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Reconstruction of Bone Using Calcium Phosphate Bone Cements: A Critical Review

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The calcium phosphate cements (CPCs) are rapidly emerging as a new technology in craniofacial surgery and will soon impact many areas of orthopedic and maxillofacial reconstructive surgery as well. These materials are, in many ways, substantially different from the previously marketed dense, crystalline, hydroxyapatite (HA) ceramic materials of the 1980s. The CPCs are blends of amorphous and crystalline calcium phosphate compounds and set to produce HA. These materials 1) have x-ray diffraction spectra similar to the mineral phase of bone, 2) set endothermically at body temperature, 3) are capable of being injected into fractures or bone defects, 4) have compressive strengths equal to or greater than bone, 5) form chemical bonds to the host bone, and 6) may exhibit osteoconductive properties. This review provides an overall commentary on the different types of CPCs, emphasizing those materials currently on the market or soon to emerge in the marketplace.

The search for an injectable, moldable material to augment bone repair has been the quest of many researchers and surgeons interested in accelerating healing of bone fractures or in reconstructing bone defects. In the 1980s, interest developed in using hydroxyapatite (HA) to augment bone defects and to coat both dental and orthopedic implants. HAs were first produced by processing calcium and phosphate compounds at elevated temperatures, resulting in preformed, dense, crystalline ceramics with little bioactivity other than forming a chemical bond to bone.[1] This first generation of HA bone substitutes were used to augment the alveolus of the maxilla and mandible, to reconstruct periodontal defects, and as a craniofacial augmentation material.[2-5]

Calcium phosphate cements (CPCs) are the second generation of HA bone substitutes. CPCs have been developed as a moldable treatment modality that chemically bonds to the host bone, restores contour, and augments the biomechanical properties of the injured or reconstructed region. Some of these materials have relatively long working times, set at physiologic temperature, and may be directly injected percutaneously into a fractured region or bone defect. The purpose of this article is to review the chemistry and physical properties of these new products, with specific reference to their applications in dentistry and in maxillofacial/craniofacial surgery.

Chemistry of the Nonceramic Calcium Phosphate Cements

HA is the essential crystalline component of the calcified components of the skeleton and is the principal mineral in bone, enamel, dentin, and cementum. Hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$) has been produced synthetically since the early 1970s and has been used clinically since the early 1980s.[6] Currently, 2 forms of HA may be produced: ceramic and nonceramic. The early HA implants were sintered, a process that caused fusion of crystals by heating them at elevated temperature. Sintered HA is essentially a nonresorbable ceramic. Ceramic HA is synthesized in crystal form and at an acid pH. It is later sintered at 800 to 1,300°F, forming a fused, solid mass. Nonceramic materials (of which CPCs are an example), are pro-

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Table 1. PROPERTIES OF CALCIUM PHOSPHATE CEMENTS

	Bone Source	∝-BSM Embarc	Norian SRS/CRS
Components	Tetracalcium phosphate (TTCP), $Ca_4(PO_4)_2O$, and DCPD	Decarbonated ACP and either DCPD, calcium metaphosphate, heptacalcium phosphate, calcium pyrophosphate, or TCP	Monocalcium phosphate, ∝-tricalcium phosphate, calcium carbonate
Compressive strength	36 MPa (for first 24 hours)	?	55 MPa
Resorbable	Minimally	Yes	Completely
Commercially available	Yes	Yes	Yes
Pore diameter	2-5 nm	?	300Å
Initial setting time	10-15 min	15-20 min	10 min
Final setting time	4 hours	1 hour	12 hours
Osteoconductive	Yes	Yes	Yes
Sets in presence of fluid	No (must be kept dry)	Yes	Yes

duced by the direct crystallization of HA in vivo. No heat is required to form a structurally stable implant. It appears that the lack of fusion of nonceramic materials allows slow resorption over time. Biologically, it is replaced by woven bone as the material resorbs. In the United States, 3 nonceramic CPCs have been developed for clinical use (Table 1). All are Food and Drug Administration-approved for craniofacial/dental applications.

