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Effectiveness and therapeutic safety using β-tricalcium phosphate in oral bone defects

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Abstract

Aim: To determine the effectiveness and therapeutic safety with β-tricalcium phosphate (Biograft-G®) in oral bone defects.

Methods: A Phase III, multicenter, uncontrolled clinical trial (Classification of medical devices), to assess the Biograft-G® Biomaterials Center, University of Havana was made. All the population of the clinical trial was choose from four Cuban provinces and 121 patients was the sample selected for the studies. All the patients gave their consent to participate. The patients included in the study were: ages between 18 and 75 years, both sexes that could be treated surgically. Patients with malignant neoplasms of any location, diabetic patients who were decompensated or difficult to control, immunosuppressed or immunosuppressed, and mentally retarded patients were excluded. Surgeries were performed in patients requiring dental extraction, alveolar ridge reconstruction, periodontal and periapical surgery. The main variable was a clinical and radiographic appearance, evaluated in four periods (7 days, 1, 3 and 6 months) and levels: Success and Failure.

Results: An effectiveness of 97.5% for β-tricalcium phosphate (Biograft-G®) was demonstrated. In all the periods of clinical and radiographic evaluation of it showed gradually reabsorption similar to surrounding healthy tissue, until the complete degradation of the biomaterial. It was determined that adverse treatment (infection, delamination of the material, tenderness and pain) events behaved low.

Conclusion: It was concluded high effectiveness and safety of treatment with Biograft-G® in complex oral surgery, with minimal and mild adverse events to treatment.

Introduction

The bone is classified as a specialized connective tissue consisting of inorganic and organic substances, which give properties such as hardness and elasticity. These tissue influence in a normal bone physiology because it involves a complex interaction between blood minerals (specially calcium and phosphorus), regulation of certain hormones, the activity of bone cells (osteoblasts and osteoclasts) and tensile forces and stretching own body [1].

When the bone tissue of the maxilla or mandible is damaged, it regenerates spontaneously. However, healing is a slow process that can be improved by applying different Biomaterials [1,2].

The dental alveolus is the holes that support the teeth and these cause that it is a special portion of the oral human bone very studied by scientists. As in other bone sites, alveolar bone depends on the functional stimulation of the teeth to maintain their morphology. The remodeling of the aforementioned holes occurs with new bone when the dental organs are lost. The way to do this restoration is called alveolar ridge and it is provide a certain height and thickness. When remodeling occurs spontaneously usually atrophic alveolar ridges (AAR) are obtained that cause difficulties for prosthetic rehabilitation [3-5]. Just this fact justifies the use of surgical techniques and implantable materials, bone substitutes and roots, to remodel the alveolar ridge and prevent their reabsorption [4-7]. It is important that biomaterials used in the surgical process be biocompatible, non-toxic, non-carcinogenic or mutagenic, have good mechanical properties and be tolerated in the short, medium and long term.

Among the mentioned materials are hydroxyapatites (HA) and β-tricalcium phosphate (TCP), which have proven welfare and safety in many biomedical specialties [1,8,9]. The hydroxyapatites interact with the adjacent bone tissue acting as matrix on which is deposited the newly formed bone, high hardness and the stability that provides a mechanical reinforcement of repaired bone [7,10-13]. However, the excellent clinical results reported, it is recognized that the repaired bone is extremely resistant to carving, being a disadvantage for those

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cases where you can place metal implants [14-16].

This property increases the use of resorbable materials such as TCP whose main attraction is that the implanted material is degraded at a rate that allows it to be replaced by a bone tissue with radiographic and histological appearance similar to the neighbor tissues [17-21]. On this background, the Biomaterials Center at the University of Havana (BIOMAT, Cuba) has developed a biodegradable and implantable ceramic (four different size granules) for bone repair, based on β-TCP, called Biograft-G®. The chemical-physical and preclinical evaluations have demonstrated its high quality, with no evidence of adverse reactions [22]. For these reasons a clinical study to demonstrate the effectiveness and safety of treatment with Biograft-G® in the repair of the oral bone complex was done.

Methods

Phase III (Medical Classification of medical devices) clinical, multicentric, uncontrolled research, with bone lesions suitable for applying Biograft-G® as filler, was performed. The universe of study was the population of four provinces of Cuba and the sample contained 121 patients from five health institutions who met inclusion criteria, exclusion and diagnosis (retained or incurable teeth indicated for extraction, periodontal and periapical alveolar ridge reconstruction atrophic surgery) in the period from February 2010 to February 2015. In Figures 1 and 2 it is shown clinical and radiographically one tooth for extraction due to root fracture.

