Magnesium-Based Bone Cement and Bone Void Filler: Preliminary Experimental Studies

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Abstract: Bone cement has great potential in craniofacial surgery in the repair of osseous defects secondary to surgery or trauma. This includes the use of bone cement as a bone void filler for full-thickness cranial defects and as augmentation of deficient bones. Ideally, this material should be easily available, biocompatible, resorbable, bone inductive, and have adhesive qualities to bone. Calcium-based bone cements have some of these qualities but have a higher than desirable failure rate. OsteoCrete, a new magnesium-based bone cement and bone void filler, was compared to Norian in critical-sized skull defects and cementing bone flaps in rabbits. Both materials were successful; however, OsteoCrete had a faster resorption and replacement by bone rate than Norian. Bone flap position and apparent stability were also superior with OsteoCrete. There were no adverse reactions to either cement. A magnesium-based bone cement presents with advantages when compared with a comparator calcium-based cement in craniofacial surgery.

Key Words: Cranial, bone cement

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Calcium-based bone void fillers and cements are commonly used in the repair of osseous cranial defects secondary to surgery and trauma. This includes large and small full-thickness cranial defects and the augmentation of contour deficient bones.[1–3] In addition, they are used to reconstruct defects in skull base, mastoid surgery and frontal sinus ablation.[4] They provide strength and are biodegradable scaffold, and while generally successful, these bone substitutes are not yet the perfect graft material. Material rejection with defects more than 25 cm^2 is seen from 8% to 25% of the time. Bone replacement from calcium phosphate cements is nonexistent to incomplete, and they universally lack adhesive abilities.[5,6] Bone ingrowth is desirable, as it could serve to decrease the brittleness and increase the strength of the hydroxyapatite. Gosain et al[5] found approximately a 28% bone replacement of a 20% hydroxyapatite paste, whereas de Bruij[7] found a 25% replacement of a 80% hydroxyapatite and 20% tricalcium phosphate cement. Some calcium phosphate cements are difficult to mold and can fragment or dissolve in fluids, although fixation to the underlying bone must be mechanical in nature. Hydroxyapatite-based bone cements are widely used and have a low morbidity but may have complication rates as high as 32%. The material may fail secondary to loosening, chipping with multiple fractures, and subsequent resorption.[8–10] In addition, they may be susceptible to breakdown when exposed to liquids such as cerebrospinal fluids or seromas.[10] Recently, a magnesium-based bone cement has shown significant adhesive qualities and increased bone induction and replacement in orthopedic research.[11]

MATERIALS AND METHODS

The goal of this study was to test the efficacy of a new magnesium-based bone cement, OsteoCrete, for filling voids and securing repositioned cranial facial bone fragments. The test subjects selected were New Zealand white rabbits divided into 2 study groups (test and control articles); each study group was divided into 3 time points (2, 12, and 24 wk). All test subjects received an unfilled cranial bone defect, a contralateral filled cranial bone defect, and a repositioned cranial bone flap. The test (OsteoCrete) and control articles (Norian) were used to reposition and secure the bone flaps and fill the ipsilateral cranial bone defect. The contralateral bone defect was left as the untreated control (Fig. 1).

Test Subjects, Study Groups, and Time Points

The 24 test subjects (New Zealand white rabbits) were divided evenly between test and control article study groups. Each study group contained 3 time points (Figs. 2–5):

Two animals per 2-week time point per study group (4 test subjects) with 2 receiving a left side cranial bone flap and defect, one treated with OsteoCrete and one treated with Norian, and 2 receiving a right side cranial bone flap and defect, also one treated with OsteoCrete and one treated with Norian. Each of the 4 test subjects received a contralateral untreated cranial bone defect.

Five animals per 12-week time point per study group (10 test subjects) with 6 receiving a left side cranial bone flap and defect, 3 treated with OsteoCrete and 3 treated with Norian, and 4 receiving a right side cranial bone flap and defect, with 2 treated with OsteoCrete and 2 treated with Norian. Each of the 10 test subjects received a contralateral untreated cranial bone defect.

