Utilization of Autogenous Bone, Bioactive Glasses, and Calcium Phosphate Cement in Surgical Mandibular Bone Defects in *Cebus apella* Monkeys

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Purpose: *The purpose of the present study was to evaluate the histologic results of bone cavities that were surgically created in the mandibles of* Cebus apella *monkeys and filled with autogenous bone, PerioGlas, FillerBone, or Bone Source.* ***Materials and Methods:*** *Surgical cavities 5 mm in diameter were prepared through both mandibular cortices in the mandibular angle region. The cavities were randomly filled, and the animals were divided into groups according to the material employed: Group 1 cavities were filled with autogenous corticocancellous bone; group 2 cavities were filled with calcium phosphate cement (BoneSource); and group 3 and group 4 cavities were filled with bioactive glass (FillerBone and PerioGlas, respectively). After 180 days the animals were sacrificed, and specimens were prepared following routine laboratory procedures for hematoxylin/eosin staining and histologic evaluation.* ***Results:*** *The histologic analysis showed that autogenous bone allowed total repair of the bone defects; bioactive glasses (FillerBone and PerioGlas) allowed total repair of the defects with intimate contact of the remaining granules and newly formed bone; and the cavities filled with calcium phosphate cement (BoneSource) were generally filled by connective fibrous tissue, and the material was almost totally resorbed.* ***Discussion:*** *The autogenous bone, FillerBone, and PerioGlas provided results similar to those in the current literature, showing that autogenous bone is the best choice for filling critical-size defects. Synthetic implanted materials demonstrated biocompatibility, but the bioglasses demonstrated osteoconductive activity that did not occur with calcium phosphate (BoneSource).* ***Conclusion:*** *According to the methodology used in this study, it can be concluded that the utilization of autogenous bone and bioactive glasses permitted the repair of surgically created critical-size defects by newly formed bone; the synthetic implanted materials demonstrated biocompatibility, and the bioactive glasses demonstrated osteoconductive activity. The PerioGlas was mostly resorbed and replaced by bone and the remaining granules were in close contact with bone; the FillerBone showed many granules in contact with the newly formed bone; BoneSource did not permit repair of the critical-size defects, and the defects were generally filled by connective fibrous tissue.* INT J ORAL MAXILLOFAC IMPLANTS 2004;19:73–79

Key words: *bioactive glass, calcium phosphate cement, osteogenesis*

Autogenous bone is considered ideal for filling bony defects, especially large defects resulting from cysts and tumors, alveolar resorption, and periodontal bony defects—all of which leave insufficient bone for the placement of implants. The cancellous portion is usually used and it is rich in mesenchymal cells, which are generally involved in osteogenesis. However, clinical situations, such as the size of the bony defect, absence of enough donor tissue, or the need for a second intervention, may preclude its use.

The development and studies of biomaterials have improved the characteristics and properties of potential synthetic bony substitutes.[1] Among others, hydroxyapatite (HA) and bioactive glasses have demonstrated biocompatibility and direct contact with bone.[2–6]

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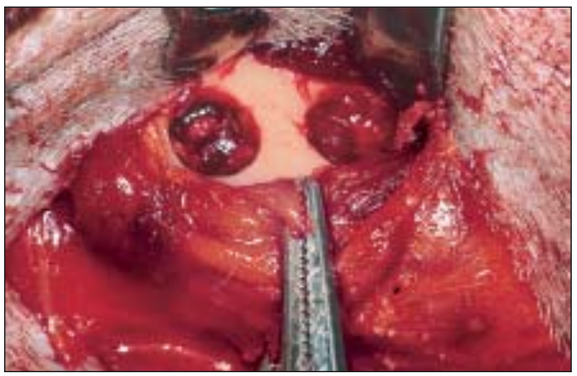

Fig 1 The surgical defects were prepared bilaterally through both mandibular cortices, with a diameter of 5 mm, in the mandibular angle region.