Prior to inclusion, all patients were given the specifications of the treatment, which was part of informed consent. In cases of acceptance, a document was signed by the patient and the investigator. From the methodological, scientific and ethical point of view, the research project was reviewed, evaluated and approved by the Ethics Committee of each participating institution and by the Review Committee created for this clinical research at the coordinating institution, University Dental Clinic of Bauta, Artemisa. All patients had Data Collection Notebook (DCN) which included general patient information, informed consent, number, condition and type of surgical process, as well as all evaluations completed.

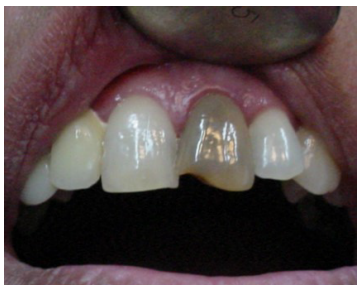

Figure 1. Tooth extraction indicated.

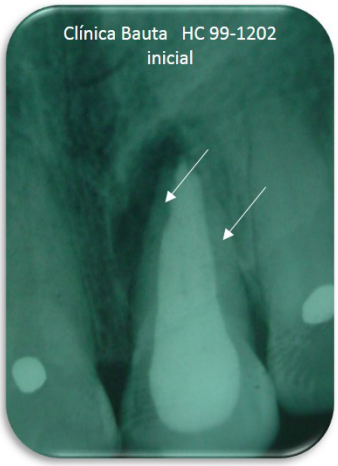

Figure 2. X-rays of root fracture.

The inclusion criteria were age ranges between 18 and 50 years, both sexes, Cuban citizens regardless of race, who gave writing consent to participate, following the Helsinki's principles and the bioethics rules that governing clinical investigations [23,24]. It excluded patients with habits (tobacco and alcohol), difficult to control diabetics, immunosuppressed, mentally retarded, pregnant women and individuals who refused inclusion. It was excluded too the patients was interrupted them implantation surgery or who did not attend the evaluations were applied.

The biomaterial used named Biograft-G® was manufactured by Biomaterials Center, University of Havana, Cuba in form of resorbable, synthetic, dense, ceramic β-TCP granules. The biomaterial was defined as implantable medical devices, Class II b, with Certificate of Registration (Code 87 LMN), at Center for the State Control of Medicaments, Equipment and Medical Devices (CEDMED), Ministry of Public Health, Cuba and the study is registered in the Cuban Clinical Trials Public Registry [25]. The Biograft-G® is a β-TCP (with purity crystalline tricalcium phosphate) 95% minimum, granulate, white, with molar ratio Ca/P = 1.50, stored in a cool dry place, and sterilized by dry heat or autoclave. The drugs used in the clinical study were with Lidocaine 2% with epinephrine anesthetic (Liorad Laboratories, Cuba) and Dipyrone (Medsol Laboratories, Cuba).

The application of Biograft-G® was conducted after obtaining a bone site carefully clean, following of the conventional techniques of each intervention (Figure 3). The granulates were soaked with blood from the surgical site, and implanted into the prepared cavity, from the defect´s depths to the access port (Figure 4).

This procedure is performed under gentle pressure on the Biograft-G® cover by a collagen membrane (Membracel-O, Celina Laboratories, Argentine) which it was placed to allow guided tissue

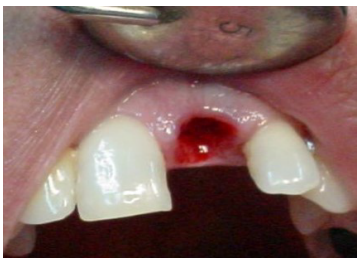

Figure 3. Surgical site carefully clean.

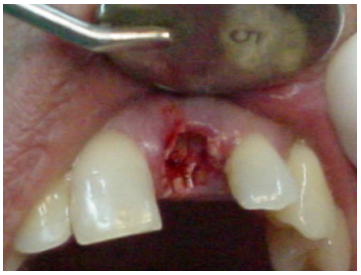

Figure 4. Biograft-G grains in surgical site.

regeneration (Figure 5). The union of the soft tissue was performed with sutures (Silk 3.00) or Tisuacryl® tissue adhesive (BIOMAT, Cuba) like it shows at figure 6. The suture has to be removed between 7 and 15 days. The Tisuacryl® doesn't have to be removed.

