Experimental Facial Augmentation With Hydroxyapatite Cement

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Objective: To study the results of implantation of preformed hydroxyapatite (HA) disks and HA cement in onlay augmentation.

Methods: In this prospective study involving 16 adult New Zealand rabbits, HA disk and HA cement samples were implanted separately and together along the bony and cartilaginous nasal dorsum as well as over the supraorbital bone. Gross and histologic examinations of the implants were performed at intervals ranging from 3 to 24 months.

Results: There was no evidence of infection, adverse reaction, or implant extrusion in the 15 rabbits surviving the planned period. Grossly, all rabbits had prominent noses and supraorbital regions that were immobile on digital palpation. No measurable change in HA disk height and width was noted but there was a 15% decrease in height and width in the HA cement implant. Microscopically, preformed HA disks were found to be enclosed in a vascularized fibrous capsule. When disks were combined with HA cement, a vascular fibrous capsule was still noted around the implant but there was osteoconversion in the underlying cement layer. Used alone, HA cement underwent both osteoconversion and osteointegration. Neither the preformed HA disk with and without HA cement nor the HA cement alone elicited giant cell reaction or inflammatory changes. The HA cement alone was found to have microscopic fissures at the edges.

Conclusion: This animal study suggests that preformed HA implants and HA cement, alone or in combination, can be used to augment the non-stress-bearing craniofacial skeleton.

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Hydroxyapatite (HA) cement has several advantages as an alloplast for craniofacial augmentation. Hydroxyapatite naturally makes up 60% to 70% of bone substance and, unlike many other implants available today, HA cement implants do not foster an inflammatory or foreign body response because of their remarkable biocompatibility. Their osteoconductivity (ie, their ability to foster osteoconversion and osteointegration), coupled with a lack of adverse soft tissue response, greatly minimizes the risk of rejection or migration. Osteoconversion refers to the ability of bone to grow within and replace the substance of the implant, whereas osteointegration refers to the implant becoming solidly attached to bone. Reported applications of HA cement include, but are not limited to, dental augmentation, frontal sinus obliteration, cranial defect reconstruction, and repair of cerebrospinal fluid leak.

In addition to favorable tissue interaction, HA cement contours easily, sets in about 15 minutes, and converts to solid HA in about 4 to 6 hours.

Methods

This study was approved by the Saint Louis University Animal Care Committee. Surgery was performed prospectively under general endotracheal anesthesia in sterile conditions on 16 adult New Zealand rabbits. A single weight-adjusted intramuscular dose of the antibiotic enrofloxacin was given. Ketamine (15 mg/kg) was administered intravenously as an initial anesthetic. An incision extending from the left lateral nasal alar base to the vertex of the scalp was made, and buprenorphine (0.05 mg/kg) was then administered intramuscularly for further anesthesia. The skin and subcutaneous tissues were dissected to expose the areas to be implanted. After placement of the implants, and of titanium microscrews for implant height reference, the wounds were closed in subcutaneous and superficial layers with absorbable sutures.
Initially, 3 rabbits received along the nasal dorsum a preformed half-cylinder HA implant 6 mm in diameter and 12 mm in length. The cranial portion of the half cylinder was placed in a subperiosteal pocket and its caudal portion in a supraperichondrial position. Because of a seesaw effect caused by the rigidity of these implants and their flat base, they had minimal contact with the underlying soft tissue and did not integrate in the bone. Although none of the 3 rabbits had nasal implant problems or displacement, the protocol was revised to use HA cement on the nasal dorsum instead of the rigid half cylinder. In the remaining 13 animals, HA cement was placed on the bony (subperiosteal) and cartilaginous (supraperichondrial) nasal dorsum. All 16 rabbits were then implanted with a preformed HA disk (3.5 mm in height and 6 mm in diameter) on one supraorbital ridge and with HA cement on the other, both underneath the periosteum (Figure 2). Of these 16 HA disks, 8 were placed directly on the bone and 8 were placed on a thin layer of HA cement. The cement was obtained by mixing into a paste 5-g units of sterile HA powder with approximately 0.3 mL of sterile water per gram of powder.