Bioactive glass is a material composed of calcium and sodium ions, phosphate, and silicon dioxide. In its solid form, it has been used in orthopedics, otolarngology, and dentistry after extraction to maintain the alveolar ridge.[7,8] In dentistry a particular form of bioactive glass is designed for the treatment of periodontal bone defects, filling of alveolar sockets, and augmentation of alveolar ridges. The size of the irregularly shaped particles ranges from 90 to 710 µm. When bioactive glass comes into contact with tissue fluids, a series of chemical reactions occur, which result in the formation of a hydroxycarbonateapatite layer (HCA) on the surface of the particles. Organic ground substance proteins, such as chondroitin sulfate and glycosaminoglycans, become incorporated into the HCA as it forms. Osteoblasts are attracted to the HCA layer and release organic constituents, followed by mineralization. The speed of bone growth around bioactive glass particles has been shown to be rapid and the newly formed bone to be denser.[1,6,9]

Calcium phosphate cement (CPC) may directly initiate osteogenesis or promote osteoconduction when placed in contact with host bone. All CPCs are formulated as solid and liquid components that, when mixed in predetermined proportions, react to form HA. The final reactant will determine whether the end product will be nonresorbable, minimally resorbable, or completely resorbable. The powder component usually consists of 2 or more calcium phosphate compounds, whereas the liquid component is water, saline, or sodium phosphate. Some of the calcium and phosphate compounds involved in bone and mineral formation, or as implants, are dicalcium phosphate, octacalcium phosphate, amorphous calcium phosphate, tricalcium phosphate, and HA. Studies have not reported that these materials cause foreign-body reactions or other forms of chronic inflammatory response.[10–19]

The purpose of this study was to compare histologically 2 bioactive glasses, a CPC, and autogenous bone as fillers for surgically created critical-size bone defects in the jaws of *Cebus apella* monkeys.

MATERIALS AND METHODS

Four young adult male monkeys were used *(Cebus apella)* with weight ranging from 2.0 to 2.5 kg and age determined as described by Schultz.[20] Before surgery, the animals were maintained in the Primate Procreation Nucleus, Dental School, Araçatuba, UNESP, and were fed bananas, corn, rations, eggs, and varied fruits. After fasting 15 hours, the animals were weighed and anesthetized with thionembutal, aqueous solution, in the dosage of 30 mg/kg. At this time, penicillin G-procaine and penicillin G-potassic crystalline with streptomycin (300,000 IU veterinary) were administered in a single dose intramuscularly for each animal.

The submandibular regions of each animal were cleansed with povidone-iodine solution. To avoid excessive bleeding, a solution of adrenaline (1:400,000) was infiltrated along the area to be incised. The incision was made on the skin of the animal in the submandibular region, with subsequent dissection of the subcutaneous tissue and platysma muscle. The masseter was incised, so that the mandibular angle was exposed. The procedure was done bilaterally. With a pneumatic handpiece and trephine (5 mm in diameter; Implant Innovations/3i, Palm Beach Gardens, FL) and under external and intense irrigation with physiologic saline solution, 2 cavities were prepared in each mandibular cortex on each side (Fig 1). All preparations had a diameter of 5 mm, which are critical-size defects for *Cebus apella* monkeys.[21]

At this time, the cavities were divided randomly into 4 groups according to the material used for filling them:

- Group 1: filled with tibial autogenous medullar bone
- Group 2: filled with CPC (BoneSource, Stryker Leibinger, Freiburg, Germany) after preparation according to manufacturer instructions (1.25 mL water/5 g of powder)
- Group 3: filled with bioactive glass (FillerBone, Taipei, Taiwan)
- Group 4: filled with bioactive glass (PerioGlas, US Biomaterials, Alachua, FL)

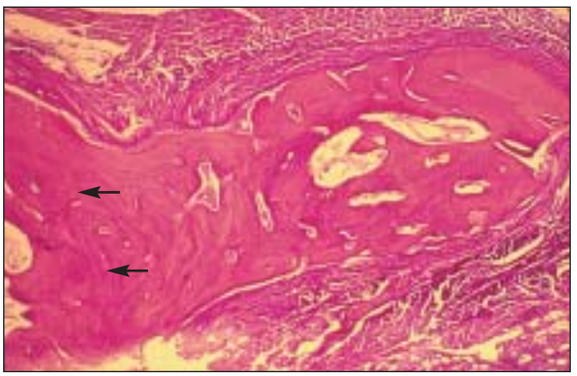

Fig 2 Group 1 defect (autogenous bone) showing cavity filled with newly formed bone. Note the presence of reversion lines *(arrows)* separating the newly formed bone from the pre-existing bone (hematoxylin-eosin; ×25).

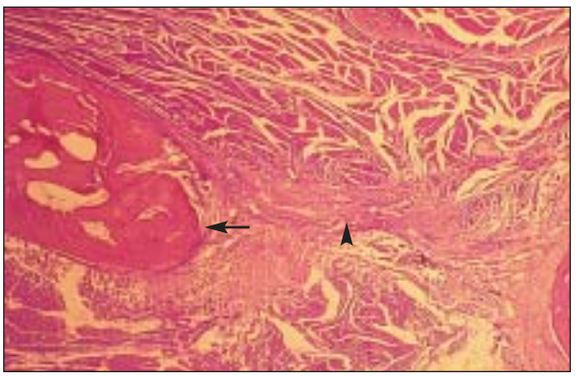

Fig 3 Group 2 defect (BoneSource) cavity filled by connective fibrous tissue *(arrowhead)*. Note the remodeling at the edge of the cavity *(arrows)* (hematoxylin-eosin; ×25).

