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Use of autologous bone marrow rich in stem cells as an osteoinducer in maxillary sinus elevation

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Abstract

Aim: To study the results that can be obtained when performing sinus lift technique by lateral opening with piezo surgery using as graft material a mixture of autologous bone marrow without any treatment and Bio-Oss (60:40) measuring the amount of bone tissue formed in the maxillary sinuses, the percentage of final vital bone obtained in the grafts and the success rate of the implants placed in those sinuses.

Materials and methods: 23 maxillary sinus lifting were performed in 13 patients (10 bilateral, 3 unilateral) using a mixture of bone marrow taken from distal femur with a xenograft (Bio-Oss) Lateral window sinus elevation technique using piezo surgery was used in all cases. 49 implants were placed and loaded. Graft volume, height and density were measure. Besides percentages of new bone, biomaterial remnant and connective tissue were also measure.

Results: Mean volume obtained was 1668 mm3, mean height was 10.9 mm and bone density was 648 HU. Percentage of new bone, biomaterial remnant and connective obtained were 37.08, 16.77 and 45.22 respectively. Finally, the percentage of success of the implants inserted in these grafted sinuses was 96%

Conclusions: The use of a mixture of Bio-Oss with bone marrow obtained from the distal femur seems to be an efficient combination to obtain an adequate percentage of vital bone when sinus lifting is performed. Besides good results can be achieved when implants with microtextured surface are used in this type of sinus graft.

Introduction

The use of stem cells obtained from bone marrow as a therapeutic method is widespread [1] The bone marrow stem cells have been shown to facilitate the healing of different tissues including [2,3]. It contains hematopoietic stem cells and stromal cells that also contain mesenchymal stem cells (MSCs) that differentiate to various lineages [4].

Bone marrow with a high content of Stem Cells (SC) has been widely used in orthopedic procedures, for example, for the regeneration of cartilage at the distal end of the femur, at the medial end of the tibia or in the hips, as well as in other joints [5].

Hernigou *et al.* (2020) showed excellent results in the treatment of osteoarthritis of the knee when injected bone marrow into this joint [6], as well as in the hip [7] and non-unions in the tibia [8] or other long bones [9] using different concentrations of progenitor cells [10].

In addition to being used alone, stem cells can be combined with biomaterials to improve bone formation [11] Thus, for example, Coquelin L *et al.* (2012) used SC mixed with three different human bone allografts obtaining very good results [12].

In the field of dentistry there are different uses, ranging from trying to obtain dental tissues to obtain bone tissue [13]

Maxillary reconstruction has involved stem cells, especially mesenchymal cells [14], mixing them with osteoconductive materials or scaldfols [15]. Different works show an increase in the efficiency of these reconstructions using this combination showing better results than others osteoinducers [16-18].

One of the most complex situations to regenerate are very atrophic maxillary sinuses, where the receptor bed is practically a cortical therefore with little vascularity [19,20].

Some studies show that the use of stem cells obtained from bone marrow mixed with osteoconductors has shown efficacy in improving the percentage of final vital bone in this type of procedure [21] as well as [22].

Rickert *et al* (2011) used stem cells from bone marrow obtained from posterior iliac crest [23]. They used an aspiration syringe previously sprayed with heparin and filled with 8ml of citric acid for obtaining the bone marrow, and them they isolated and concentrated the SC before mixing with a xenograft (Bio-Oss) for sinus graft. They compared this mixture against a mix of autologous bone and the same xenograft, obtaining better results when SC were used.

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In a previous works carried out by our group, bone marrow obtained from the distal femur was used instead, but without using any anticoagulant; the marrow was used without any type of processing and was mixed with the same xenograft (Bio-Oss) obtaining also an increase in the final vital bone in the graft [21]. In this investigation, the extraction technique used was according to the work of Ibanez JR *et al.* (2006); In their research bone marrow from iliac crest and also from the distal femur were used [24].

