

### III. Kyphoplasty and Nucleus Pulposus Prosthesis

## Vertebroplasty and kyphoplasty: filler materials

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#### Abstract

Over 700,000 osteoporotic compression fractures occur each year in the United States, twice the number of hip fractures. These vertebral fractures, most of which occur in the elderly, represent significant personal and societal burdens. Percutaneous vertebroplasty (PVP) is a minimally invasive method that involves the percutaneous injection of polymethylmethacrylate (PMMA) into a collapsed vertebral body to stabilize the vertebra. Kyphoplasty is an advanced minimally invasive technique with a number of potential advantages over PVP, including lower risk of cement extravasation and better restoration of vertebral body height and spinal biomechanics. The filling materials used for both these techniques require good biocompatibility, good biomechanical strength and stiffness, and good radiopacity for the fluoroscopy guided procedures. New filler materials (synthetic bone substitutes, e.g., composite resin materials, calcium phosphate or calcium sulfate cements) in addition to new PMMA formulations are now available for clinical use. In this review paper, we will focus on the issues and characteristics of these filler materials as they pertain to vertebral augmentation procedures. © 2005 Elsevier Inc. All rights reserved.

#### Keywords:

Vertebroplasty; Kyphoplasty; Polymethylmethacrylate; Calcium phosphate cement; Calcium sulfate cement; Vertebral compression fracture

#### Introduction

Vertebral augmentation has been widely adopted to treat vertebral body compression fractures caused by varied pathologies including hemangioma, multiple myeloma, osteolytic metastases, and primary or secondary osteoporosis. The material used during augmentation requires specific biomechanical and biological properties to support the spinal column. Because this procedure is usually performed under fluoroscopy, the material must be radiopaque to track filler material movement and detect or avoid material leak that may cause neurological or other tissue injury. Because the filler

material is deposited into a load-bearing environment, it must be able to withstand cyclic and static complex loading patterns. Also by virtue of the percutaneous surgical technique, the filler material handling characteristics must be amenable to easy preparation, appropriate flow, and polymerization or crystallization characteristics. Determining the suitability of any one of the available materials will depend on an understanding of its material properties, including the biomechanical, biological, radiopaque properties, and handling characteristics (Table 1). This review will focus on these issues as related to various filler materials and additives used for vertebral augmentation.

FDA device/drug status: approved for this indication (polymethylmethacrylate bone cement); investigational/ not approved (synthetic bone substitutes).

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#### Vertebroplasty and kyphoplasty

Percutaneous vertebroplasty, first conceived in 1984 in France, by Galibert and Deramond [1], involves the injection of a mixture of polymethylmethacrylate bone cement (PMMA) and a contrast agent, typically barium sulfate, into the vertebral bodies using fluoroscopic or occasionally computed tomography guidance, or rarely both. Early vertebroplasty procedures were designed to alleviate pain and to stabilize the fractured vertebral bodies in patients with

