K970400

SUMMARY OF SAFETY AND EFFECTIVENESS
BONESOURCE® HYDROXYAPATITE CEMENT (HAC)
FOR FACIAL AUGMENTATION

MAY - 2 1997

I. GENERAL INFORMATION

Classification Name:	Prosthesis, Chin, Internal
Common Name:	Hydroxyapatite Cement (HAC)
Device Trade Name:	BoneSource® Hydroxyapatite Cement (HAC)
Classification Code:	79FWP
Submitter's Name & Address:	Osteogenics Inc. 250 East Arapaho Road Richardson, Texas 75081 (972) 918-8361
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II. PREDICATE DEVICE

BoneSource® is claimed to be substantially equivalent to MEDPOR® Surgical Implants (porous polyethylene) manufactured by Porex Surgical Inc. of College Park, Georgia. MEDPOR® Surgical Implants were cleared by FDA under 510(k) K922489 on September 2, 1992.

III. DEVICE DESCRIPTION

BoneSource® Hydroxyapatite Cement (HAC) is a self-setting, calcium phosphate cement that hardens in an aqueous environment at body temperature and consists solely of calcium phosphate compounds. The cement is mixed freshly at the time of implantation and can be applied directly onto the area requiring augmentation. BoneSource® remains malleable for up to 20 minutes during which time it can be contoured as desired.

BoneSource® is composed of two phosphates of calcium (i.e., dicalcium phosphate and tetracalcium phosphate). At the time of use, BoneSource® is combined with sterile water, sterile saline or sodium phosphate solution (.25M), and under in-vitro conditions (37°C), hardens in approximately 20 minutes. An isothermic setting reaction occurs which yields pure hydroxyapatite after four hours with no significant dimensional changes and no by-products. The compressive strength of BoneSource® is ≥ 50 MPa. The pH of the BoneSource® paste during the setting reaction has been determined to be in the range of 6.5 to 8.5. As a consequence of its apatitic nature, the product is highly

compatible with both soft and hard tissue. Approximately 45% of the implant volume consists of micropores (the remainder is solid) with an average pore size of <1 micron in diameter. This small pore diameter serves to inhibit the passage of infection-causing microorganisms.

IV. INDICATIONS FOR USE

BoneSource® Hydroxyapatite Cement (HAC) is cement indicated for the augmentation or restoration of bony contour in the craniofacial skeleton.

V. IN-VITRO TESTING

In-vitro testing was performed using BoneSource® Hydroxyapatite Cement to define safety and effectiveness parameters. A summary is presented below:

X-ray Diffraction

X-ray diffraction was utilized to demonstrate the BoneSource® HAC reaction setting time. X-ray diffraction patterns taken before hardening and after hardening demonstrate that the setting reaction is complete after four hours. In addition, these x-ray diffraction patterns also demonstrate that the device becomes totally apatitic with no by-products present.

pH Value Determination

The pH of the BoneSource® paste during setting has been determined to be in the range of 6.5 to 8.5. This pH range was verified by laboratory testing in which pH values were measured both during and after setting.

Dimensional Verification

Under in-vitro conditions (37°C), BoneSource® hardens in approximately 20 minutes with no significant dimensional changes. Dimensions of BoneSource® HAC after setting were evaluated by comparing the dimensions of molds with the dimensions of fully "set" samples prepared from the same molds. No shrinkage was observed.

VI. ANIMAL TESTING

Well controlled animal studies were conducted to further verify safety and effectiveness parameters of BoneSource® Hydroxyapatite Cement. Summaries of these studies are presented below:

"Facial Skeletal Augmentation Using Hydroxyapatite Cement"

Six dogs underwent augmentation of the supraorbital ridges bilaterally with hydroxyapatite. On one side, the hydroxyapatite was inserted into a previously created subperiosteal pocket. On the other side, the cement was contained within a collagen membrane tube and then inserted into a similar subperiosteal pocket. The hypothesis was that cement contained within a collagen membrane tubule would demonstrate easier handling during surgery as compared with the uncontained cement. In the study, two dogs were sacrificed at three months, two at six months and two at nine months. All implants maintained their original augmented height throughout the duration of the study and were well tolerated without extrusion or migration, and no significant sustained inflammatory response was observed. Histologic studies performed at three, six and nine months revealed that when the cement was placed directly onto bone, progressive replacement of the implant by bone without a loss of volume was observed. The

mechanism of bone replacement appears to be related to osteoconductive properties of nonceramic hydroxyapatite. When placed in contact with bone, it induces osteoid deposition at the interface. This front of the osteoid advances into the implant, with the implant serving as a scaffold through which bone can grow.