The possibility of using the distal end of the femur as an alternative to the iliac crest was confirmed by Narbona, Vaquero and Fernández (2011) [25]. They compared the number of MSC that can be obtained from iliac crest, from tibiae and form the distal femur showing that although more cells can be obtain from iliac crest, the number of cells that be collected from the femur were also clinically adequate. In another paper the same authors confirm the efficacy of bone marrow from the distal femur when comparing the number and quality of the MSCs of this place with the iliac crest [26].

The aim of the present work is to study the results that can be obtained when performing sinus lift technique by lateral opening with piezo surgery using as graft material a mixture of autologous bone marrow without any treatment and Bio-Oss (60:40) measuring the amount of bone tissue formed in the maxillary sinuses, the percentage of final vital bone obtained in the grafts and the success rate of the implants placed in those sinuses.

Material and methods

Between June 2008 to August 2018, 23 maxillary sinus lifting were performed in 13 patients (10 bilateral, 3 unilateral) aged from 51 to 74 years old. After 9 months 49 implants were placed and 4 months later were loaded. Just before implant placement, volume and height obtained with the graft were measure in CBCT scans. Bone density was also measure in Hounsfield Units (HU) using Blue Sky Plan software. During implant surgery 11 biopsies were taken for histologic analysis. Besides resonance frequency analysis (RFA) of the implants was performed.

All the patients signed an informed consent form and the study was carried out in accordance with the International Ethical Guidelines for the Research and Biomedical Experimentation on Human Beings (Declaration of Helsinki 2008), ensuring the protection and confidentiality of patient data.

Surgical protocol

The surgeries were carried out during the regular courses of the Career of Specialization in Oral Implantology of the Catholic University of Cordoba, Argentine and in the author's private practice. Each patient was treated by two different operators, but exactly under the same protocol.

Lateral window sinus elevation technique [27] using piezo surgery [28] was used in all cases.

After opening the lateral window and controlled that the sinus mucosae was intact, an orthopedic surgeon anesthetized the lateral aspect of the lower end of the femur above the lateral epicondyle. Then with a 4 mm diameter trocar the cutaneous planes were crossed to pierce the thin bone immediately above the lateral epicondyle. Once the drilling was done, 5 to 10 cm3 of bone marrow was extracted with a 20 cm3 plastic syringe without any anticoagulant [29] (Figure 1).

The bone marrow was mix with anorganic bovine bone (ABB) (Bio-Oss, Geistlich Pharma AG Bahnhofstrasse 40 CH - 6110 Wolhusen)

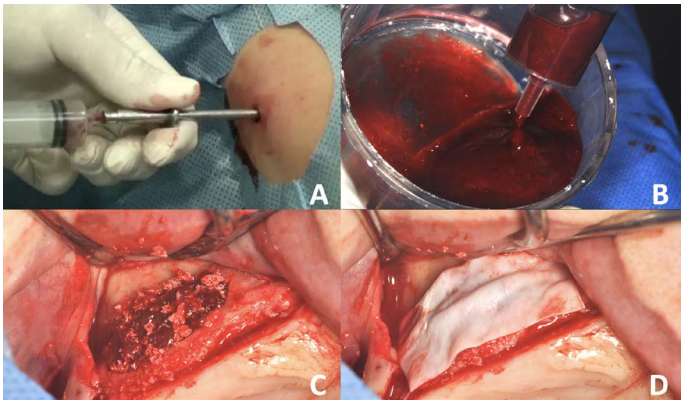

Figure 1. 1A - Extraction bone marrow from distal femur, 1B - Bone marrow, 1C - Maxillary sinus grafted with bone marrow mixed with Bio-Oss, 1D - Collagen membrane (Bio-Gide) for lateral window closing

large particles (1-2um) in a 60: 40 proportion. The mix was used for grafting the sinus, and the lateral window was covered with a native collagen membrane (Bio-Gide, Geistlich Pharma AG Bahnhofstrasse 40 CH - 6110 Wolhusen) Nylon suture was used to close the tissues.

