote the healing of soft tissue and hard tissue justifying the results obtained through this method: despite large perforations or sinus mucosa removal with this technique, the procedure of sinus lift can be completed obtaining over time an optimal maturation of bone tissue and osteointegration of the inserted implants in high percentage of cases (24, 25).

We must observe that the post-surgery bleeding (especially by night) from the ipsilateral nostril to the treated side, as well as the presence of blood in the sputum in the first 2-3 days after surgery was almost constant. The bleeding, mainly nocturnal, was modest and never required any treatment (pharmacological or surgical) to be controlled. Another possible complication, quite common in maxillary sinus lifts where a perforation of the sinus membrane occurs, is post-surgical sinusitis: among the 18 patients of this work only 2 patients had a sinus radiopacity image with modest symptoms at the radiological control performed after 2 months, while after 12 months the same condition affected only one patient, the other being radiologically healed.

Although the preservation of integrity of the sinus mucosa is a fundamental element to correctly complete the sinus lift procedure, a quite frequent complication is its perforation which, if excessive in dimensions, can lead to the interruption of the procedure. To reduce this risk, several less invasive regenerative techniques have been developed or different tools have been designed to facilitate the method. On the contrary, this work shows how it is possible to complete the procedure even in case of severe perforation or total removal of the sinus membrane following surgical cleaning of the cavity for purulent or cystic inflammatory pathologies. In fact, in all cases it has been possible to complete the sinus lift procedure both in case of large perforations and in case of complete removal of the Schneiderian membrane; in these cases, the sinus has been treated by totally removing the oedematous and polypoid mucosa, full of purulent material, completing at the same time surgical sinus lift despite the fact that there was no more sinus mucosa. This was possible thanks to the adhesive capability of the autologous fibrin present in the PRGF-Endoret and to its biologic effects that allowed to place the heterologous graft material without its dispersion into the sinus and its osteointegration. In addition, the presence of humoral immunity proteins concentrated in PRGF prevents the bacterial colonization of the graft ensuring a progressive growth of the sinus mucosa above the graft itself.

Both radiologically and surgically, the presence of new healthy sinus mucosa that internally covered the walls of the maxillary sinus and regenerated bone was detected. Also, in terms of implant healing we have shown a high percentage of osteointegration (94.6% implant success at 12 months and 36 months follow-up), slightly lower than that obtained in native bone. Only two out of 37 implants were lost in the first month after insertion, regardless of whether they were placed at the same time of bone regeneration or delayed in time. Obviously, the inserted implants had to ensure adequate primary stability, although the insertion torque could be very low (sometimes less than 10 Ncm).

Analysing these results, we may conclude that the use of PRGF allowed to complete the sinus lift even in case of severe perforation of the sinus mucosa or its total removal thanks to its capability to stabilize the graft, its antibacterial and antifungal activity and its anabolic effect and favouring bone regeneration.

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