Table 1  
Injectable bone cement

Injectable bone cement	Manufacturer	Materials (description, feature)	References
Polymethylmethacrylate (PMMA)			
Simplex P	Stryker Orthopaedics, Mahwah, NJ, USA	(Powder) 75% w/w methylmethacrylate–styrene–copolymer, 10% w/w barium sulfate, 15% w/w polymethyl methacrylate, (Liquid) 97.4% v/v methylmethacrylate (monomer), 2.6% v/v <i>N, N</i> -dimethyl- <i>p</i> -toluidine, 75 ± 15 ppm hydroquinone	[16,18,61,89]
HV-R	Kyphon, Inc., Sunnyvale, CA, USA	(Powder) 68% w/w methylmethacrylate–styrene–copolymer, 30% w/w barium sulfate, 2% w/w benzoyl peroxide, (Liquid) 99.1% v/v methylmethacrylate (monomer), 0.9% v/v <i>N, N</i> -dimethyl- <i>p</i> -toluidine, 75 ppm hydroquinone	
Palacos R	Biomet Orthopedics, Inc., Warsaw, IN, USA	(Powder) 81.8% w/w methyl acrylate, methylmethacrylate, 14.9% w/w zirconium dioxide, 0.78% w/w benzoyl peroxide, 2.4% chlorophyll, (Liquid) 96% v/v methyl methacrylate (monomer), 2.0% v/v <i>N, N</i> -dimethyl- <i>p</i> -toluidine, 0.40 mg chlorophyll	[16–18]
DePuy 1 (CMW)	DePuy Orthopaedics, Inc., Warsaw, IN, USA	(Powder) 88.85% w/w polymethyl methylmethacrylate, 9.1% w/w barium sulfate, 2.05% w/w benzoyl peroxide, (Liquid) 98.18% v/v methylmethacrylate (monomer), 0.82% v/v <i>N, N</i> -dimethyl- <i>p</i> -toluidine, 25 mg hydroquinone	[16,17]
Osteobond	Zimmer Inc., Warsaw, IN, USA	(Powder) 88.75% w/w polymethyl methylmethacrylate–styrene, 10% w/w barium sulfate, 0.0125% w/w benzoyl peroxide, (Liquid) 97.3% v/v methylmethacrylate (monomer), 2.7% v/v <i>N, N</i> -dimethyl- <i>p</i> -toluidine, 80 ppm hydroquinone	[16–18]
Composite material			
Cortoss	Orthovita Inc., Malvern, PA, USA	(Resin components) (2,2-bis-4-(2-Hydroxy-3-methacryloxypropoxy)phenylpropane, (2,2-bis-4-(2-methacryloxy-ethoxy)phenylpropane, triethylene glycol diemethacrylate, 2,2'-(4-methylphenyl)imino bis-ethanol, benzoylperoxide 98%, 2-hydroxy-4-methoxy-benzophenone, 2,6-di- <i>tert</i> -butyl- <i>p</i> -cresol, (Reinforcing components) silane treated combeite glass-ceramic, (Na <sub>2</sub> O-CaO-P <sub>2</sub> O <sub>5</sub> -SiO <sub>2</sub> ), silane treated baria-boroalumno-silicate glass (BaO-B <sub>2</sub> O <sub>3</sub> -Al <sub>2</sub> O <sub>3</sub> -SiO <sub>2</sub> ), silane treated amorphous silicon dioxide (SiO <sub>2</sub> ), methacryloxypropyltrimethoxysilane	[18,58,59]
Calcium phosphate cement (CPC)			
BoneSource	Stryker Orthopaedics, Mahwah, NJ, USA	(Powder) 72.3% w/w tetracalcium phosphate, 27.7% w/w dicalcium phosphate anhydrous, (Fluid) 0.25 mol/L phosphate solution and distilled water-(Ca9.970 (HPO <sub>4</sub> )0.080(PO <sub>4</sub> )5.892(CO <sub>3</sub> )0.080(OH)1.944)	[31–34,44,45]
SRS	Norian Corp., Cupertino, CA, USA	(Powder) monocalcium phosphate, monohydrate, tricalcium phosphate, and calcium carbonate, (Fluid) sodium phosphate solution. (Ca8.8(HPO <sub>4</sub> )0.7(PO <sub>4</sub> )4.5(CO <sub>3</sub> )0.7(OH)1.3)	[32,37,38]
Alpha-BSM	ETEX Corporation, Cambridge, MA, USA	(Powder) amorphous calcium phosphate in combination with an acid calcium phosphate, dicalcium phosphate dehydrate, (Liquid) 0.9% sodium chloride	[35,36]
Biopex	Mitsubishi Materials, Tokyo, Japan	(Powder) α-tricalcium phosphate, tetracalcium phosphate, dicalcium phosphate, and hydroxyapatite, (Liquid) chondroitin sodium sulfate, sodium succinate, and water	[71]
Calcium sulfate cement			
BonePlast	Interpore Cross International, Irvine, CA	(Powder) calcium sulfate, (Liquid) saline	[40]

hemangiomas, metastases, other types of spine tumor, or osteoporotic compression fractures [1–4]. This technique has been shown to stabilize the vertebral body and has been successful in pain relief in 75% to 85% of patients [5–9].

Kyphoplasty, developed in the 1990s, involved the introduction of an inflatable bone tamp into the compressed vertebral body, with the intent to elevate or expand the fractured vertebrae towards its original height. This action creates a cavity which is then filled with the surgeon's choice of filler material. By reducing and fixing the fracture in this manner, kyphoplasty can restore lost height and sagittal alignment as well as restore the normal load transmission patterns from vertebrae to vertebrae [10–14].

Vertebroplasty and kyphoplasty should not be considered mutually exclusive surgical interventions in the treatment of vertebral compression fractures. These two tools lie in the spectrum from stabilization to reduction to reconstruction, and should be used after considering the most appropriate method to achieve the desired outcome. The procedures differ mainly in surgical technique, where vertebroplasty involves the injection of liquid PMMA into the closed space of a collapsed vertebral body, and kyphoplasty involves the creation of a cavity in the centrum of the vertebral body followed by a controlled cavity fill with partially cured PMMA. As implied, these differences in surgical technique dictate different handling characteristics for the filler material. During vertebroplasty the ideal material would have a longer liquid phase, working time, and a very short set time. During kyphoplasty the ideal material should have a short liquid phase and a longer partially cured "doughy" phase working time.

### Polymethylmethacrylate (PMMA)

Polymethylmethacrylate bone cements have been used for many years for the fixation of the metal and plastic components of joint replacement, and less frequently for the stabilization or fixation of pathological fractures with bone tumors. Charnley had first reported the use of cement in 1960 and by 1964 had studied 455 prostheses that were used for hip surgery inserted with cement [15]. In his review of cases that included 6 necropsy specimens and 43 revisions, there was no evidence of deterioration of the bond between the prosthesis and PMMA with no apparently harmful systemic effects due to the PMMA. Since this observation, PMMA has been increasingly used for a variety of orthopedic applications [16,17].

Even though no PMMA had been approved by the US Food and Drug Administration (FDA) before April 2004, it had been the material most commonly used during vertebral augmentation procedures [18]. As of April 2004, the FDA did approve the labeling of certain brands of PMMA for the treatment of pathological fractures of the vertebral body resulting from osteoporosis and tumor using a kyphoplasty technique [19].