After the control of bleeding, the cavities were randomly filled with the corresponding material, and the soft tissues were closed with 4-0 polyglactin-910 (Vicryl 4-0, Ethicon S/A, São Paulo, Brazil) sutures. In the immediate postoperative period, 20 mg of diclofenac potassium were administered through an intramuscular injection.

The animals were maintained in individual cages during the entire experimental period and sacrificed after 180 days. At the time of sacrifice they were again anesthetized, and 4 L of 0.9% heparinized saline solution were infused to wash the circulatory system. After that, 4 L of neutral 10% formaldehyde were infused. The jaws were dissected and the specimens were isolated with the surgical cavities. After routine laboratory procedures,[21] the specimens were embedded in paraffin and histologic serial sections were prepared. These were 6 μm thick and prepared as transverse sections of the specimens. Tissue reaction, newly formed bone, bone characteristics, and presence or absence of the implanted materials were evaluated.

RESULTS

The animals did not present any complications following the immediate postoperative period until sacrifice, and no materials were rejected. The histologic evaluation revealed the following results.

Group 1: Autogenous Bone

The cavities filled by autogenous bone were completely repaired by newly formed bone (Fig 2), characterized by the organization of Haversian systems. Reversion lines were seen delineating newly formed bone and pre-existing bone. The newly formed bone demonstrated other features of the Haversian system, presenting a larger number of osteocytes that showed immaturity in relation to the surrounding bone, thus indicating a process of bone repair.

Group 2: BoneSource

The cavities filled by the CPC (BoneSource) were not filled totally by newly formed bone but contained fibrous connective tissue (Fig 3). A small amount of material could be seen in close contact with muscle. The bony edges of the cavities were remodeled (Fig 3). Granules of the material were surrounded by a thin layer of connective tissue, without the presence of chronic or acute inflammatory reaction.

Group 3: FillerBone

The cavities were filled by newly formed bone involving granules of the material (Fig 4). Granules of the material were in close contact with the newly formed bone without the presence of fibrous connective tissue and with osteocytes in close contact with the material (Fig 4). The granules that contacted muscle and periosteum were surrounded by a thin layer of fibrous connective tissue without the presence of chronic or acute inflammatory reactions (Fig 5). The granules showed great variation in shape and size.

Group 4: PerioGlas

The cavities were totally filled by newly formed bone. Reversion lines delineated newly formed bone and pre-existing bone (Fig 6). The newly formed bone demonstrated other features of the Haversian system, presenting a larger number of osteocytes that showed immaturity in relation to the surrounding bone, indicating a process of bone repair. Few granules could be seen, and when present, they were surrounded by newly formed bone and in close

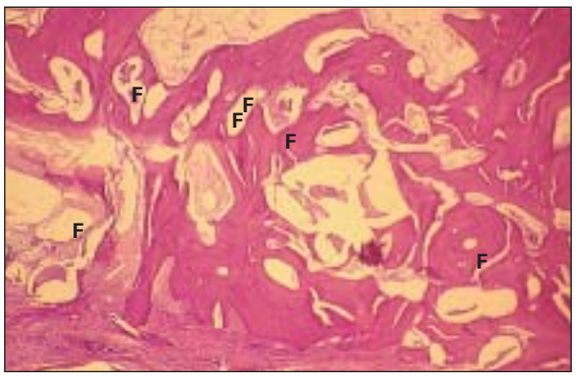

Fig 4 Group 3 defect (FillerBone). The cavity is filled with newly formed bone, with granules of the material (F) bone (hematoxylin-eosin; ×25).

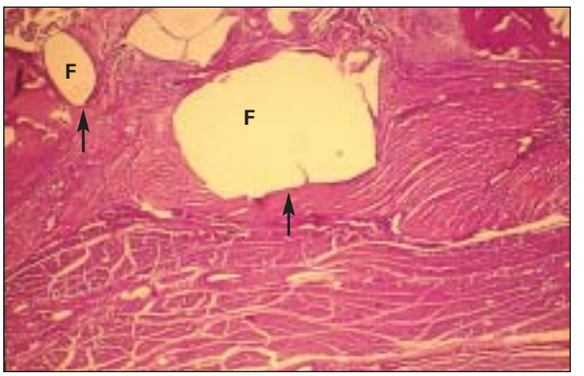

Fig 5 Group 3 defect (FillerBone). Section showing a granule of the material involved by muscle (F). Note the contact between muscle and granule, without inflammatory reaction *(arrows)* (hematoxylin-eosin; ×63).