To assess any changes in the final implant height, titanium microscrews were placed in the bone through the implants or adjacent to them. The final height of the implanted microscrews was measured with calipers. Two rabbits were then humanely killed at 3-, 6-, 9-, 12-, 18-, and 24-month intervals. The gross morphology of the implants was assessed by digital palpation and scalar measurement. The superficial soft tissues were then removed, leaving the implant capsule intact, and calipers were used to measure the length and height of the implants. Gross and histologic examinations of the implants were performed.

The specimens were removed en bloc to include the implants with the underlying bone and/or cartilage. They were then fixed, sectioned, and stained with mineralized bone stain and toluidine blue, without decalcification, at the Harrington Arthritis Research Center, Phoenix, Ariz.

**RESULTS**

One of the 3 recipients of a half-cylinder HA implant was killed at 6 months because of a lower gastrointestinal disorder unrelated to the implants. There was no evidence of infection, implant extrusion, fluid collection, or other adverse reaction in any of the remaining 15 rabbits. Grossly, all rabbits were noted to have firm, prominent nasal dorsums and supraorbital regions where the HA disk and cement implants had been placed, and these areas were immobile on digital palpation. The height and width of the HA disks were maintained but, based on height and width measurements, the HA cement showed a 15% decrease in overall volume. On gross examination there was increased resorption of the HA cement overlying the cartilaginous dorsum. The HA disks with underlying HA cement maintained their overall size more consistently than HA cement alone. This was observed in the supraorbital bone implants, and also when comparing the nasal dorsum results of the 3 original rabbits (implanted with firm HA half-cylinders) and the subsequent 13 rabbits (implanted with HA cement). Inflammatory response to HA was minimal to none on histologic examination (Figures 3, 4, 5, 6, 7, 8, and 9).

Microscopically, the preformed HA disks were found to have a vascularized fibrous capsule (Figure 7). When combined with HA cement (Figure 8), a vascular fibrous capsule was still noted around the implant but the HA cement showed osteoconversion. When placed alone, HA cement underwent both osteoconversion and osteointegration (Figure 5). The preformed HA disk with and
without HA cement and the HA cement alone appeared to elicit no giant cell reaction or inflammatory changes. Only the HA cement exhibited microscopic fissures at the periphery of the implant. The extent of osteoconversion was greater in implants that had been in place longer. None of the microscrews placed for measurement purposes were extruded or elicited infection.

**COMMENT**

Implant height and width was better maintained in the HA disks than in the HA cement alone. Additionally, when the HA cement was implanted alone, height was better preserved than width. Perhaps this is due to continued remodeling of the cement after wound closure, or because a lesser cement density at the periphery allows a greater degree of resorption and/or erosion than at more central locations (Figure 6). The 2-year follow-up of this study seems to imply long-term persistence of implant volume in non-stress-bearing areas. Several investigators have also found that the volume and shape of the HA cement implant is stable, as, through osteointegration, the substrate is slowly replaced with bony ingrowth, with minimal invasion of fibrous tissue. Unlike the 200- to 500-µm holes of the ceramic HA blocks, the 2- to 5-µm pores of the HA cement prevent internal growth of fibrous tissue, thereby maximizing osteoconductive activity. Also, it is not surprising that the HA implants exhibited greater volume permanence in preformed disks than in cement form. The cement, containing a greater proportion of water, is subject to more resorption.
spinal fluid leak. Several other studies have also found no HA resorption.

Shindo et al placed HA cement with and without a collagen membrane to contain the cement beneath the periosteum of the supraorbital ridges of dogs. They found no significant decrease in the height of the implanted material regardless of the use of the collagen membrane. However, about one half of the HA cement was resorbed and replaced by bone in the area without the collagen membrane, whereas a fibrous union between the implant and bone, without HA cement resorption, developed in the side with a collagen membrane. This suggests that, although it prevents cement resorption, the collagen membrane prevents osteoconversion by acting as a barrier for osteoid deposition.

Lykins et al and others carried out fronto-orbital craniotomies on kittens with HA cement reconstruction, and also used the cement to obliterate the left frontal sinus. Five months after implantation they performed gross and morphometric measurements and noted some differences in orbital height and skull width. They attributed these changes to skull growth and cranial sutural disruption, however, and not to significant HA cement resorption.