Five animals per 24-week time point per study group (10 test subjects) with 6 receiving a right side cranial bone flap and defect, 3 treated with OsteoCrete and 3 treated with Norian, and 4 receiving a left side cranial bone flap and defect, with 2 treated with OsteoCrete and 2 treated with Norian. Each of the 10 test subjects received a contralateral untreated cranial bone defect.

At the appropriate posttreatment time interval, animals were killed, and necropsy evaluation was performed. The inner and outer surfaces of the craniotomy and bone flap sites were evaluated grossly

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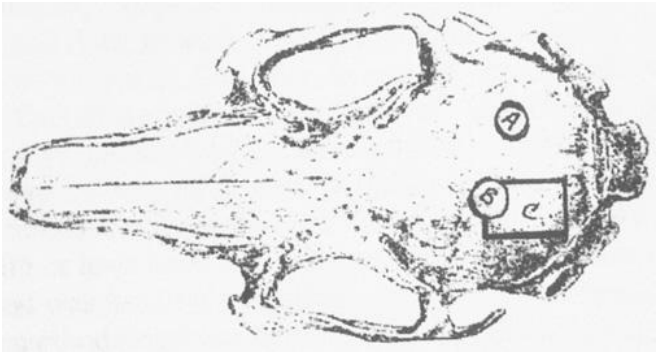

FIGURE 1. Rabbit skull drawing showing the placement of the bone flap and craniotomy holes.

as was the brain. The brain and skull were placed in 10% formalin for fixation by immersion. The skull bone samples at this time were also radiographed.

After at least 48 hours fixation, the bone specimens were then placed in 10% nitric acid solution for overnight decalcification. After this, transverse sections were trimmed of the surgical areas.

The following criteria were evaluated using a grading scheme: Width of the remaining craniotomy hole (gap width) was expressed in millimeters. Density of bone growth across the craniotomy hole (infill density): 1 to 5, in gradients of 20%. Degree of inflammation associated with the craniotomy and/or cement: 1 to 5, minimal, mild, moderate, and severe. Persistence of bone cement, expressed categorically as a percentage using the as baseline: 1 to 5 in 20% increments. Displacement of the bone flap from 0, which was none, to a 3, which was greater than 2 mm. Less than 2 mm was considered insignificant clinically; thus, a 1 was a 1-mm displacement, and a 2 was a displacement up to 2 mm. Coronal and axial radiographs were taken at the time of explantation in all animals. All radiographs were evaluated on a qualitative basis and double blinded as to bone cement type and time. The following criteria were used for evaluation:

1. Critical size defect infill bone density
   1 = Less than 25% density
   2 = Less than 50% density
   3 = Normal density
   4 = Greater than 25% density
   5 = Greater than 50% density

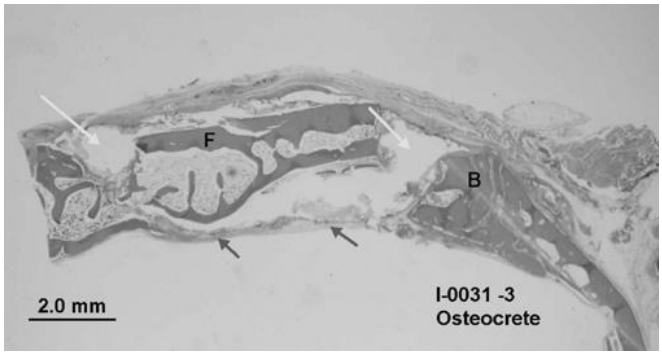

FIGURE 2. OsteoCrete, 2 weeks, bone flap site. Flap in the center of the image (F) bordered by bone of the calvarium (B). Large amount of persistent cement material is marked by the light arrows. The dura mater is slightly thickened, dark arrows.