PMMA is reportedly bioinert and shows good biocompatibility over long-term follow-up. Several inherent advantages to PMMA include familiarity for orthopedic surgeons, ease of handling, good biomechanical strength and stiffness, and cost-effectiveness. Several disadvantages, on the other hand, include: no biologic potential to remodel or integrate into the surrounding bone, no direct bone apposition, excessive inherent stiffness, high polymerization temperature, and potential monomer toxicity. Although good clinical results have been reported in several series of both vertebroplasty and kyphoplasty procedures [3,10–13,20–23], it is still unclear whether some component of the pain relief is secondary to the mechanical stabilization, chemical toxicity, or thermal necrosis of surrounding tissues and nerve ends. The concern regarding thermal bone necrosis is still theoretical, as to date, there has been no obvious evidence to support this (Fig. 1) [24,25]. In a baboon vertebral augmentation study, there were a few necrotic segment of bone present in both the vertebroplasty and kyphoplasty vertebrae. It was not, however, clear that the necrosis was caused by a PMMA polymerization process [24].

In a histological evaluation we identified particles consistent with cement and/or barium sulfate in vascular spaces in human vertebrae obtained from surgical excision and autopsy cases [25]. These findings are consistent with the clinical observation of occasional embolization of cement after vertebral augmentation [26–30]. Scanning electron microscopy and energy dispersive radiograph spectroscopy of the specimens confirmed the presence of barium sulfate within the vessels (Fig. 1). Although the clinical significance of these findings is still uncertain, it would seem appropriate to avoid injecting cement under high pressure.

### Ceramic bone cements

Significant interest has been expressed by the surgeon community for a synthetic bone substitute capable of remodeling or integrating into the surrounding bone. Calcium phosphate cement offers the potential for resorption of the cement over time and replacement with new bone as a biological method to restore vertebral body mass and avoid any potential thermal effects of PMMA [31–35]. This material is also expected to work as an optimum carrier for osteoinductive proteins [36].

Preclinical animal studies and human pilot studies have shown that these calcium phosphate cements are highly osteoconductive and undergo gradual remodeling with time [37–42]. There are only a few published manuscripts reporting histologic data with calcium phosphate cement in vertebroplasty model [31,43–45]. In general the cement undergoes resorption and remodeling, that was apparent as fragmentation with vascular invasion and bone ingrowth into the material. The reports also described evidence of osteoclastic resorption of the cement and direct bone apposition in a pattern that suggested remodeling similar to that

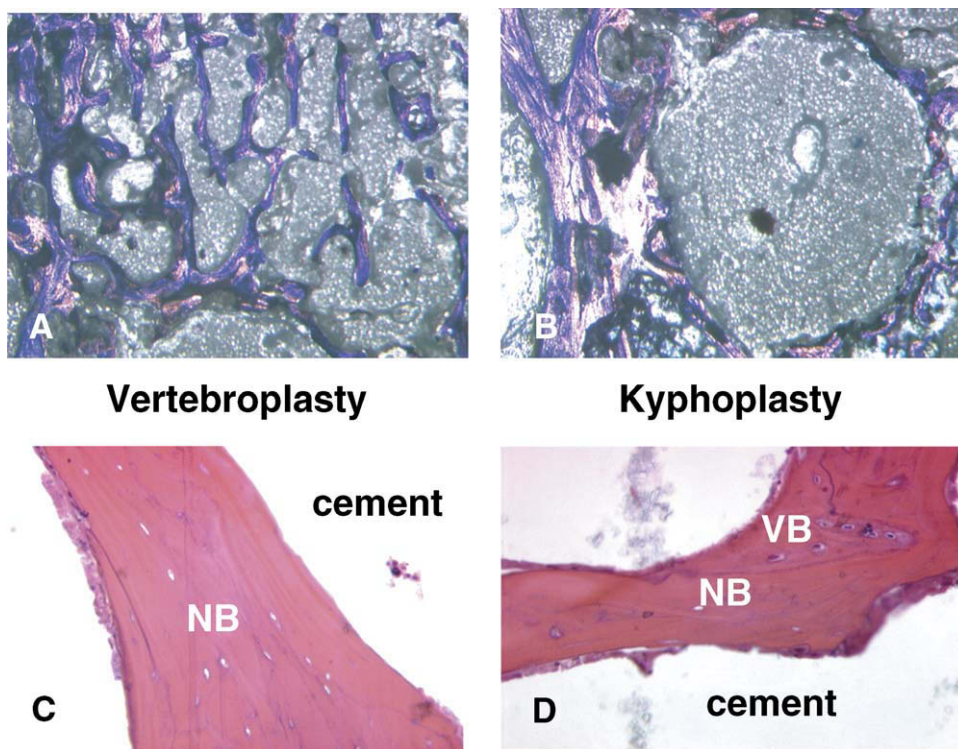


Fig. 1. Vertebroplasty versus kyphoplasty in baboon model [24]. Although there are a few necrotic segments of bone in both vertebroplasty and kyphoplasty groups, there was no clear evidence of obvious thermal necrosis from polymethylmethacrylate polymerization. (A) Cement area of vertebroplasty. (B) Cement area of kyphoplasty (undecalcified section: Giemsa stain). (C) Necrotic segment of bone in vertebroplasty section. (D) Necrotic segment of bone in kyphoplasty section (decalcified section: hematoxylin and eosin stain; NB=necrotic bone; VB=viable bone).

of normal bone. Turner et al. tested both PMMA and calcium phosphate cement (BoneSource; Stryker Orthopaedics, Mahwah, NJ) in a canine vertebral body defect. In their study, both materials were well integrated histologically, but calcium phosphate underwent resorption and remodeling, and demonstrated excellent biocompatibility and osteoconductivity [44]. Takikawa et al. also reported greater than 80% direct apposition to cancellous bone in postoperative osteopenic sheep vertebrae at 3, 6, 12, and 24 months (Fig. 2) [45]. A number of hydroxyapatite and calcium phosphate cements also have been biomechanically tested [46–48]. In vitro, most are able to restore mechanical integrity to the vertebral body [49–51].

