Osteogenics Inc.

JUN 27 1996

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SUMMARY OF SAFETY AND EFFECTIVENESS
BONESOURCE™ HYDROXYAPATITE CEMENT (HAC)

I. GENERAL INFORMATION

Classification Name:	Methyl methacrylate for cranioplasty
Common Name:	Hydroxyapatite Cement (HAC)
Device Trade Name:	BoneSource™ Hydroxyapatite Cement (HAC)
Classification Code:	87GXP
Submitter's Name & Address:	Osteogenics, Inc. 250 East Arapaho Road Richardson, Texas 75081 (214) 918-8361
Establishment Registration No:	2183449
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Summary Preparation Date:	July 14, 1995

II. PREDICATE DEVICE

BoneSource™ is claimed to be substantially equivalent in design and function to CranioPlastic™, manufactured by L.D. Caulk Company of Milford, Delaware and distributed by Codman and Shurtleff, Inc. of Randolph, Massachusetts. CranioPlastic™ was cleared by FDA under 510(k) K873689 on October 26, 1987.

III. DEVICE DESCRIPTION

The Osteogenics 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 into the defect to fill the void. BoneSource™ remains malleable for approximately 20 minutes during which time it can be contoured to custom-fit the defect. The setting reaction is complete after four hours.

BoneSource™ is fabricated by combining two phosphates of calcium (i.e., dicalcium phosphate and tetracalcium phosphate). At the time of use, BoneSource™ is combined with sterile water which results in an isothermic setting reaction yielding pure HAC after four hours. This reaction is illustrated below:

HAC Setting Reaction

$$Ca_4(PO_4)_2O + CaHPO_4 + [2H_2O] \longrightarrow Ca_5(PO_4)_3OH + [2H_2O]$$

tetracalcium phosphate (BoneSource™) + dicalcium phosphate → hydroxyapatite

Under in-vitro conditions (37°C), the product hardens in approximately 20 minutes. After four hours, the reaction is complete, yielding pure hydroxyapatite 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 <6 microns in diameter. This small pore diameter serves to inhibit the passage of infection-causing microorganisms. BoneSource™ is supplied sterile and is intended for single use only.

IV. INDICATIONS FOR USE

The Osteogenics BoneSource™ Hydroxyapatite Cement (HAC) is a self-setting, calcium phosphate cement intended for use in the repair of neurosurgical burr holes, contiguous craniotomy cuts and other cranial defects with a surface area no larger than 25cm^2 per defect.

V. IN-VITRO TESTING

In-vitro testing was performed using BoneSource™ Hydroxyapatite Cement in order to demonstrate substantial equivalence to polymethylmethacrylate and to define safety and effectiveness parameters. In addition to fundamental device characterization, the following testing was performed. 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, and are also consistent with values previously reported in published scientific literature.

Dimensional Verification

Under in-vitro conditions (37°C), BoneSource™ hardens in approximately 20 minutes with no significant dimensional changes. Dimensional changes of HAC after setting were evaluated by measuring the dimensions of the molds used in the preparation of the diametral tensile strength and compressive strength samples and comparing these dimensions with the HAC specimens prepared from the same molds. A small sample expansion was noted, but is not statistically significant.

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:

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 2.5cm 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. A summary of these tests is presented below:

In Vitro Cytotoxicity Using Agarose Overlay:
Non-toxic: non-toxic to L-929 cells

Guinea Pig Delayed Contact Sensitization Test
Non-irritant: none of the animals in the study showed abnormal clinical signs during the test period.

Salmonella Mammalian Mutagenicity Assessment/Ames Assay
Non-mutagenic

Limulus Amebocyte Lysate (LAL) Endotoxin Test
Non-pyrogenic: no detectable level of endotoxin.

USP Intramuscular Implant Test

Non-toxic effect: the difference between the average encapsulation score for BoneSource™ implants and negative control implants was zero for each animal. The overall score difference for all implantation sites was also zero.

30-Day HAC Cranial Implant Test

Ten, 4.0 mm diameter cranial defects were successfully created in the parietal bone of two dogs (i.e., five defects in each dog). Four of the five defects in each dog were filled with BoneSource™ Hydroxyapatite Cement; the fifth defect in each dog was left empty to serve as a control. At the end of 30 days, a blinded histopathological evaluation of the defects was performed. Histopathology revealed that the defects were filled with fibrin, fibrous tissue and new bone. Much of the new bone extended from the edges of the defect. Osteogenesis was evident at all sites in both animals. There was no evidence of infection and no toxicity of the bone surrounding any of the defects.