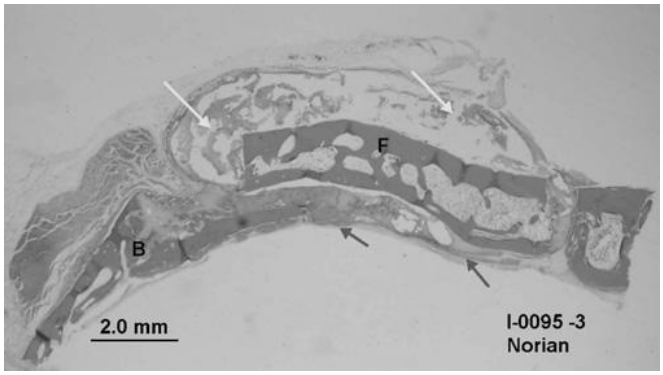

FIGURE 3. Norian, 2 weeks, flap site. The bone flap (F) is surrounded by abundant bone cement (light arrows). The bone of the calvarium is seen in (B), and the dark arrows indicate the slightly thickened dura mater.

2. Flap area bone density
   1 = Less than 25% density
   2 = Less than 50% density
   3 = Normal density
   4 = Greater than 25% density
   5 = Greater than 50% density

3. Flap position
   0 = No displacement noted
   1 = Displacement up to 1 mm
   2 = Displacement greater than 1 and up to 2 mm
   3 = Displacement greater than 2 mm

All test subjects were fasted for 12 hours before surgical manipulation. Restraint was ensured by the use of stainless steel rabbit restrainers, allowing easy placement of auricular venous and arterial catheters. Anesthetic induction was achieved with 10 mg/kg of xylazine intravenously and 10.0 mg/kg of ketamine. Aesthetic maintenance was continued by the use of 2% to 5% isoflurane in oxygen at a flow rate of 2 L/min.

Surgical Procedure

A sagittal skin incision was made across the dorsal aspect of the cranial bone and subperiosteal dissection preformed for full exposure. Bilateral cranial defects consisted of a burr hole

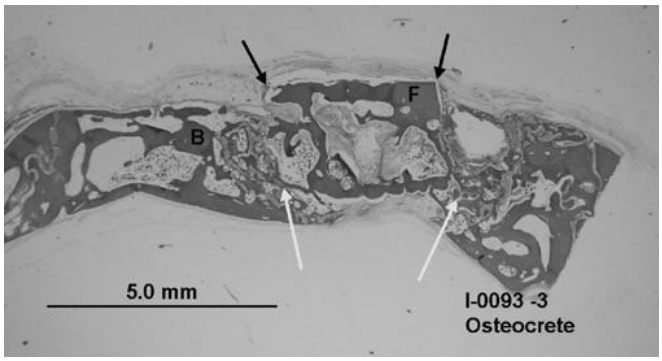

FIGURE 4. OsteoCrete, 24 weeks, flap site. The flap (F) is marked by the black arrows, and there is a bridging bone between the flap and the calvarium (B). Note the very slight upward displacement of the flap (score, 1).

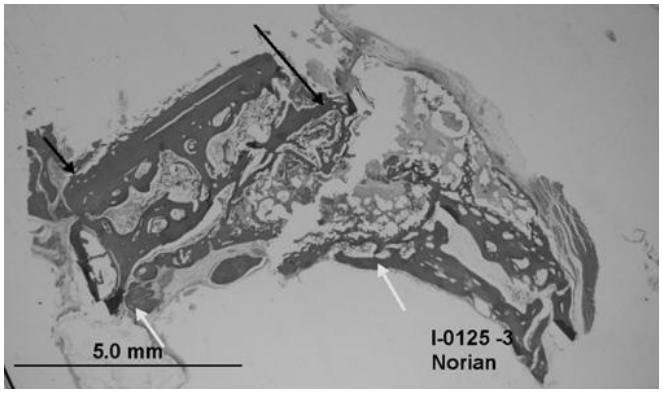

FIGURE 5. Norian, 24 weeks, flap site. The bone flap is between the black arrows and is surrounded by persistent cement material and some new bone. Note the upward displacement of the flap (score, 3).