Calcium sulfate, more commonly known as plaster of Paris, has a long clinical history for use as a bone graft substitute in various skeletal sites. This material is injectable, osteoconductive, and cures with a limited exothermic reaction. Turner et al. reported their histologic analysis using calcium sulfate bone graft substitute in a canine medullary defect [52]. In this study, sequential radiographs at 2, 6, and 13 weeks demonstrated progressive resorption of the bolus of calcium sulfate within the defect. Histologically at 13 weeks, all of the medullary defects treated with calcium sulfate demonstrated prominent osteoblastic rimming of the newly woven bone. Higher magnification showed residual calcium sulfate incorporated into the newly woven bone and

in the immediate area, which continues to provide an osteoconductive scaffolding. Similar studies using several different proportions of calcium sulfate hydroxyapatite/tricalcium phosphate (HA/TCP) composites in a canine metaphyseal defect model showed that increasing the proportion of HA/TCP could reduce the rates of dissolution, with no negative effect on bone formation, whereas higher proportions of calcium sulfate are still associated with rapid dissolution and less net mineral content [53]. Calcium sulfate paste has also been shown to significantly augment pull-out strength when used for augmentation of pedicle screw fixation [54]. However, this material is rapidly resorbed [55–57], it might not be able to support spinal alignment while it is remodeling, therefore it would likely be inappropriate for use in a vertebral augmentation procedure.

Other problems with these calcium phosphate and sulfate cements include their low viscosity, handling characteristics different from those of PMMA, and high cost. These products are true cements, that is, ions in suspension. As such they exhibit thixotropic properties in that when pressurized in a confined space such as a delivery tube, the suspension dewater, leaving chalk that cannot advance through a tube or even percolate through the interstices of the bone. Many synthetic bone substitute cements are currently being developed, but none are yet readily available for use in the spine.

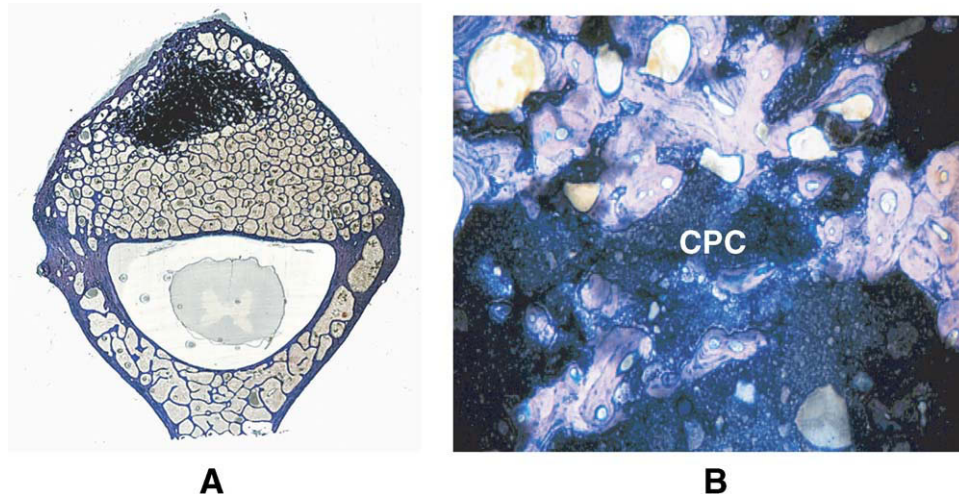


Fig. 2. Calcium phosphate cement in osteopenic sheep vertebra [45]. (A) Specimen (sheep vertebra). Axial section of sheep vertebra 2 years after the surgery. A cavity was created in the vertebral body, and calcium phosphate cement (BoneSource; Stryker Orthopaedics, Mahwah, NJ) was injected into the cavity. (B) Bone apposition to calcium phosphate cement (CPC). Higher magnification shows direct bone apposition to injected calcium phosphate cement 2 years after the surgery.

### Composite materials

Composite materials (acrylic cements in conjunction with ceramics) are bioactive, highly radiopaque, and feature excellent mechanical properties [58,59]. One such material, Cortoss (terpolymer resin reinforced with combeite glass-ceramic particles; Orthovita, Malvern, PA) is currently undergoing clinical trials for vertebroplasty and kyphoplasty and has initially been reported to be a viable alternative to PMMA, but its osteoconductivity in human vertebrae is still unknown.

### Additives

#### Antibiotics

Antibiotics are sometimes added to PMMA before mixing as a prophylactic measure against infection [20,60]. These antibiotics can affect the mechanical properties of the cured PMMA. Research has shown that adding various types of antibiotics to PMMA, in quantities less than 2 g per standard packet of polymer powder, does not adversely affect its mechanical properties, although quantities exceeding 2 g did weaken them [61,62]. However, other studies did find a significant decrease in mechanical strength between cement mixed aqueous of gentamicin versus powdered gentamicin [62]. To avoid the potential risk of these changes to the cement's properties, some physicians use an intravenous administration of antibiotics before surgical intervention instead of mixing them into PMMA [63].