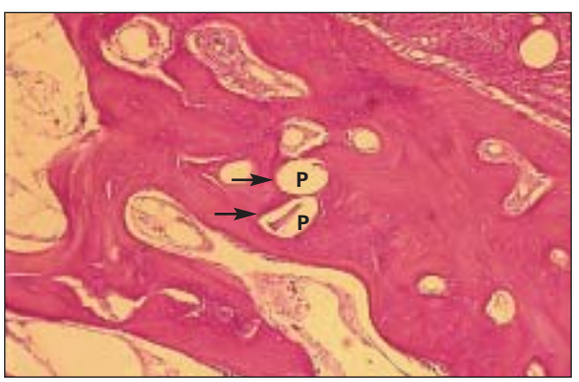

Fig 6 Group 4 defect (PerioGlas). The cavity is filled by newly formed bone involving small amount of granules (P). Note the presence of a reversion line separating the newly formed bone from the pre-existing bone *(arrows)* (hematoxylin-eosin; ×25).

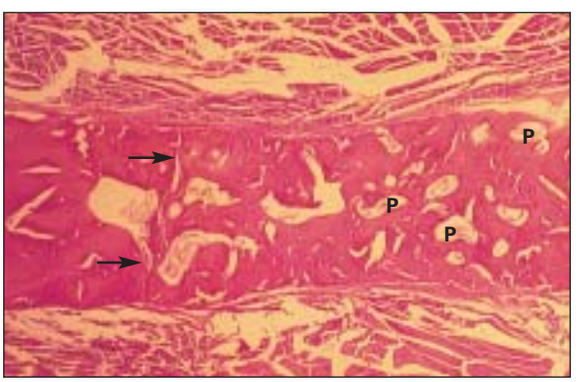

Fig 7 Group 4 defect (PerioGlas). The cavity is filled by newly formed bone involving small amount of granules of the material (P). Note the contact between bone and granules *(arrows)* (hematoxylin-eosin; ×63).

contact with it, without the presence of fibrous connective tissue between the material and bone (Fig 7). Some granules were in contact with muscle and periosteum and were surrounded by a thin layer of fibrous connective tissue, without the presence of chronic or acute inflammatory reaction. The remaining granules had shapes and sizes that were more regular than the granules of FillerBone.

DISCUSSION

The cavities filled by autogenous bone were totally repaired by newly formed bone, demonstrating that autogenous bone is still the best material for filling critical-size bone defects, as noted by other authors.[5,22–27] The success of autogenous bone is related to vascularization of the bed site, adequate covering by soft tissue, and quantity and viability of the osteoprogenitor cells. Thus, cancellous and corticocancellous bone are the ideal materials for filling these sites.[5,22–27] In the present study, the bed sites had these characteristics, and the bone used was tibial autogenous corticocancellous bone.

Biocompatibility of the bioactive glasses was demonstrated histologically by the characteristics of the tissue inside and surrounding the granules in the bone.[21,28–34] Remaining granules found in the soft tissue were not involved with an acute or chronic inflammatory reaction; only a thin layer of fibrous connective tissue was evident. However, dissolution of the central part of the granules with newly formed bone inside of them was not seen histologically, as described by Schepers and Ducheyne,[35] Macneil and coworkers,[36] and Vogel and associates.[37] Similar results were seen in a previous study.[21] Bioactive glasses caused few alterations in the cellular characteristics of the osteoblasts in vitro,[18,38] inhibited the osteoclasts in cell cultures,[18] and showed high activity of alkaline

phosphatase surrounding the granules,[38] demonstrating their osteoconductive activity.

The material aspect inside the newly formed bone suggested that the process of formation of chambers in the granules had occurred, as a result of the removal of the gel-like silicate allowing bone formation around the inside of the bioactive glass granules.[21,31,32,35,36] This demonstrated osteoconductive activity and the fact that the material provided a good scaffold for bone formation.

In comparing histologically the 2 types of bioactive glasses used in this study (FillerBone and PerioGlas), the authors noted that the FillerBone did not have regularly shaped and sized granules, differing from the PerioGlas. However, the osteoconductive properties of the FillerBone were not affected, because newly formed bone totally filled the group 3 defects, with a great quantity of granules. Fetner and coworkers[28] used 2 types of PerioGlas with a different granule size and observed that the difference in size did not affect bone neoformation. The irregularity of the granules caused slow reabsorption of the material but did not change the osteoconductive capacity. What needs to be considered is that the timing of surgery in an area to be filled with this material, when mature bone is needed, should be postponed, especially in the placement of implants.