Results

The response within seven days of treatment was shown in Table 1 where 12/121 patients (9.9%) had Regular evaluation. This is explained, because it is invasive treatments to soft tissue, described with similar response in other studies [15]. However, in radiographic evaluation all patients were success (more than 90% of biomaterial displayed), indicating a correct filling.

One month after the treatment (Table 2), it could see that 11/12 patients went to good evaluation and radiographic changes did not exist. This fact match with Trisi [17] who observed radiopacity at same time period, with minimal integration aspect. Von Doernberg also [20] suggested that in resorbable materials, a healing is observed when radiopacity is decreasing and replaced by new bone. García-Roco [25] also agrees with previous in visualize radiographically stable all the restorations if it find radiopaque areas and disappearance of the difference between the material and the adjacent bone. The Failure case

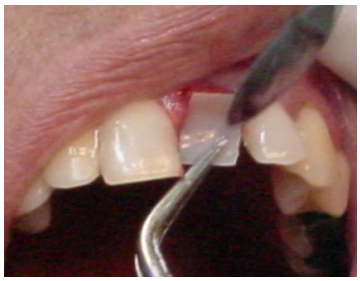

Figure 5. Collagen membrane.

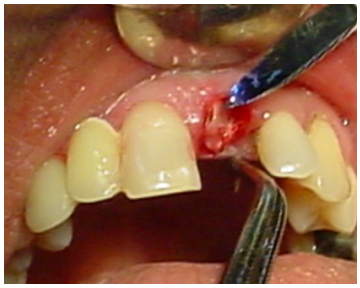

Figure 6. Tisuacryl in surgical site.

Table 1. Clinical and radiographic response at 7 days.

Clinical	Freq.	%	Radiographic	Freq.	%
Good	108	89.3	Success	120	99.2
Regular	12	9.9	Failure	0	0
Bad	0	0	Lost	1	0.8
Lost	1	0.8	Total	121	100
Total	121	100.0			

Absolute frequency = Freq. Percentage = %

Table 2. Clinical and Radiographic response to one month.

Clinical	Freq.	%	Radiographic	Freq.	%
Good	118	97.5	Success	119	98.3
Regular	1	0.8	Failure	1	0.8
Bad	1	0.8	Lost	1	0.8
Lost	1	0.8	Total	121	100.0
Total	121	100.0			

was a patient who presented infection and pain in alternative 2-3 days periods during a month. It was decided to remove the material and categorizing as a Failure, although it was not related to biomaterial, because it was a traumatic extraction. Regular response was due to a nasal polyp near the surgical site. The remaining patients (97.5%) were assessed as Good, because at this stage had already passed the time of surgical trauma.

At 3 months (Table 3) the response was that 116/121 patients (95.9%) were evaluated as Success from clinical and radiographic point of view. The patients evaluated as Bad can be described as one corresponded to a worsening of clinical symptoms of nasal polyp above mentioned, although it was radiographically successful, it was necessary to indicate a treatment to improve the change made ear-nose and throat. The second patient presented a vestibular fistula with pus out on a tooth from the surgical stage and it was detected poor condition of the root surface. A radiographic evaluation of TCP granulates showed that 70% is observed without reabsorb, but with little radiographic contrast. The patient evaluated as Regular was reflected as a pain caused by slight dentinal hyperesthesia, with no significant inflammation of the gums.

The clinical and radiographic responses at 6 months are shown in Table 4. It was observed that 97.5% of patients were recovered. The patient who presented the nasal polyp was listed as successfully cured. Failure by fistula and infection, was treated and to perform the extraction was again included in the study, presented satisfactory evolution without reaction to the implanted biomaterial, Biograft-G®.

Regarding the existence of filler in the bone cavity (Table 5), at 7 days can be observed an average of 96%, a proper filling of the defects (Figure 7). Similar evolution is observed after one month, verifying the absence of exfoliation (Figure 8).

At 3 months it shows that the material remains on average by 73% without radiolucency appear, which corresponds to the expected resorption (Figure 9). At 6 months, the presence of the material had the average value 44%, indicating that the resorption continues (Figure 10).

Lozada [16] raised similar situation after three weeks, a dense connective tissue and newly formed bone trabeculae, which persists after three months until to 12 months when there is a new formation

Table 3. Clinical and Radiographic response at three months.