VIII. Clinical Testing

In order to assess the safety and effectiveness of BoneSource™ Hydroxyapatite Cement for use in the repair of cranial burr holes, contiguous craniotomy cuts and other cranial defects, a non-randomized clinical investigational study was conducted under an approved Investigational Device Exemption. The study was initiated on September 11, 1991 involving three sites and a total enrollment of 103 patients presenting 175 cranial defects. The clinical investigation postoperative evaluation period is 24 months.

Effectiveness

The effectiveness of BoneSource™ Hydroxyapatite Cement, for its intended use, is assessed by radiographic evaluation (x-ray or CAT Scan) of the implant's stability as determined by volume loss at each postoperative interval. Effectiveness is 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 is 97% with 11 implants not yet evaluated at the 24 Month interval and 31 implants not yet due for 24 Month follow-up. During the course of this investigation, there have been only four implants categorized as failures. These four implants presented with volume loss in excess of 10% and are considered by the Medical Monitor to be due to inadequate drainage of excess wound fluid present at the implant site. There are no other instances of volume loss in excess of 10%. All other instances of volume loss are less than or equal to 10% and are also attributed to inadequate drainage during implantation; however these small volume losses are not considered to be clinically significant. While a total of 20 implants underwent explantation of greater than 25% volume, none are considered by the Investigator and Medical Monitor to be device-related, but are attributable to patient-related conditions such the reoccurrence of tumor formation.

Based upon the survival analysis and resulting survival rate of 97%, 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 the defects presenting in this investigation.

Safety

The safety of BoneSource™ Hydroxyapatite Cement is 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 Values

Laboratory data were collected at all postoperative intervals in order to monitor the subject's levels of calcium, chloride, sodium, potassium, bicarbonate and phosphate. The mean laboratory values, as well as, mean within-patient percent changes were identified for each blood chemistry parameter at each interval and presented against baseline to the Month 12 and to the Month 24 interval. Additionally, each blood chemistry parameter was assessed against the normal laboratory range for each site. Those values which fell outside these normal ranges were further reviewed as compared to clinical panic ranges as defined by Wolfson, W.L., Eds., *Laboratory Test Handbook.*

Calcium levels demonstrated slight hemodilution during the interval immediately postoperatively, and in the follow-up period there is a statistical difference among baseline and Month 12 and among baseline and Month 24. However, the mean within-patient percent change averaged only 3.21% and 4.21 at each respective interval. These percent changes are not considered clinically significant. Furthermore, the minimum and maximum calcium levels are well within the *Laboratory Test Handbook* range.

Sodium demonstrated statistical significance among baseline and Month 24 only; however, it should be noted that the mean within-patient change from baseline averaged only 1.01%. Additionally, the minimum and maximum sodium levels are well within the handbook range. Potassium demonstrated a statistical significance among baseline and Month 12 and among baseline and Month 24. However, none of the values for potassium are considered to be clinically significant.

Chloride, bicarbonate and phosphate demonstrated no statistical significance among baseline, Month 12 and Month 24 values. Although six patients demonstrated chloride levels slightly above the handbook "high", these levels presented at early postoperative intervals and dropped to clinically non-significant levels during the remainder of the follow-up intervals. Of the six patients, four underwent intradural surgery; abnormal electrolyte levels are commonly observed in this type of surgery.

Complications

Complications are divided into two groups: defect-specific complications and patient-specific complications. Defect-specific complications include edema, redness, tenderness, seroma, hematoma, tissue thinning 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, 135 implants (77.59%) presented no complications at any postoperative or follow-up interval. Twenty-six implants (14.86%) presented only one complication and only 14 (8.00%) presented two or more complications.

Edema was the most frequently reported complication with an overall incidence rate of 13.71%, followed by tenderness which demonstrated an overall incidence rate of 10.86%. The majority of reports for these complications occurred at the interval immediately postoperatively and at the Month 1 interval resolving shortly thereafter and is not uncommon following cranial surgery. The incidence of edema and tenderness is not occurring at a rate considered to be untoward for this patient population.

Additional complications reported during this investigation include seroma, "other" (i.e. open, mucous cyst, mucocele reformation and open wound), tissue thinning, redness and hematoma. However, these complications demonstrated overall incidence rates of 5.71%, 4.57%, 2.86%, 2.86% and 0.57% respectively.

The majority of patients had no defect-specific complications reported at any interval. Of those complications reported, most were not related to the device and no complication reported poses a serious or life-threatening effect to the safety of the patient. Therefore, BoneSource™ Hydroxyapatite Cement is considered to perform satisfactorily at each implant site.

Patient-specific complications include headache, sinusitis, fever, systemic infection, surgical site 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, 68 (66.02%) presented with no patient-related complications at any postoperative or follow-up interval. Twenty-one (20.39%) presented with only one complication and only 14 (13.59%) presented with two or more complications.