Baker et al reviewed the records of 61 pediatric patients who had undergone HA cement reconstruction of craniofacial defects. The patients were followed up from 16 to 36 months (mean, 20 months). The authors noted no deviations from the norm in head circumference growth curves, and made no comments about the possibility of gradual HA cement erosion over time (this is consistent with our finding a minimal erosion over 24 months). Additionally, 7 of the 61 patients had complications (there were visible irregularities in 2 patients, a postoperative drain fused to HA cement in 1 patient, and subcutaneous fluid accumulations refactory to needle aspiration that required open drainage in 4 patients). Fluid collection, which did not occur in our rabbit model, can be attributed to larger sample size, larger operative site, and increased likelihood of minor postoperative head trauma in a pediatric population.

In their study, Burstein et al attributed the successful use of the HA cement to the creation of a periosteal envelope, the watertight closure of the wound, and prolonged closed drainage of the surgical field, believing that these techniques maximize the ability of the HA cement to dry and consolidate. Interestingly, they also achieved faster drying times using monosodium phosphate (10 minutes) instead of sterile water (20 minutes). For the last 20 patients of the study, 1 g of cephalosporin was added per 10 g of HA powder. The authors concluded that incorporating antibiotics in HA cement might have applications in the treatment of osteomyelitis.

Baker et al reported using a different type of bone paste, carbonated calcium phosphate paste (CCPP), to reconstruct craniofacial defects in 16 adult and pediatric patients. Complications included 1 wound infection and 1 case of cement microfragmentation, but the authors concluded that this material was promising as a bone substitute as 1 patient underwent successful malar augmentation. Manufacturers purport that CCPP undergoes complete osteoconversion; however, studies have only been performed in stress-bearing models. Compared with HA cement, which requires 10 to 20 minutes to harden (depending on the solvent) and has a final compressive strength ± SD of 66.1 ± 5.0 MPa and a tensile strength of 10.8 ± 1.0 MPa, CCPP is reported to require approximately 10 minutes to harden and to achieve a final compressive strength of 55 MPa and a tensile strength of 2.1 MPa. Moreover, whereas HA cement is radiodense, CCPP is radiopaque and can be applied repeatedly after drying without compromise of the overall augmentation strength. Therefore, CCPP seems to show promise for use in facial augmentation; however, studies specifically for this purpose have not been performed.

The immobility of HA implants in our study is most likely attributable to 2 different processes. The HA disks became enclosed in fibrous capsules, and the HA cement underwent osteoconversion and osteointegration (Figures 5, 7, and 8). As mentioned above, the larger pore size of the HA disk allows the cellular ingrowth of a fibrous capsule. Maas et al reported similar findings of porous implants forming fibrous capsules rather than un-
derning ongoing osteoconversion. In their study, porous black pyrolyzed carbon and polytetrafluorethylene, polyamide filament mesh, and ultra–high-density porous polyethylene all demonstrated this pattern. Only 6 of their 24 porous implants were noted to be stable on underlying bone after 3 months.

In our study, osteoconversion was found in the HA cement when it served as either an interface between the preformed implant and bone or an onlay, and vascularized fibrous capsules were found on preformed HA disk implants. No fissures were noted in the HA disk implants; and although fissures were noted in the HA cement implants, none of the rabbits showed any morbidities and none of the specimens showed significant resorption. It is likely that the fluid content of the HA cement is resorbed over time, which contributes to the observed decrease in volume. One could therefore suggest to slightly overcorrect planned facial augmentation, as subtle volume reduction may occur over time.

Inflammatory response to HA was minimal to none on histologic examination (Figures 3–9), and this biocompatibility reduces the risk of implant extrusion, in contrast to alloplasts such as methylmethacrylate, injectable silicone, ultra–high-density porous polyethylene, or porous pyrolyzed carbon and polytetrafluorethylene. Ideally, implant material for facial augmentation should not elicit infection, should contour with ease, maintain a stable size and shape over time, be radiolucent to allow future diagnostic radiography, and be nonallergenic, noncarcinogenic, and synthetic (to eliminate donor morbidity or disease transmission). As evidenced by the data, HA cement has shown promise in many of the criteria listed above. This animal study presents findings that support the use of preformed and cement HA implants, alone or in combination, to reliably augment the non–stress-bearing craniofacial skeleton.

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REFERENCES