It was generally believed that because CPCs are resorbable, bone was formed via an osteoconductive mechanism. However, the relatively nonreactive nature of CPCs has recently been challenged. The CPCs may directly initiate osteogenesis or promote osteoconduction when placed in direct contact with host bone. These data are derived from studies in which HA has been documented to form bone heterotopically. Magan and Ripamonti[7] showed that coral-derived HA discs form bone heterotopically in intramuscular sites of nonhuman primates. However, this form of solid HA is minimally resorbed and is not formed in a chemical reaction using calcium and phosphate as starting materials. Additionally, it appears that this heterotopic osteogenesis is species specific. Evidence for this is derived from studies in which no bone was formed when coral-derived porous HA was implanted heterotopically in rabbits and dogs.[8]

Properties of the CPCs

To obtain the maximum biologic use of the CPCs, some working knowledge of their basic chemistry is necessary. All CPCs are formulated as solid and liquid components that, when mixed in predetermined proportions, react to form HA. This final reactant is important because it determines 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 either water, saline, or sodium phosphate. Some of the calcium and phosphate compounds involved in bone and mineral formation, or as implants, are listed in Table 2. These materials have been well characterized chemically and have not been reported to cause foreign body reactions or other forms of chronic inflammatory response.[9]

The physicochemical reaction that occurs during mixing of the solid and liquid components of CPCs is complex. Briefly, when different calcium phosphate salts are mixed in an aqueous environment, dissolution, precipitation, and finally phase transformation occurs. The process leading to final phase transformation of the different forms of calcium phosphate salts is dependent on their solubility product constant and pH. It is important to realize that water is not a

Table 2. CALCIUM AND PHOSPHATE COMPOUNDS

Formula	Name	Molar Ca/P	Abbreviation	Solubility	Acidity	Thermodynamic Stability
$Ca(HPO_4) \cdot H_2O$	Dicalcium phosphate dihydrate	1.0	DCPD	+++++	+++++	+
$Ca_4H(PO_4)_3$	Octacalcium phosphate	1.33	OCP	++++	++++	++
$Ca_9H(PO_4)_6$ (var.)	Amorphous calcium phosphate	1.3-1.5	ACP	+++	+++	+++
$Ca_3(PO_4)_2$	Tricalcium phosphate	1.5	TCP	++	++	++++
$Ca_{10}(PO_4)_6(OH)_2$	Hydroxyapatite	1.67	HA	+	+	+++++

reactant in the setting reaction of the cement, but that it allows dissolution of the solids and precipitation of the products. The nature of the apatite makes the final form biocompatible and promotes a chemical bond to the host bone. Hence, the classification of these compounds as cements.

The CPCs have an inherent compressive strength at the final set that can govern their utility. Compressive strength may be altered by varying the crystallinity of the HA or the particle size of the materials used in the solid phase. Because CPCs are relatively insoluble at neutral and alkaline pHs, their porosity is related to the ratios of powder to liquid used in the starting mixture. Obviously, a material with a high porosity would be expected to have low compressive strength. Materials with a high compressive strength would be expected to find utility where they would stabilize nondisplaced bone fractures or comminutions, or for cranioplasty in regions requiring a large amount of soft tissue support. Materials with low compressive strength could be expected to function equally well to bridge small bone defects, as a root canal filling material, or as a method for reconstructing infrabony periodontal defects.

The Prototype CPC (Bone Source)

A self-setting cement incorporating calcium phosphate as the major component was first reported by Brown and Chow.[10] The material consists of tetracalcium phosphate ($Ca_4[PO_4]_2O$) and dicalcium phosphate dihydrate ($CaHPO_4 \cdot H_2O$), which are mixed with water in a powder-to-liquid ratio of 4:1. The Brown-Chow material has undergone more investigation than any other CPC. Initial studies with this material showed that it was not mutagenic, that it sets to pure HA, that it has excellent biocompatibility, and that it is slowly resorbed.[9] When mixed with water, the material forms a paste, which is molded to the desired shape and contoured intraoperatively. The Brown-Chow material begins to set in 10 to 15 minutes and converts to HA as the final product, with a final set occurring in 4 hours.[11] It later attains a mean compressive strength of 36 MPa for the first 24 hours. After setting to a hard mass, only trace amounts of the initial reactants are converted to HA. During the setting reaction, octacalcium phosphate ($Ca_8H_2[PO_4]_6 \cdot 5H_2O$) forms and supersaturates the water phase. It has been suggested that octacalcium phosphate forms as an intermediate because it is a more rapidly forming phase than HA.[11]

One problem observed by clinicians who have used the Brown-Chow material has been the relatively long time needed for the material to harden. Blood and tissue fluids, which contact the setting mass shortly after initial placement, can significantly delay the final set. The addition of sodium phosphate to the liquid phase accelerates the setting reaction by lowering the pH and allowing a more rapid dissolution of the solids. This has significantly improved the delayed setting time associated with this material.