Headache was the most frequently reported patient-specific complication with an overall incidence rate of 16.5%. These reports are distributed throughout the follow-up intervals with the majority considered to be not device related and furthermore, are not unanticipated given the subjects' preoperative and operative circumstances. Reports of headache following cranial surgery are commonly observed up to 12 months postoperatively. Sinusitis follows in frequency with an overall incidence rate of 11.7%. The majority of patients (5 out of 8) presenting with sinusitis were diagnosed preoperatively with sinus-related defects and are considered to be predisposed to the complication. The reports for the remaining three patients are not considered to be device-related.

Complications identified as "other" demonstrated an overall incidence rate of 9.71% and reports range from aseptic meningitis to insomnia. None of the complications identified as "other" are considered to be definitely device-related. Dizziness demonstrated an overall incidence rate of 7.77%; however, none of these reports are considered to be device-related.

Surgical site infection, presenting in six patients, demonstrated an overall incidence rate of 5.83%. Two of these patients presented with localized infection resulting in explantation. The first received BoneSource™ implants over bone and fat graft material in which a chronic pseudomonas infection developed; the second developed a residual sinus infection. The remaining four patients presenting with surgical site infection did not require explantation.

Although the overall incidence rate for surgical site infection is 5.83%, none of these events are considered to be definitely related to the device. Material characterization of BoneSource™ indicates the device to have an average pore size of less than 6 microns, thus inhibiting the passage of infection-causing microorganisms. Therefore, it is unlikely that sterile BoneSource™ would cause or contribute to a surgical site infection. Additionally, it should be noted infection resulting in explantation (three patients) demonstrates a rate of 2.9% which compares favorably to the 5%[1] infection rate for acrylics. Therefore, with regard to surgical site infection, BoneSource™ Hydroxyapatite Cement is considered to perform satisfactorily.

The remaining patient-specific complications, systemic infection and GI symptoms demonstrate an overall incidence rate of 3.88% each. Seizures, diplopia and fever demonstrate an overall incidence rate of 2.91%, 2.91% and 1.94% respectively. None of these complications are considered to be related to the device.

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

[1] Clinical literature analysis of 16 articles presenting prospective studies performed on acrylic implants.

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, resulting in a 95% explantation of the device. The Investigator reports, however, that the remaining 5% of implant has plugged the defect and 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), with the exception of those values identified, all laboratory values are within clinically normal ranges. Therefore, the presence of BoneSource™ Hydroxyapatite Cement is not expected to adversely effect laboratory values. The incidence of complications and adverse events are not occurring at a rate considered to be untoward for the patient population. Therefore, based upon these clinical data, BoneSource™ Hydroxyapatite Cement is considered to be safe and effective for the stated indication and performs as well as, or better than, CranioPlastic™ (PMMA).

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 in design and function to CranioPlastic™, manufactured by L.D. Caulk Company of Milford, Delaware and distributed by Codman and Shurtleff, Inc. of Randolph, Massachusetts. CranioPlastic™ was cleared by FDA under 510(k) K873689 on October 26, 1987.

COMPARISON OF TECHNOLOGICAL CHARACTERISTICS		
FEATURE	BONESOURCE™ HAC	CRANIOPLASTIC™ (PMMA)
Design	Self-setting material intended to fill, seal and conform to cranial defects.	Self-setting material intended to fill, seal and conform to cranial defects.
Function/ Intended Use	For use in the repair of craniotomy/burr holes, contiguous craniectomy cuts and other cranial defects with a surface area no larger than 25cm² per defect.	For repair of cranial defects.
Material	hydroxyapatite cement (HAC)	poly methyl methacrylate (PMMA)
Chemical Composition	tetracalcium phosphate (72.9%) dicalcium phosphate (27.1%)	methyl methacrylate polymer (79.6%); methyl methacrylate styrene copolymer (19.9%); benzoyl peroxide (0.5%)
Setting Time	~20 minutes at 37°C (physiologic conditions)	13-15 minutes at 23°C to 28°C
Chemical Reaction	Isothermic	Exothermic (up to 100°C), cooling by water recommended.
Compressive Strength	≥ 50 MPa	70 MPa

XI. CONCLUSION

BoneSource™ is claimed to be substantially equivalent in design and function to CranioPlastic™. The conclusions drawn from in-vitro, animal, biocompatibility and clinical testing demonstrate that BoneSource™ Hydroxyapatite Cement is safe and effective and performs as well as or better than CranioPlastic™ (polymethylmethacrylate) for the stated indication. In addition, these tests demonstrate that BoneSource™ Hydroxyapatite Cement is well accepted by host tissue with no evidence of local or systemic adverse effects related to the device.