Hydroxyapatite Cement: Basic Chemistry and Histologic Properties

Nine cats were implanted with hydroxyapatite cement disks, applied directly to the surface of the calvarium. The animals were sacrificed at three, six and nine months after implantation, with no toxic reactions, extruded implants, disk migrations, wound infections nor fibrous encapsulation found. When in direct contact with viable bone, bone growth occurred into the implants, and over time, the disks were resorbed and replaced at a rate in direct proportion to surface area. Implant replacement by bone is postulated to occur through a combination of implant resorption coupled with osteoconduction.

Hydroxyapatite Cement: Obliteration and Reconstruction of the Cat Frontal Sinus

Nine cats underwent unilateral removal of the frontal sinus followed by a reconstruction of the area with non-sterile hydroxyapatite cement. The non-operated side of each cat was used as the control. The animals were sacrificed at six, 12 and 18 months postoperatively. Computed tomography and radiographs confirmed progressive replacement of the implants with bone over time. There were no postoperative mortalities, complications, wound infections or wound related complications. No implants were infected or extruded and no depressions were detected in the reconstruction areas. Examination revealed excellent integration of the implant to the surrounding bone and differed little in appearance from the surrounding non-operated frontal bone. There was no loss of volume or significant change in implant contour. Its use in this study without sterilization supports HAC's ability to resist infection unlike most other alloplastic implants.

Experimental Hydroxyapatite Cement Cranioplasty

Six cats underwent bilateral reconstruction of 2.5 cm diameter full thickness critical-sized parietal skull defects with hydroxyapatite cement. In these animals, one side was reconstructed with 100% hydroxyapatite and the other side was reconstructed with a mixture of 50% hydroxyapatite/50% ground autogenous bone. The animals were sacrificed at six and 12 months with no wound infections or structural failures observed, and the implants were well tolerated histologically. Examination of decalcified and undecalcified sections revealed progressive replacement of the cement by new bone and soft tissue without a change in the shape or volume of the hydroxyapatite reconstructed areas. New bone comprised 77.3% of the tissue replacing the hydroxyapatite implants and 64.7% of the tissue replacing the hydroxyapatite/ground autogenous bone implants. Replacement of the hydroxyapatite cement implants by new bone is postulated to occur by a continuation of osteoconduction and implant resorption.

Three additional cats were prepared as positive and negative controls. The control animals underwent unilateral reconstruction with methyl methacrylate; the opposite sides received no reconstruction. The control animals were sacrificed at six months. None of the unreconstructed control defects was completely filled with repair bone. All methyl methacrylate reconstructed defects demonstrated foreign body giant cell formation and fibrous encapsulation of the implants and no new bone growth.

VII. BIOCOMPATIBILITY TESTING

Biocompatibility testing was conducted and performed in accordance with the Good Laboratory Practice regulation in order to assess the microbiological and toxicological impact of BoneSource® Hydroxyapatite Cement. The results of these tests demonstrated no toxic, mutagenic, or irritating effect from BoneSource®.

VIII. CLINICAL TESTING

BoneSource® Hydroxyapatite Cement was the subject of a non-randomized clinical study conducted under an approved IDE for the evaluation of BoneSource® HAC in the repair of cranial burr holes, contiguous craniotomy cuts and other cranial defects. The study involved three sites, a total enrollment of 103 patients presenting 175 cranial defects, and a postoperative evaluation period of 24 months. These data were presented to FDA in support of K953339, which was cleared on June 27, 1996.

Effectiveness

The effectiveness of BoneSource® Hydroxyapatite Cement in cranial defects was assessed by radiographic evaluation of the implant's stability as determined by volume loss at each postoperative interval. Effectiveness was also assessed by an evaluation of all device explants and the relation of the explantation to the device.

Statistical analysis was performed on effectiveness data based upon an implant survival analysis utilizing the Life-Table Method. The cumulative survival rate of BoneSource® Hydroxyapaptite Cement was 81.32%. Note: this survival rate of 81.32% reflects incidences of volume loss in excess of 10% due to technical error; and reflects all explants as failures though none were considered by the Investigator and Medical Monitor to be device-related, but attributable to patient-related conditions.

Based upon the survival analysis and resulting survival rate of 81.32%, BoneSource® Hydroxyapatite Cement is demonstrated to be effective regardless of the demographic characteristics of age, gender, race and medical history, and more importantly, to be effective regardless of the clinical characteristics of the implants such as cause, type, location and dimensions of these cranial defects.