Elution rate of antibiotics from various cements has also been reported [64–68]. Ethell et al. tested the elution characteristics of ceftiofur and liquid and powdered gentamicin and amikacin from polymethylmethacrylate and hydroxyapatite cement [67]. They found that the elution of antibiotics from

hydroxyapatite cement was greater than from PMMA and gentamicin- and amikacin-impregnated PMMA and hydroxyapatite cement released bactericidal concentrations of antibiotic for at least 30 days. Masri et al. examined antibiotic elution from tobramycin-loaded bone cement blocks of three different surface patterns with different surface area-to-volume ratios [66]. They showed significantly greater tobramycin-elution rate in the surface pattern with the increased surface area-to volume ratio.

#### Radiopaque agents

PMMA intended for orthopedic reconstruction often has barium sulfate added as an opacifier for radiographic evaluation. Simplex P originally contained 10% barium sulfate by weight. This percentage allows standard radiographic examination for joint reconstructions, but this is insufficient for fluoroscopic visualization during vertebral augmentation. Radiopaque substances, such as tantalum powder, tungsten, barium sulfate, or zirconium dioxide, have been added to PMMA to facilitate fluoroscopic visualization to monitor possible cement extravasation [20,60,69]. In Europe, tungsten and tantalum powder are commonly used opacifiers, but these substances are not approved by the US FDA as opacifiers for PMMA cement. Therefore sterile barium sulfate is commonly added to PMMA powder in the United States. Previous studies have shown that the addition of barium sulfate can reduce cement strength and stiffness [70–72], but the potential clinical importance of these changes in strength and stiffness of cement for use in the vertebral body are uncertain. Barium sulfate may also affect polymerization temperature. One study showed that maximum polymerization temperature for Simplex P with 30% and 60% barium sulfate by weight was 60° and 40° Celsius, respectively [73]. A second similar study showed no significant difference in

peak polymerization temperature between a PMMA cement with 10% and 0% barium sulfate [71]. The addition of barium sulfate and zirconium dioxide to PMMA also has been examined in association with bone resorption [74,75]. Although the addition of zirconium dioxide caused a significant increase in bone resorption, Sabokbar et al. showed that increase was 50% less than that of cement-containing barium sulfate [74]. Wimhurst et al. reported that PMMA with zirconium dioxide did not show a significant increase in bone resorption [75]. Clinically, one report showed that foreign body giant cells and mononuclear macrophages containing cement particles and/or barium sulfate were identified in the thin membrane surrounding the PMMA in human vertebrae (Figs. 3 and 4) [25]. However, to our knowledge, there is no report describing bone resorption associated with cement particles and/or barium sulfate in clinical cases.

The synthetic bone substitutes (eg, calcium phosphate cements) by virtue of their chemical composition are inherently radiopaque but may still require radiopaque additives to increase their visualization.

### Practical issues

Because vertebral augmentation is more commonly performed today, new or modified PMMA formulations are being used. Modifications to these fillers may vary from physician to physician and among procedures. These modifications may include increasing the amount of contrast agent (eg, barium sulfate) to improve visualization under the fluoroscope and changing the consistency and handling properties to address procedural goals (eg, proportion of monomer vs. polymer). The viscosity and working time of cement are critical considerations because of the difficulty of forcing cement to flow through relatively small needles and the risk of inadvertently cementing the needles into the vertebral body. Especially in vertebroplasty, surgeons commonly alter the mixture of monomer-powder ratio to decrease the viscosity and to increase the working time.

To date, no standardized formulations, biomechanical standards, or safety guidelines exist for the methods of preparing or modifying PMMA or any other bone void filler for use in the spine.

### Biomechanical properties

Biomechanically the single level vertebral fracture model has been used to study the effect of an experimental vertebral compression fracture augmented with cement (Table 2). Stiffness and strength of the vertebral body have been reported to improve to varying degrees dependent upon cement type and volume used, bone mineral density of the vertebrae, and experimental technique used [47,49–51,76–84]. For example, the failure load of vertebrae has been reported to increase with prophylactic cement augmentation [47,76,81] and with cement augmentation of fractures [49–51,77–79,82,83]. Stiffness from prophylactic augmentation has also been reported to increase [47,76], or to remain the same [81]. Stiffness after fracture augmentation has been reported to increase [50,76,78,82], to remain unchanged [77,83], and even to reduce [47,49,51,79,84]. This variation in stiffness probably results from the experimental method used (prophylactic augmentation or fracture augmentation), level of spine used (thoracic, lumbar or both), volume of cement fill, and the bone mineral density of the specimens. The minimum fill volume percent reported for a fracture augmentation effect on strength was 16% [82] and 25–30% for a fracture augmentation effect on stiffness [50,82]. For prophylactic augmentation, Higgins et al. reported 20% fill volume for effect on strength [81]. Berlemann et al. [85] demonstrated no significant changes in strength and stiffness after single augmentation of the pair with cement fill volume of 23% in thoracic vertebral pairs.