After 9 months CBCT scans were taken in order to control the sinus grafting results and planning the implants placement surgery Figure 2.

Dual acid-etched surface tapered implants (Full Osseotite Tapered, Biomet 3i Palm Beach Gardens Fl USA) were inserted.

During implant placement surgery 11 biopsies were taken using a 3 mm external diameter trephine and immediately fixed in 10% formaldehyde. The sample was processed for histological and histomorphometric analysis with the aim of measure new bone (NB), xenograft (Bio-Oss) remnant (BR) and connective tissue (CT)

After implant placement RFA was performed with Osstell ISQ (Osstell, Stampgatan 14 SE 411 01 Gothenburg Sweden) instrument to obtain implant stability quotient (ISQ)as described by Ibanez, Tahhan and Ibanez (2014) [30].

Four to six months later implants were loaded with the protheses according to treatment plan.

Treatment of the samples for histology and histomorphometry

Samples were decalcified, dehydrated, included in paraffin and mounted in a microtome with a disposable blade to obtain cuts from 3 to 10 microns thick. Them stained with hematoxylin and eosin and prepared for subsequent microscopic study.

For measurements, Image Pro-Plus v4.52 morphometry software was used on digitized microscopic images of the biopsies with 40X optical magnification. The digitalization was carried out using a Carl Zeiss optical microscope with camera incorporated. (Carl Zeiss -Axiocam Ic 5). If the panoramic magnification was insufficient to determine the type of tissue observed in any sector, higher magnifications were used.

The tissue to be measured was determined according to its histological characteristics, both by staining and by the shape and specific details. The specific procedure for measuring consisted in delimiting these areas with the tool provided by the software. For contrasting and well-defined paths, automatic edge detection was selected while the areas that were diffuse, faded or torn during the cutting process were delimited manually. Measurements corresponding to NB tissue were made first, then BR and finally TC was obtained by

mathematical calculation. The data obtained were tabulated in an Excel spreadsheet for subsequent statistical analysis.

Bone density in CBCT scans

The CBCT DICOM images were processed with Blue Sky Plan 3 program (Blue Sky Bio, USA) in normal mode where the panoramic view was observed. The area of grafted bone was identified and differentiated from the native maxillary bone of each case and the measurement of the residual maxillary bone was taken at the point of least height. Then, in the sagittal section of the tomographic study that corresponds to the area of greatest volume of the grafted bone, the height of the grafting taken. In the same sagital view the center was identified and the first measurement of bone density was made, whose value is expressed in gray scale represented by software as Hounsfield Units (HU). Four measurements were also made from the first measurement: 2mm coronal, 2mm apical, 2mm mesial and 2mm distal. This allowed to take the average of the five values as a single value for each case. The bone density values obtained from the delimited areas were compared and the corresponding statistical analysis was performed.

Graft volume in CBCT scans

In the same scans and with the same software graft volume obtained was calculated. In the panoramic view the length of the graft was measure while the width and height were measure in a sagittal view. With these 3 values the volume was calculate for each sinus.

Results

All the sinus procedures had an uneventful heal. The mean volume obtained was 1668 mm3 (min 652 mm max 3105.80 mm3) The height achieved was between a maximum of 15,2 mm and a minimoon of 8 mm with a mean of 10,9 mm. The mean of bone density was 648 HU (min 368 HU max 998).

The distribution of new bone, xenograft (Bio-Oss) remnant and connective tissue obtained is shown in table 1 while an example of the histologic samples is shown in figure 3.

Forty-seven implants of the 49-implant placed were successful. The mean ISQ obtained at implants placement was 63.3.

Discussion

All the maxillary sinus treated were successful and an adequate graft volume was obtained. The percentages of new bone, biomaterial remnant and connective tissue were 37.08, 16.77 and 45.22 respectively. Finally, the percentage of success of the implants inserted in these grafted sinuses was 96%.