Safety

The safety of BoneSource® Hydroxyapatite Cement was evaluated for all patients at all postoperative intervals throughout the duration of the of the 24-month follow-up and is assessed by the observations of laboratory data, postoperative complications and adverse events. Laboratory data were collected at all postoperative intervals in order to monitor the subject's levels of calcium, chloride, sodium, potassium, bicarbonate and phosphate.

Complications are divided into two groups: defect-specific complications and patient-specific complications. Defect-specific complications include edema, redness, tenderness, seroma, hematoma, tissue thinning, sinusitis and surgical site infection and "other", and were tabulated according to relation to the device and to the interval in which the complication occurred. Of the 175 implants enrolled in this investigation, the majority presented no complications at any postoperative or follow-up interval.

Patient-specific complications include headache, fever, systemic infection, dizziness, GI symptoms, seizures and diplopia, and are tabulated according to relation to the device and to the interval in which the complication occurred. Of the 103 patients enrolled in this clinical investigation, the majority presented no patient-related complications at any postoperative or follow-up interval.

Adverse Events/Death

During the course of this clinical investigation, unanticipated adverse events were reported for five patients. Of the five patients presenting with adverse events two died from cancer, but neither are considered to be device-related. Of the remaining three patients presenting adverse events, one patient suffered a stroke following deep brain tumor removal with postoperative refractory pneumonia requiring a tracheotomy. Another developed a hematoma formation beneath the implant; and the last patient (protocol violation) presented with a life-threatening cerebral spinal fluid leak and was injected with BoneSource® through the nostril in an emergency situation. Subsequently, extrusion of hydroxyapatite cement fragments was observed; however, the remaining portion of the implant is functioning properly. None of the adverse events reported during the course of this investigation are considered to be related to BoneSource® Hydroxyapatite Cement when administered as intended.

Conclusion

The safety of BoneSource® Hydroxyapatite Cement was assessed by the evaluation of laboratory data, postoperative complications and adverse events. Based upon evaluation of blood chemistry levels (i.e., calcium, chloride, sodium, potassium, bicarbonate and phosphate) the presence of BoneSource® Hydroxyapatite Cement is not expected to adversely effect laboratory values. The incidence of complications and adverse events is not occurring at a rate considered to be untoward for the patient population. Based upon these clinical data, BoneSource® Hydroxyapatite Cement was considered safe and effective for cranial defects, and is also considered to be safe and effective for facial augmentation.

IX. STERILIZATION

BoneSource® is provided sterile and is for single use only. Sterilization is achieved by gamma irradiation in compliance with ANSI/AAMI ST32-1991, Method I.

X. SUBSTANTIAL EQUIVALENCE

BoneSource® is claimed to be substantially equivalent to MEPOR Surgical Implants manufactured by Porex Surgical Inc. of College Park, Georgia and cleared by FDA under 510(k) K922489 on September 2, 1992.

COMPARISON OF TECHNOLOGICAL CHARACTERISTICS		
FEATURE	BONESOURCE® HAC	MEDPOR® POREX
Design	Self-setting calcium phosphate compound (powder) that when combined with sterile water forms malleable paste for easy custom-contouring. The material hardens in approximately 20 minutes and converts to pure hydroxyapatite, a	Linear, high-density polyethylene with interconnecting open pore structure. Supplied in blocks, sheets and preformed shapes. Contouring requires scalpel for cutting and shaping, taking care to avoid sharp edges which could result in trauma to surrounding tissue.

	constituent of natural bone, after four hours.	
Function/ Intended Use	Augmentation or restoration of bony contour in the craniofacial skeleton.	Augmentation or restoration of bony contours in the craniofacial skeleton.
Mechanism of Action	Incorporation by normal bone remodeling and replacement activity.	Tissue ingrowth through interconnecting pore structure.
Material	hydroxyapatite cement (HAC)	porous high-density polyethylene
Chemical Composition	tetracalcium phosphate (72.9%) dicalcium phosphate (27.1%)	polyethylene
Setting Time	~20 minutes at 37°C	NA
Contouring	Malleable paste; contouring achieved with spatula or finger.	Block, sheets or preformed implants. Contouring requires cutting and/or heating.
Chemical Reaction	Isothermic	No reaction at the time of use
Compressive Strength	≥ 50 MPa	50 - 70 MPa

XI. CONCLUSION

BoneSource® is claimed to be substantially equivalent to MEDPOR® Surgical Implant (porous polyethylene). The conclusions drawn from in-vitro, animal, biocompatibility and clinical testing demonstrate that BoneSource® Hydroxyapatite Cement is safe and effective, well accepted by host tissue with no evidence of local or systemic adverse effects related to the device and performs as well as or better than MEDPOR® Surgical Implants for facial augmentation/restoration.