Jasper et al. tested the effect of varying the monomer-to-polymer ratio on the compressive properties of cylindrical specimens of Cranioplastic [86]. They reported that increasing the monomer to polymer ratio (0.40 to 1.07 mL/g) of

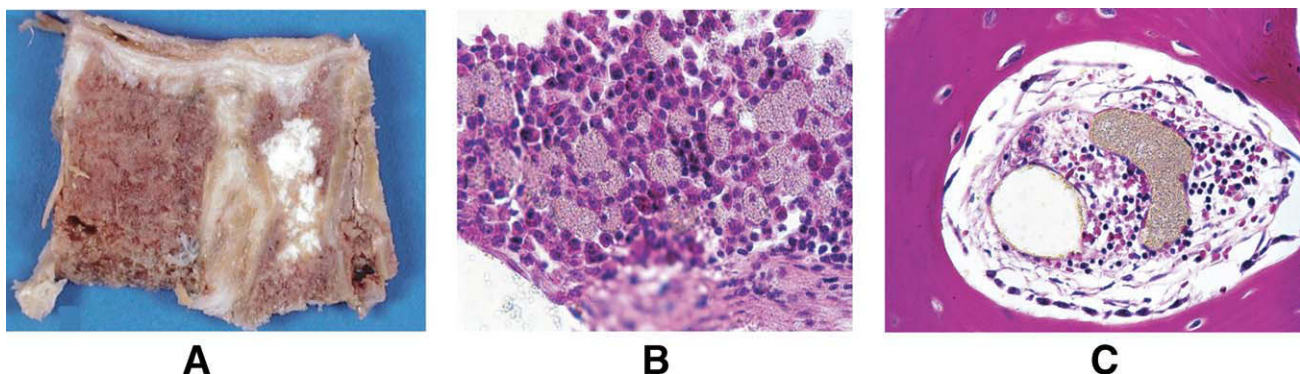


Fig. 3. Cement in human vertebral body treated by kyphoplasty for painful osteoporotic compression fractures [25]. (A) Autopsy specimen. Vertebrae retrieved from autopsy contains polymethylmethacrylate interdigitating into cancellous bone. (B) Cement phagocytosis. Cement particles and/or barium sulfate are phagocytosed by foreign body giant cells. (C) Cement particles and/or barium sulfate within vascular space. Photograph shows cement particles and/or barium sulfate within vascular spaces in vertebra harvested 1 month after the surgery.