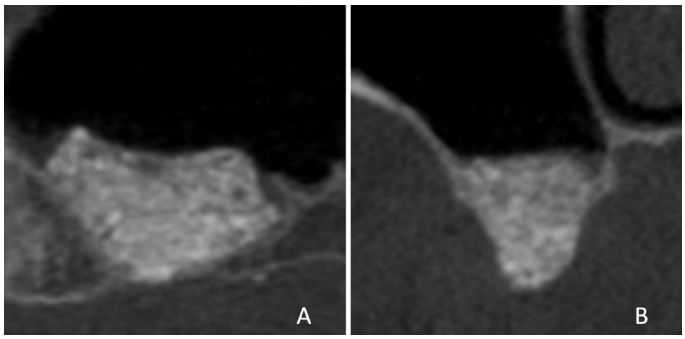

Figure 2. 2A - Grafted sinus after 9 months panoramic view, 2B - Grafted sinus after 9 months sagittal view

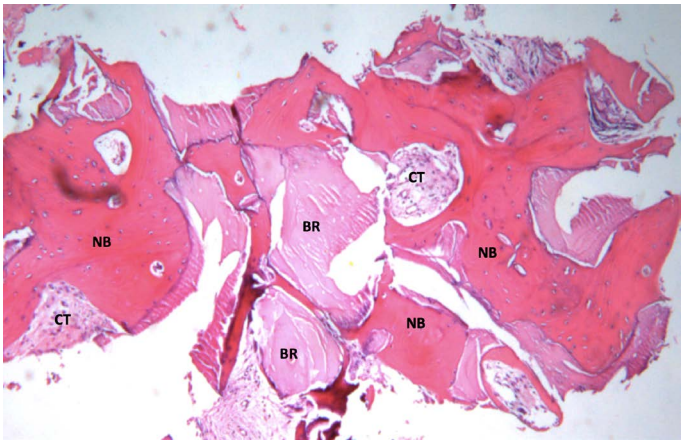

Figure 3. Histologic section showing areas of new bone (NB), Bio-Oss remnant (BR) and connective tissue (CT)

Table 1. Percentages of NB, BR and CT of each of the biopsies analyzed

Sample	New Bone %	Bio-Oss Remnant%	Conective Tissue %
A	52.10%	13.00%	34,.0%
B	25.50%	33.80%	40.70%
C	39.20%	18.80%	42.00%
D	25.40%	12.00%	62.60%
E	28.30%	10.50%	61.20%
F	40.20%	8.80%	51.00%
G	41.50%	12.50%	46.00%
H	47.10%	11.60%	41.30%
I	38.30%	34.50%	27.20%
J	38%	11%	51%
K	35.90%	15%	40.10%
Mean	37.08%	16.77%	45.22%

Hundred percent of the sinus heal normally. This result is similar or better than similar researches using bone marrow [22,29]. Rickert *et al.* (2011) treated bilateral sinus using Bio-Oss mixed with autologous bone in one side and Bio-Oss seeded with mononuclear stem cells harvested from the posterior iliac crest in the other side. Healing was uneventful in 11 of the 12 patients treated [23]. Similar results were achieved by Ferreira *et al.* 2009 [31], Jensen *et al.* (2007) [32] and others (Wallace et al. 2005, Barone et al. 2005) when treated maxillary cases using xenograft alone or with autogenous bone but without bone marrow [33,34].

The volume for implants placement obtained at the sinus grafted was adequate. (mean 1668 mm3) This value is similar to obtained in other researches. Cabrera, Tahhan and Ibanez (2017) obtained a mean volume of 2.117mm3 +/- 630,0 in a study using Bio-Oss alone as graft biomaterial [35] while Sbordone et al (2013) obtained a mean of 1230 mm3 [36].