The utilization of bioactive glasses in periodontal bone defects has produced satisfactory clinical and radiographic results, as seen by new bone formation after implantation of the material.[1,21,39,40] Newly formed bone was observed in the present study with both the bioactive glasses that were used.

The CPCs represent a new group of materials for bone augmentation and reconstruction. BoneSource resorption has been described by Schmitz and associates[41] as slow and gradual. For a material to become integrated in bone, it is desirable that it maintain its shape indefinitely. However, this did not occur in the present study, because a small amount of material was found in the defects treated by BoneSource, and this was not replaced by bone, permitting the filling of the defects by fibrous connective tissue, a result that differs from those of other studies.[11,12,14,15,42–45] The present results could be related to the fact that the material did not induce adequate osteoconductive activity, or it degraded quickly, or possibly it was displaced after its setting because of local bleeding or because of the size of the defect (critical-size defect). Kurashina and colleagues[12] proposed that a dry surgical field is necessary to prevent dislocation of the cement after its setting. This is not always possible in surgeries, despite the bed site, which in the present study was an area of muscle insertion that might prevent displacement of the material. Knaack and associates,[43] in femoral defects in dogs, observed only 1.7% of the CPC (BSM Embrac, Walter Lorenz Surgical, Jacksonville, FL) remaining after 4 weeks in the defects. While faster resorption of the material was demonstrated, bone neoformation was also seen. Frankenburg and associates[10] observed blood vessels penetrating into Norian SRS cement (Synthes, Oberdorf, Switzerland) in tibial defects in dogs and osteoclasts removing material in areas of bone neoformation. Total resorption of the Norian SRS cement was seen after 16 weeks.

The mechanism of bone repair induced by the CPCs would involve the adsorption of growth factors by the HA and the direct effect of the calcium phosphate.[46] Many growth factors in the bone matrix can be adsorbed into the HA and then modulate local cellular differentiation. The calcium phosphate ions are mitogenic to fibroblasts, causing differentiation and thus formation of osteoid tissue, which activates the osteoblasts in the bed site to produce bone.[41,47] It is questionable whether the CPCs are dense enough to act as a barrier to free the diffusion of hormones, growth factors, and cytokines, making only the peripheral area of the material responsible for modulation of the osteoconduction.[41] This may explain the fact that only the borders of the cavities showed remodeling of a small amount of newly formed bone.

The results obtained with BoneSource indicated that its utilization in periodontal bone defects probably would be negative, as demonstrated by Brown and coworkers.[48] They attributed the failure of this material in the treatment of periodontal bone defects to 3 possibilities: micromovements (50 to 100 μm) that occurred during mastication, causing fractures or dislocation of the material; no or very little porosity of the material to permit bone neoformation; or bacterial contamination and colonization of the material before bone neoformation took place. Lovelace and colleagues[39] suggested that the pore size would confer resistance to bacterial infection, but infection across the gingival sulcus could surround the implanted material. In the present study, infection and/or expulsion of the CPC was not observed.

The residual material in the soft tissue was surrounded by a thin layer of fibrous connective tissue without an acute or chronic inflammatory reaction, demonstrating, despite a long period of analysis, biocompatibility as described in the literature.[4,11,40,44,45,49] No evidence was found that would contraindicate the use of CPC in bone defects surrounding endosseous implants. Bifano and associates[4] used BoneSource for alveolar ridge augmentation without the placement of implants.

Perhaps the use of autogenous bone with bioactive glasses, or other biomaterials for filling bone defects, especially critical-size defects, would decrease the amount of autogenous bone necessary for this repair and would enhance the properties of bone and biomaterials to improve the bone repair. More studies are necessary to prove the benefits of the CPCs.

CONCLUSIONS

According to the methodology used in this investigation, it can be concluded that the utilization of autogenous bone, FillerBone, and PerioGlas permitted the repair of surgically created critical-size defects by the formation of new bone. The synthetic implanted materials demonstrated biocompatibility, and FillerBone and PerioGlas suggested osteoconductive activity that did not occur with BoneSource. The PerioGlas was generally resorbed and replaced by bone, while the remaining granules were in close contact with the bone. The FillerBone had many granules in close contact with the newly formed bone. The BoneSource did not permit repair of the surgical defects and the defects were filled by fibrous connective tissue.

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