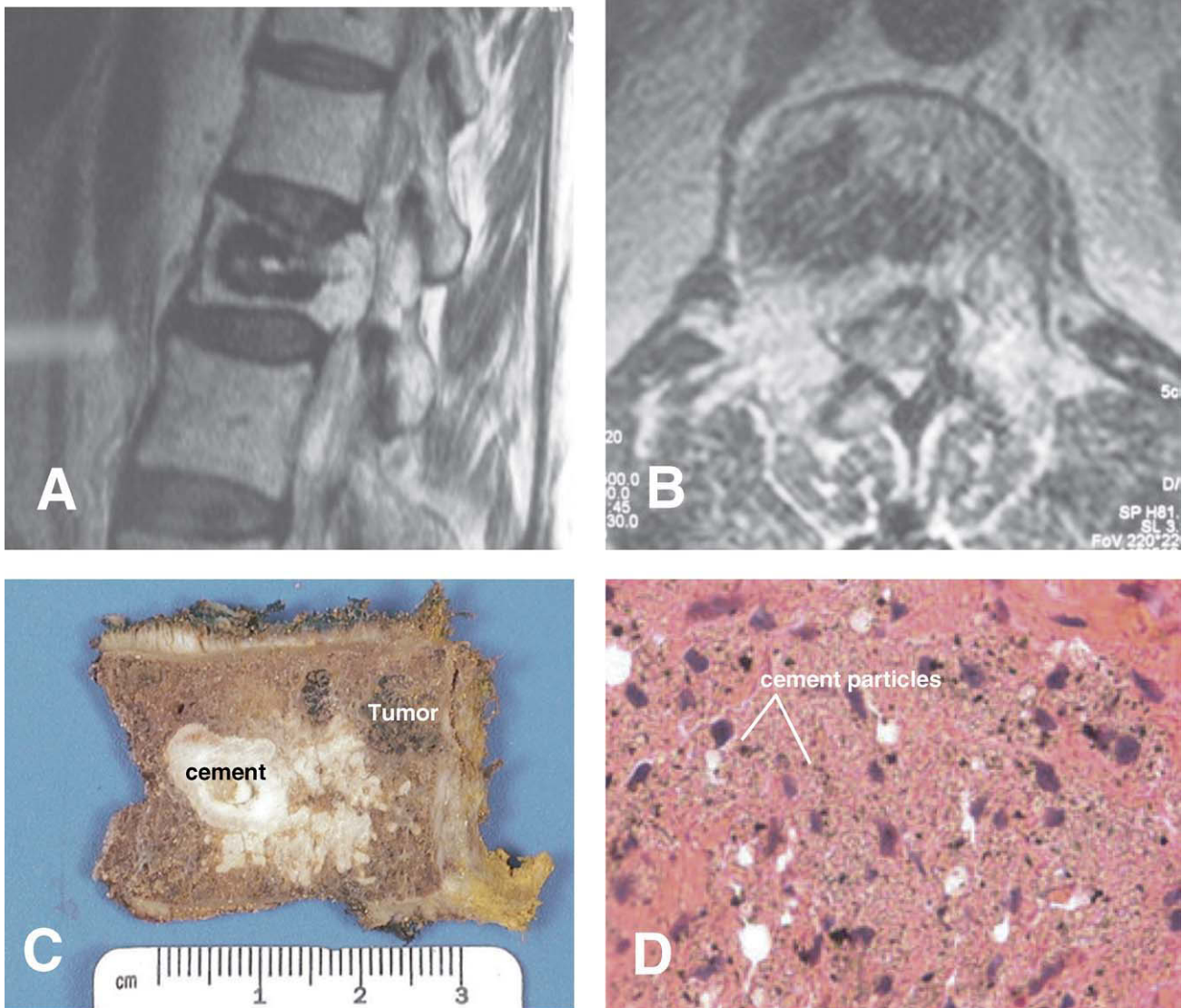


Fig. 4. Polymethylmethacrylate in human vertebral body treated by kyphoplasty for painful hemangioma. (A) T1-weighted sagittal magnetic resonance imaging (MRI) image. T2-weighted sagittal MRI image shows osteolytic region (low intensity area) with compressed spinal cord suggesting recurrent hemangioma. (B) MRI axial view. T2-weighted axial magnetic resonance imaging shows that the spinal cord was decompressed, suggesting recurrent tumor. (C) Surgical section. Axial section of vertebral body shows recurrent hemangioma and polymethylmethacrylate deposited by kyphoplasty. (D) Cement and/or barium sulfate particles. Photograph showing cement particles and/or barium sulfate phagocytosed by foreign body giant cells.

cement significantly reduced ultimate compressive strength, yield strength, and elastic modulus of the cement. The authors estimated the actual mixture ratio used in vertebral augmentation to be between 0.60 to 0.74 mL/g (the manufacturer's recommended ratio: 0.57 mL/g), resulting in a reduction in strength of 16% for this range of ratios. Belkoff et al. tested initial strength and stiffness of compressed and crushed cadaveric vertebral bodies augmented with different types of filler materials [77]. They concluded that bipedicular injection of Simplex P (Stryker Orthopaedics, Mahwah, NJ) and Osteobond (Zimmer, Warsaw, IN) restored vertebral body stiffness to initial values, whereas vertebral bodies augmented with Cranioplastic (DePuy International, Ltd.,

Blackpool, England) were significantly less stiff than in their initial state. Antibiotics or radiopaque agents are often added to the cement powder during the preparation, and these modifications change the material properties [20,69].

#### Osteoconductivity and bone apposition

An osteoconductive material promotes bone apposition along its surface. The term "osteosconduction" is not absolute, and is best understood when used in the context of a comparative study in which variables of the substrate material, porosity, surface geometry, and surface chemistry are

Table 2  
The different reported augmentation effects in literature

Author, year [ref]	Filler material	VP/KP	Model, augmentation type	Stiffness	Strength
Mermelstein et al., 1998 [97]	CaPO <sub>4</sub>	Transpedicular fill	Multilevel, post fracture	Increased	Not tested
Belkoff et al., 1999 [77]	PMMA	VP	Single, post fracture	Variable	Increased
Tohmeh et al., 1999 [83]	PMMA	VP	Single, post fracture	Increased	Increased
Bai et al., 1999 [76]	PMMA and CaPO <sub>4</sub>	VP	Single, prophylactic and post fracture	Increased for both PMMA and CaPO <sub>4</sub> , in both prophylactic and post fracture tests	Increased for both PMMA and CaPO <sub>4</sub> in both prophylactic and post fracture tests
Wilson et al., 2000 [98]	PMMA	VP and KP	Multilevel, post fracture	Increased for both VP and KP	Not reported
Dean et al., 2000 [99]	PMMA	VP	Single, prophylactic	Not reported	Increased
Belkoff et al., 2000 [49]	PMMA and Orthocomp	VP	Single, post fracture	PMMA reduced, Orthocomp increased	Increased for both PMMA and Orthocomp
Ikeuchi et al., 2001 [100]	CaPO <sub>4</sub>	VP	Single, prophylactic	Not tested	Increased
Belkoff et al., 2001 [79]	PMMA and hydroxyapatite	VP	Single, post fracture	Reduced for both PMMA and hydroxyapatite	Increased for both PMMA and hydroxyapatite
Belkoff et al., 2001 [51]	PMMA and hydroxyapatite	KP	Single, post fracture	Reduced for both PMMA and hydroxyapatite	PMMA increased, hydroxyapatite reduced
Belkoff et al., 2001 [80]	PMMA	VP and KP	Single, post fracture	KP increased, VP reduced	VP and KP increased
Liebschner et al., 2001 [46]	PMMA	VP	FE, post fracture	Increased	Not reported
Heini et al., 2001 [50]	PMMA and CaPO <sub>4</sub>	VP	Single, prophylactic	Increased for both PMMA and CaPO <sub>4</sub>	Increased for both PMMA and CaPO <sub>4</sub>
Belkoff et al., 2001 [78]	PMMA and Orthocomp	VP	Single, post fracture	Increased for both PMMA and Orthocomp	Increased for both PMMA and Orthocomp
Hitchon et al., 2001 [101]	PMMA and hydroxyapatite	VP	Multilevel, post fracture	Increased for both PMMA and hydroxyapatite	Not reported
Lim et al., 2002 [47]	PMMA and CaPO <sub>4</sub>	VP	Single, prophylactic and post fracture	Reduced for both PMMA and CaPO <sub>4</sub> in post fracture augmentation, and increased with prophylactic augmentation	Increased for both PMMA and CaPO <sub>4</sub> in both post fracture and prophylactic augmentation
Berlemann et al., 2002 [85]	PMMA	VP	Multilevel prophylactic	No change in stiffness	Reduced strength
Tomita et al., 2003 [84]	PMMA and CaPO <sub>4</sub>	VP and KP	Single, post fracture	Reduced in KP with both PMMA and CaPO <sub>4</sub> , increased in VP with both PMMA and CaPO <sub>4</sub>	Increased for both KP and VP and both PMMA and CaPO <sub>4</sub>
Higgins et al., 2003 [81]	PMMA	VP	Single, prophylactic	Unchanged	Increased
Molloy et al., 2003 [82]	PMMA	VP	Single, post fracture	Increased	Increased
Polikeit et al., 2003 [102]	PMMA	VP	FE, multilevel, prophylactic	Increased	Increased
Baroud et al., 2003 [103]	PMMA	VP	FE, multilevel, prophylactic	Increased	Not reported
Sun et al., 2004 [104]	PMMA	VP	FE, single, prophylactic	Increased	Increased
Tomita et al., 2004 [105]	PMMA and CaPO <sub>4</sub>	KP	Single, post fracture	Decreased with both PMMA and CaPO <sub>4</sub>	Increased with both PMMA and CaPO <sub>4</sub>
Kayanja et al., 2005 [14]	PMMA	KP	Multilevel, post fracture	Reduced	Unchanged
Kayanja et al., 2005 *	PMMA	KP	Multilevel, prophylactic	Reduced	Unchanged
Kayanja et al., 2005 [106]	PMMA	KP	Multilevel, post fracture	Unchanged	Unchanged