ANIMAL AND HUMAN STUDIES

The Brown-Chow material, marketed by Howmedica Leibinger Inc. (Dallas, TX) as Bone Source, has been used to augment the supraorbital ridge in dogs,[12] as well as in a variety of skull base defects. It was also used in 24 patients, to augment or obliterate the frontal and ethmoid sinus regions and mastoid cavities.[13] When these patients were observed for 2 years, it was necessary to remove the material in only 1 patient. Kveton et al[14,15] reported on the 2-year follow-up of 15 patients who underwent Bone Source reconstruction for translabyrinthine, middle cranial fossa, and suboccipital craniectomy[14,15]; no complications were reported. The material has also been used to assist in sealing cerebrospinal fluid leaks in transtemporal surgery.[16] Lew et al[17] studied the reconstruction of craniofacial defects with Bone Source in beagle dogs.[17] The percentage of bone present in the defects at 3 and 6 months was greater than sites repaired with human demineralized bone. Bifano et al[18] examined the potential for Bone Source to augment edentulous ridges in mixed-breed canines. They reported no loss of the implanted material, as well as the absence of acute or chronic inflammation. The material was osteoconductive, with new periosteal and endosteal bone formation remote from the material.

Apatitic Calcium Phosphate Bone Substitute (∝-Bone Substitute Material [BSM], Embarc)

This material, which was first developed by a group of investigators at ETEX Corp, is marketed by Walter Lorenz Surgical (Jacksonville, FL) as Embarc. It is prepared as a blend of amorphous and crystalline calcium phosphate precursors and saline, which harden at 37°C to form a poorly crystalline apatitic calcium phosphate. The material has been designed to be injected as a paste and to set endothermically at body temperature within 15 to 20 minutes. It also has a relatively long working time before use (no setting after 1 hour at room temperature) and is fully resorbable when set. The paste is composed of a decarbonated amorphous calcium phosphate combined with a second calcium phosphate compound (either dicalcium phosphate dihydrate, calcium metaphosphate, heptacalcium phosphate, calcium pyrophosphate, or tricalcium phosphate) in a proportion to provide a Ca/P ratio characteristic of an apatitic calcium phosphate.[19,20] The calcium phosphate precursors are then

hydrated with 0.7 to 0.9 mL saline per gram of precursor powder.

ANIMAL AND HUMAN STUDIES

Knaack et al[20] studied the efficacy of ∝-BSM in a dog femoral slot model. New bone formation occurred in 3 weeks as the material resorbed. This new bone formation appeared to form in an osteoconductive fashion. The boundary between old and new bone was indistinguishable at 26 weeks, and only 1.7% of residual implanted ∝-BSM was observed at 4 weeks. This decreased to 0.36% at 26 weeks. The material is believed to remodel physiologically to form new bone that has the strength of normal, unoperated, bone at 12 weeks.

Carbonated Calcium Phosphate Cement (Norian Skeletal Repair System [SRS])

The Norian Skeletal Repair System/Craniofacial Repair System (SRS/CRS, Norian Corp, Cupertino, CA) is a fully resorbable CPC that is designed to augment fracture repair via the in situ formation of the mineral phase of bone.[21] The material consists of monocalcium phosphate, ∝-tricalcium phosphate, and calcium carbonate, which are mixed with sodium phosphate to form a paste. The paste is injectable and forms dahllite in an isothermic reaction at physiologic temperature and pH. Dahllite is a carbonated form of apatite with a molar calcium-to-phosphate ratio of 1.67:1 that contains 4% to 6% carbonate by weight. The setting reaction is 85% to 90% complete at 12 hours. The material attains a final compressive strength of 55 MPa (the compressive strength of cancellous bone is 1.9 ± 0.14 MPa) and a tensile strength of 2.1 MPa (the tensile strength of cancellous bone is 2.42 ± 0.16 MPa).[22,23] The set material has a median average pore diameter of 300 Å. This suggests that it may be resistant to penetration by microorganisms. The dahllite formed is biocompatible, osteoconductive, and is remodeled through the same mechanisms as normal bone.