AQ6 approximately 1 cm in diameter with use of an Integra Cranial Access Kit. One of these burr holes was left unfilled as a negative untreated control. Any bleeding from the burr hole was subsequently stopped by use of a bone wax. The contralateral burr hole bone defect allowed introduction of a drill for full completion of an approximately sized 1 × 1.5 cm^2 bone flap. The bone flap was subsequently removed and then repositioned and secured with one of the 2 comparative bone cements: OsteoCrete (test article) or Norian (comparative control article). Once the bone flap has been cemented into place, the ipsilateral cranial burr hole is also filled with the same article, either OsteoCrete or Norian. The site of the cranial flap will alternate contralaterally as described previously under the heading Test Subjects, Study Groups, and Time Points. Cranial skin incisions were closed, and animals survived

AQ7 according to the schedule list in the previously supplied table

AQ8 labeled "Animal Tracking." Animals were killed and explanted tissues collected according to the following schedule (mean [SD]): 2 weeks (2 d), 12 weeks (2 d), and 24 weeks (2 d).

RESULTS

The in vivo portion of this study can be considered a success on the following parameters: the study proceeded without major incidents or complications. Pathologic findings on the one unexpected mortality revealed no evidence that this death was associated with neither the test article nor the study manipulations. During the study, it was possible to carry out the intended surgical implantations and observations as described in the protocol. For all animals, the anesthetic procedure at the time of surgery was successfully completed. Twenty-three of the 24 animals included in the study survived to the scheduled time points. Hematology and chemistry values were judged normal for all animals. No animal in this study required intervention based on any hematology or chemistry results obtained during the study period. There were no severe adverse effects from the test articles noted in the veterinary records. The test subjects were free of postoperative morbidity related to the manipulations or test article. One test subject died postoperatively before reaching the assigned time point. Rabbit I0128, a 24-week time point left side Norian-treated (control article) test subject, died at 8 weeks 4 days after the procedure. Histologic evaluation by a veterinary pathologist revealed degenerative changes in the myocardial arteries, with some mild cardiomyocyte degeneration, of unknown primary cause. No other significant lesions were found. Cardiomyopathy of undetermined cause is the presumed cause of death. There is no indication that study manipulations or the control article contributed to this animal's death. This animal was excluded from summary analysis.

Hematology and Serum Chemistry

Quarantine blood work on all test subjects showed no adverse results. None of the preoperative quarantine hematology or serum chemistry parameters were indicative of any preprocedural morbidity.

It must be noted that end point hematology and serum chemistry blood samples on the four 2-week time point test subjects were not submitted for analysis; therefore, no parameters on this time point are available. End point hematology and serum chemistry parameters on all remaining test subjects, time points 12 and 24 weeks, revealed no abnormal results. None of these postprocedural hematology or serum chemistry parameters were indicative of any postprocedural morbidity. There were no biologically significant differences between groups.

Pathology

Study findings are suggestive that both the test article and the comparator control article provide structural stability while allowing bone growth over and through the cements. Both the test and comparator control articles act to some degree as a barrier to bone ingrowth to the cranial defects created as compared with the unfilled contralateral control sites. Although with OsteoCrete by 24 weeks, this effect is gone. In addition, it is noted that the narrower gap width and greater bone infill density scores sited for some unfilled control sites show evidence that when bone ingrowth does occur, it progresses more rapidly when cement does not first have to be reabsorbed. The bone ingrowth in the unfilled controls seems unpredictable and, in the radiographic studies, the bone in the unfilled controls is less dense than the bone ingrowth seen with the bone cements. OsteoCrete is more readily absorbed in the Norian and thus allows greater bone replacement. The differences are evident by the 12th week and remain significant at the 24-week time point. Furthermore, in the radiographic studies, OsteoCrete was associated with better bone flap position than Norian. This was not related to the operator but probably secondary to better stability of the flap with OsteoCrete.

Histology

For the 2-week time point, the mean gap width of the craniotomy hole is narrower in the OsteoCrete-treated test subjects than in the Norian-treated test subjects; both of which are more than that observed in the 4 nonfilled controls.

For the 12-week time point, the mean gap width of the craniotomy hole is narrower in OsteoCrete-treated test subjects than in Norian-treated test subjects; both of which are more than that observed in the 11 nonfilled controls.