Bone density of the grafts was measure in CBCT scans in HU obtaining a medium density of 648 HU (min 368 HU max 998). This density corresponds with a type II-III bone according to Lekholm and Zarb (1985) classification [37] or a Type II considering Norton and Gamble (2001) classification [38].

In a similar research but with other materials Sbordone et al (2013) showed a mean density of 781 HU [36]. Seiler, Ibanez and Ibanez (2019) using Bio-Oss measured 13 CBCT scans founding a mean of 625 HU [39].

The percentage of new vital bone obtained in the biopsies in the present research was high (37.08%) in relation to other studies, and

the same can be said about BR and CT. Rickert *et al* (2011) obtained a mean of 13,9% of new bone but the performed the biopsies earlier (14.8 weeks, range 13.3–15.8 weeks) The mean BR was 31.3% and the soft tissues were 52.5% These differences could be explain by the shortest period of healing used [23]. Hirata, Ueno and Moy (2017) found more percentage of NB in sinus lifting procedures using another osteoinductive material, rhBMP-2 at concentration 1.5 mg/mL with an absorbable collagen sponge (ACS). They grafted 10 sinuses obtaining 44,2% of new bone [40]. Shirmohammadi A *et al.* (2014) performed sinus elevation using Bio-Oss mixed with 20% of autogenous bone obtaining 25,3% at 5 months biopsies, lower values than the present study [41]. One the other hand, when Bio-Oss alone was used the results in terms of vital bone were variable. Norton, Odell and Cook (2003) found 25,6 % of new bone [42] and Cordaro *et al.* (2008) obtained 19.6 % [43] Besides Ferreira C *et al.* (2009) found 39% of NB [44].

In the present study 49 dual-acid etched (DAE) implants were inserted in the grafted maxillary sinus. Only 2 implants were lost. (96% success) Ibanez, Tahhan and Zamar (2003) and Ibanez *et al.* (2005) [45,46] found similar success rate in two researches using the same type of implants but in different situations different than sinus grafting. In another study that did included implants placed in sinus lifting procedures, they (Ibanez *et al.* 2020) obtained 95,59% in a 1 to 15 years follow-up [47]. Sbordone *et al.* (2009) in a research comparing sinus lifting implant success vs success in native bone areas a significative difference between both groups (85% *vs* 95,8) but the graft material used in this study was particulate chin bone [48]. In the other hand Ferreira *et al.* (2009) using Bio-Oss alone for the sinus graft obtained a 98% of success of the implants [44].

Just after implant placement, RFA was taken using Osstell ISQ device in order to measure implant stability in this type of graft procedure [30]. The mean ISQ value obtained was 63.3. This result is adequate for the type of bone achieved in the present study. Gallardo, Ibanez and Ibanez (2016) obtained a mean value of 70.5 using the same implants (n=279) but in native bone [49]. Hsu A *et al* (2016) compared the ISQ of 45 implants placed with different anchorages and obtained a mean ISQ of 75.9 when tested indirect sinus elevation implants [50]. By his side Park *et al* (2019) using tapered implants in lateral window sinus grafted obtained a mean ISQ of 68.40 for their implants, a similar result than our study [51].

Conclusions

Due to the results of this preliminary report, the use of a mixture of Bio-Oss with bone marrow obtained from the distal femur seems to be an efficient combination to obtain an adequate percentage of vital bone when sinus lifting is performed. Besides good results can be achieved when implants with microtextured surface are used in this type of sinus graft.

Authorship and Contributorship

Dr Juan Carlos Ibanez and conceived the ideas, performed most of the sinus surgeries and implant insertion, analysed the data and led the writing; Maria A Juaneda and Maria C Ibanez collaborate in the surgeries, collected and analysed the data and collaborate with the writing. Dr Santiago Ibanez conceived the ideas, performed the bone marrow extraction and collaborate with the writing.

The authors did not received any founds for the development and realization of the research.

The authors does not have any conflict of interest in relation to the present research.

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