FE=finite element; KP=kyphoplasty; PMMA=polydimethylmethacrylate; ref=reference; VP=vertebroplasty.

\* Unpublished data (manuscript submitted to *Spine*).

† Model: single=single vertebra, multilevel=2 or more vertebrae. Augmentation=prophylactic is augmentation before fracture, post fracture is augmentation after fracture.



highly controlled and defined. For example, when matched by size, shape, and surface texture, hydroxyapatite is more osteoconductive than PMMA. PMMA is usually interdigitated into the cancellous bone in vertebrae during vertebral augmentation, but it cannot be expected to promote very much direct bone apposition. One study showed that PMMA deposited into vertebral bodies appeared to be mostly surrounded by a thin fibrous membrane histologically [25]. On the other hand, alternative cements with variable osteoconductive properties have also been tested. For example, several animal studies with injectable calcium phosphate cements confirm their feasibility, mechanical effectiveness, biocompatibility, and osteoconductivity [44,45]. Moreover, Nakano et al. reported good clinical results with percutaneous vertebral augmentation using calcium phosphate cement in the treatment of osteoporotic vertebral compression fractures [87]. Takemasa and Yamamoto also reported preliminary results in a study of 38 patients who had undergone stabilization of osteoporotic vertebral compression fractures with bioactive calcium phosphate cement [88]. All patients had substantial pain relief, and radiographic evaluations showed no radiolucent zone around the cement at 3 months postoperatively.

### Complications due to the materials

Leakage of bone filler material can result in soft-tissue damage as well as nerve root impingement and cord compression. Other reported complications generally associated with the use of PMMA in the spine include PMMA embolism to the lungs, respiratory and cardiac failure, abdominal intrusions/ileus, and death [20,89]. Liquid PMMA used during vertebroplasty may also escape via venous sinuses and embolize to the lungs [28]. To date there are no published reports of PMMA pulmonary embolus with kyphoplasty.

To fully appreciate the implications of PMMA application to the spine, one must consider the volume of material, the proximity to the central circulation, and the potential for monomer toxicity. It has been established that cement monomer is arrhythmogenic and cardiotoxic at the volumes used for a total hip or knee replacement. The risk appears to be somewhere in the neighborhood of 1 in 3,000 to 1 in 5,000 [90,91]. Taking into account the volume of cement (6 cc per level) and the proximity to the spine, and then assuming one is willing to accept the same degree of risk, it seems most appropriate to limit vertebroplasty or kyphoplasty to one or two levels at any surgical setting. Kyphoplasty does have an inherent advantage over vertebroplasty because the kyphoplasty technique dictates a thicker partially cured PMMA be poured into the cavity in a controlled fashion, rather than a highly liquid PMMA forcibly injected into the closed space of the collapsed vertebral body. PMMA in its more liquid form has more “free” monomer available to enter the circulatory system. Because the liquid PMMA used during the vertebroplasty technique obeys the laws of

fluid dynamics, it will seek the path of least resistance thus readily entering the venous sinuses or exiting through the vertebral body fissures and cracks, resulting in more material leaks [92].

Ceramic bone substitutes including calcium phosphate cements may also carry an inherent systemic risk. It has been reported that calcium phosphate ions are occasionally cardiotoxic and may lead to circulatory collapse [93,94]. As such, if the crystallization process remains uncontrolled then free calcium or phosphate in suspension may enter the systemic circulation and may cause inflammatory reactions or hemodynamic collapse [95,96].

### Conclusions

Polymethylmethacrylate is an effective vertebral augmentation filler material. It is inert, biomechanically sound, and adaptable to different techniques and is cost-effective. Other bone substitutes are under development but have not yet achieved the benchmarks set by PMMA. Although reported clinical results of vertebroplasty and kyphoplasty both offer potential benefits with acceptable safety and efficacy, the choice of filler will depend on the eventual development of a material with good biomechanical and biological properties as well as good radiopacity and cost-effectiveness.

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