For the 24-week time point, the mean craniotomy hole of the simulated osteoclasis is equal between the OsteoCrete- and Norian-treated test subjects; both of which are less than that observed in the 9 nonfilled controls.

For the 2-week time point, the mean infill density of the regenerating bone is equal between the OsteoCrete- and Norian-treated test subjects; both of which are less than the mean infill density of the untreated control sites.

For the 12-week time point, the mean infill density of the regenerating bone is greater for the OsteoCrete-treated test subjects than for the Norian-treated test subjects; both of which are less than the mean infill density of the untreated control sites.

For the 24-week time point, the mean infill density of the regenerating bone is greater for the OsteoCrete-treated test subjects than for the Norian-treated test subjects; the Norian is less than the

mean infill density of the mean of the 9 untreated control sites, and the OsteoCrete is equivalent.

For the 2-week time point, the mean cellular reaction score is greater for the OsteoCrete-treated test subjects than for the Norian-treated test subjects; both of which are greater than the mean cellular reaction score for the 4 untreated controls.

For the 12-week time point, the mean cellular reaction score is greater for the OsteoCrete-treated test subjects than for the Norian-treated test subjects; both of which are greater than the mean cellular reaction score for the 4 untreated controls.

For the 24-week time point, the mean cellular reaction score is greater for the OsteoCrete-treated test subjects than for the Norian-treated test subjects; both of which are greater than the mean cellular reaction score for the 4 untreated controls.

For the 2-week time point, the persistence of cement was not evaluated.

Persistence of cement at 12 weeks demonstrates the Norian is present almost twice as much as OsteoCrete, where OsteoCrete is roughly 50% replaced.

At the 24-week period, this difference in cement persistence remains the same between OsteoCrete and Norian.

Displacement of the bone flap when measured histologically was the same between OsteoCrete and Norian, and both were at acceptable levels of minimal displacement.

Radiography

The 2-week period demonstrated minimal density of the critical-sized bone hole, normal density of the flap with OsteoCrete, and increased density with Norian. The increased density of the Norian bone flaps is because of the increased radiopaque nature of the Norian. Displacement of the flaps was the same.

The 12-week period again demonstrated minimal density in the critical-sized defect, normal density in the whole group but slightly less density in the OsteoCrete group, and increased density in the Norian group, again reflective of the increased density of the Norian cement.

The 24-week period again demonstrates no change in the density of the critical-sized defect, which remains near the lowest level. Flap density is near normal with OsteoCrete and increased with Norian. Flap displacement is minimal with OsteoCrete and increased with Norian.

CONCLUSIONS

This study determines that OsteoCrete, a synthetic bone cement/bone void filler, assists in the securing of repositioned bone flaps and with new bone ingrowth into bone void defects. No adverse effects directly related to the OsteoCrete cement were seen in the bone, meninges, or brain. The OsteoCrete bone cement/bone void filler, when used as a cranial bone cement and bone void filler, seems biologically well tolerated. The tissue reaction of OsteoCrete is only mildly more responsive than that caused by the Norian comparator. This mild cellular response is not seen to be clinically deleterious but most likely assists in the more rapid resorption and replacement of OsteoCrete by bone than Norian. OsteoCrete assists in locating and securing the bone flap in the desired position and seems to be superior to Norian for this purpose.

Evidence suggests that OsteoCrete resorbs over time, with approximately half of the material persisting to the 24 weeks' duration of this study. Application of OsteoCrete cement stimulated bony infill of the craniotomy site, resulting in partial infill of the craniotomy holes by 12 weeks and complete spanning of the craniotomy holes by 24 weeks. New bone in growth is greater and replacement by bone faster with OsteoCrete than with the comparator article Norian. OsteoCrete secured repositioning and aided bony bridging of the bone flap callus by 12 weeks, with further maturation of the response at 24 weeks. The OsteoCrete is substantially reduced at 24 weeks after application; however, 50% of the bone cement does persist to this time point. This new magnesium-based bone cement and bone void filler provides better adhesion to the bone surfaces and has a faster resorption rate; the presently used materials seem to offer greater potential in craniofacial surgery. AQ9

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