ANIMAL AND HUMAN STUDIES

The Norian SRS has shown unique utility in femoral neck fractures and distal radius fractures.[24,25] Stankewich et al[25] and Goodman et al[26] showed augmentation of femoral neck fractures with the Norian SRS cement, which significantly improved the initial stiffness and failure strength of the fractures. The cement also has been used to stabilize distal radius fractures in 6 patients and appeared to promote healing and permit early mobilization of the wrist.[24] Moore et al[27] used a CPC with a dissimilar formulation than the actual Norian SRS product to augment the fixation of pedicle spine screws. The CPC was shown to increase the in vitro pullout strength by 102% and thus it may offer an alternative to polymethylmethacrylate for the clinical enhancement of pedicle screw fixation, especially in osteopenic bone. Frankenburg et al[28] studied Norian SRS in canine tibial and femoral metaphyseal defects. The cement underwent gradual remodeling over time with blood vessels penetrating the cement. Osteoclasts were found to resorb the cement in areas of new bone formation.

The physical properties of dahllite contribute to the biocompatibility of the Norian SRS material. Over time, the material is replaced by new bone in a process resembling remodeling. In cancellous bone, this appears to be complete as early as 16 weeks after implantation.[21] Human trials have been conducted in the following applications: Colles' fractures, tibial plateau fractures, spinal reconstruction, humeral head fractures, acetabular cup revision, and frontal sinus reconstruction.

Discussion

The CPCs represent an intriguing group of new materials for bone augmentation and reconstruction. Although it may appear that all of these materials are intended for the same clinical use, their physical properties suggest otherwise. Resorption of the prototype CPC, Bone Source, is minimally documented in the literature. Current data suggest that resorption is slow. For example, human cases reoperated up to 2 years postsurgery showed that significant residual material was present. However, this should not be construed as a shortcoming. There is a need for an augmentation/reconstruction material that integrates with the host bone and maintains shape and form indefinitely.

The ∝-BSM and Norian SRS/CRS materials have been reported to form new bone by an osteoconductive process. However, this claim by the companies who produce these materials has not been substantiated in the peer-reviewed literature. To date, use of these CPCs have only been reported anecdotally, or in animal model systems that will spontaneously heal. Studies of these materials performed in a critical size defect model may allow investigators to draw more scientifically based conclusions.

The mechanism of bone healing caused by the CPCs is very likely multifactorial, involving adsorption of growth factors onto the HA as well as the direct effects of the calcium phosphate. It is well known that many polypeptide growth factors present in bone matrix may be adsorbed onto HA and thus modulate the local milieu of cells. This is supported by the many growth factor and bone morphogenetic protein/osteogenin purification protocols involving HA.[29-32] The direct effect of calcium phosphate salts is similarly intrigu-

ing. Pure powdered calcium phosphate is mitogenic for fibroblasts.[33,34] This activity has been hypothesized to occur through direct interaction of the cell membranes with the crystalline mineral surfaces. However, osteoblasts are not found in direct contact with the calcium phosphate compound, HA. A complex proteinaceous layer, usually osteoid, directly contacts the osteoblasts. After implantation of CPCs, mitogenic events could occur during either the initial mesenchymal cell contact or after osteoid degradation by osteoblast collagenase. In a dense, mineralized material such as CPC, which provides a barrier to the free diffusion of circulating hormones, growth factors, and cytokines, it is questionnable whether the local responses at the periphery of the material regulate osteoconduction.

Conclusion

CPCs appear to offer promising clinical utility. However, before widespread clinical use proceeds, stringent clinical evidence must be provided to document the manufacturer's claims. Caution must be the present course, because there is still insufficient documentation to support the claims and utility of many of the CPCs. However, if many of the purported properties of the CPCs are documented in carefully done studies reported in peer-reviewed journals, these materials have the potential to totally revolutionize the surgical management of fractures and bone defects.

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