Clinical	Freq.	%	Radiographic	Freq.	%
Good	118	95.9	Success	118	97.5
Regular	1	0.8	Failure	2	1.6
Bad	3	2.5	Lost	1	0.8
Lost	1	0.8	Total	121	100
Total	121	100.0			

Table 4. Clinical response, and radiographic at six months.

Clinical	Freq.	%	Radiographic	Freq.	%
Success	118	97,5	Success	118	97,5
Failure	2	1,6	Failure	2	1,6
Lost	1	0,8	Lost	1	0,8
Total	121	100,0	Total	121	100

Table 5. Descriptive statistics (% filler).

Radiological Response	Mean ± SD (%)
7 days	95.6 ± 0.4
1 month	94.9 ± 0.5
3 months	73 ± 1
6 months	44 ± 2

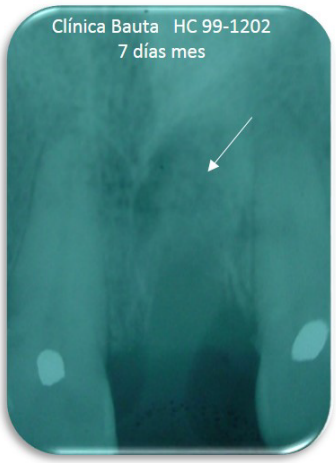

Figure 7. Seven days.

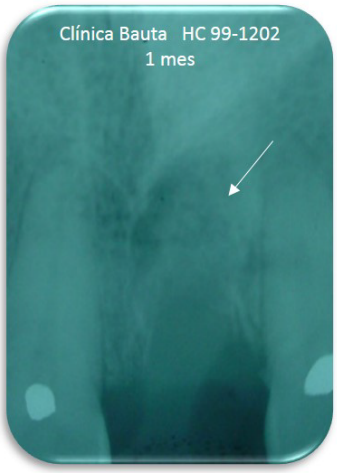

Figure 8. One month.

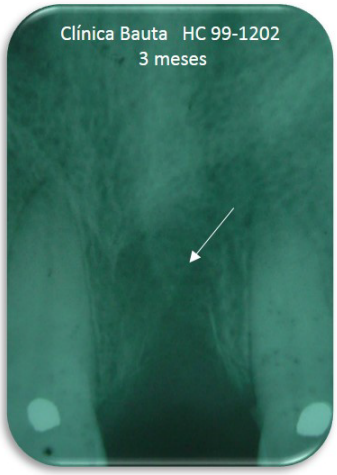

Figure 9. Three months.

and complete resorption of the material is observed.

In Table 6, it shows the final result of the study with 97.5 % of effective use of the material considering the failure not attributable to biomaterial, which not demonstrates serious adverse events in the

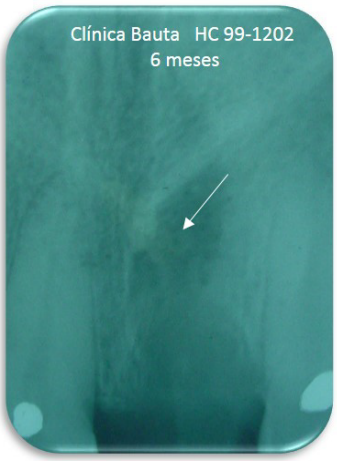

Figure 10. Six months.

Table 6. General Effectiveness.

Effectiveness	Frequency	Percent
Success	118	97.5
Failure	3	2.5
Total	121	100.0

treated cases. These satisfactory results are consistent with studies like Aguirre [26] which noted favorable tissue response implants. All these elements allowed him to infer that the β-TCP can be evaluated as nontoxic locally, with no inflammation or foreign body response in the tissue. A similar view is reflected by Delgado et al, on the implantation of Biograft G® response [22].

Biograft-G® showed a high effectiveness in the treatment which are consistent with other studies of the authors [14,17] and demonstrate the importance of reabsorbable biomaterials to fill the spaces where the bone structure could be lost and lead to the growth of a new bone while it is degradated. Other authors like Simunek, [18], consider achieve preservation of the width of the tooth socket. Mayer [19] also suggested that these techniques are able to maintain a good level of bone volume by preventing bone resorption of the alveolar ridge.

Conclusion

It was determined that Biograft-G® had high effective (97.5%) and safe in oral bone defects. In periods where the evaluation was tracked, clinical and radiographic responses was positive in most patients. Furthermore, they managed advantages in obtaining a newly formed bone tissue similar to nearby normal tissue.

Acknowledgements

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