Biomechanical characteristics of cement/gelatin mixture for prevention of cement leakage in vertebral augmentation

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Abstract

Purpose This study evaluated whether or not the addition of gelatin micro-particles into the polymethyl methacrylate (PMMA) could reduce cement infiltration in cancellous bone of vertebra.

Methods Gelatin micro-particles were prepared in various sizes and mixed with PMMA in different densities. Dynamic viscosity of the mixture was measured by a rotational rheometer. Fresh bovine vertebral bodies were sectioned into cylindrical samples. Permeability of the mixture through the samples was tested on a mechanical test machine, and calculated using Darcy's law. The PMMA/gelatin mixture also underwent compressive and bending tests, and their structures were examined by scanning electron microscopy.

Results The cement/gelatin mixture increased the viscosity. Significant reduction of cement permeability in cancellous bone was determined after the addition of the micro-particles. Micro-particles of 2 % in density and 125–250 μm in size decreased the permeability by 1/3 without any significant change of the cement viscosity. The biomechanical strength was unchanged in compression but decreased by up to 20 % in bending.

Conclusions Gelatin micro-particles significantly increased the cement viscosity, reduced the permeability in cancellous

bone of vertebra, decreased the flexural strength, but did not affect the compressive strength. Although it suggested a manageable approach in vertebral augmentation, the outcome should be further verified on a cadaveric model or an animal model before the mixture could be used safely and effectively in the clinical treatment.

Keywords PMMA · Gelatin · Vertebra · Augmentation · Biomechanics

Introduction

As an emerging minimally invasive surgery, bone-cement augmentation of percutaneous vertebroplasty (PVP) or percutaneous kyphoplasty (PKP) has been increasingly used to manage vertebral fractures related to osteoporosis, multiple myeloma, hemangioma or metastases [2–5]. In the procedure, polymethyl methacrylate (PMMA) bone cement is injected into the vertebral cavity at the defect site to refill the void and to stabilize the anterior column. The treatment provides rapid pain relief and quick recovery, prevents the vertebra from further pathological fractures, and improves quality of patient life [6, 7].

Despite its clinical success, however, cement augmentation has the risk of complications. The most serious one, with an incidence of 7–10.6 %, is cement leakage into either adjacent neurological or vascular structures [8, 9]. Although neurological complications from compression of a nerve root or the spinal cord are sometimes asymptomatic, durative pain and even partial or complete paraplegia can occur [10, 11]. Vertebral bodies adjacent to the treated one with cement leakage have a higher chance of developing a new fracture [12, 13]. Cement Leakage into the

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paraspinal vasculature may lead cement drifting into vascular system and into pulmonary artery with host blood, resulting in possible sudden death [11, 14].

Standard procedures of attempting the prevention of leakage include adjusting the viscosity (changes the powder/liquid ratio), monitoring the injection pressure or delaying the injection time until the cement becomes more solidified [15]. Previous studies have suggested that viscosity might be manipulated by temperature and injection force [16, 17]. These methods, however, demand skills as the solidification of the cement occurs in a relative short-time window.

Aiming at reduction of leakage, a new method combining PMMA with gelatin micro-particles was proposed [1]. Gelatin micro-particles could also be mixed with antibiotic or other therapeutic agents to promote regenerated tissue constructs and to achieve local controlled drug release [18–20]. The early clinical study showed reduction of 50 % leakage after the gelatin addition [1]. In spite of its promises, the method has been lacking quantitative description. Details are not available in terms of selecting injection time window, proportion of mixtures, or gelatin micro-particle size, which significantly hinders further identification of potential problems associated with the method to make it as a new standard procedure in PKP. As a result, current outcomes depend largely on the surgeon skills with uncertainties.

The purpose of this study is to evaluate three important parameters of PMMA/gelatin mixtures associated with leakage and augmentation: the viscosity, permeability in cancellous bone, and biomechanical strength of the mixture. Three critical issues will be addressed: (1) the viscosity as a function of gelatin micro-particle size and density, (2) the effect of gelatin micro-particle size and density on permeability and associated pressure, (3) possible variations in the cement strength due to inclusion of the gelatin micro-particles. Our hypothesis is that the addition of gelatin micro-particles increases the bone cement viscosity and decreases the permeability for cement infiltration in cancellous bone; and the method can maintain proper bone-cement strength required. The information gained will further help to define an optimal time window of injection, gelatin micro-particle size and density, and pressure injection.

Materials and methods

Cement viscosity was tested on a NDJ-8S rheometer (Shanghai Jingtian Electronic Instrument Co., Shanghai, China). Bone cement (Tianjin Synthetic Material Research Institute, Tianjin, China) had the two standard components PMMA powder and monomer liquid monomer. Gelatin

foam (Jinling Pharmaceutical Co., Nanjing, China) was milled into micro-particles which were further separated into three size groups using sieves: 0–125, 125–250 and 250–500 μm . These gelatin micro-particles were mixed with the PMMA powder. The ratio of gelatin to PMMA powder was predetermined as 1, 2 and 3 %. The monomer liquid was then added into the powder components, and mixed with care to avoid air bubbles. The mixed cement was placed in a beaker, stirred at a circle per second for 30 s before loaded into the rheometer. The rheometer rotator spun at a steady speed (30 r/min), and the viscosity was recorded from 20 to 90 % twisting every 30 s for 10 min.

The cement permeability in cancellous bone was tested on bovine vertebrae. A total of 25 cervical and thoracic vertebrae were harvested from fresh bovine spines. The paravertebral soft tissues were dissected and removed from each vertebra. The end plate was removed by a jigsaw. Cylindrical core samples were harvested from vertebral body with an inner diameter of 15 mm by a trephine. The porosity of the samples was defined as the sample pore volume divided by the sample volume, where the pore volume was measured as the subtraction of the dry weight from the water-submerging weight divided by the water density. The permeability test protocol was reported previously [15–17]. In brief, the bone core was first placed into a 10 ml syringe. PMMA and gelatin particles were mixed and stirred. The mixture was then poured into the syringe and pushed by the plunger. Vents were made near the upper rim of the plunger. The syringe was rigidly mounted on an Instron E10000 mechanical testing system (Instron Co., Canton, MA), and the plunger was tightly fitted to the moving crosshead. Cement infiltration through cancellous bone was under the plunger pressure at a speed of 6 cm/min. Pressure–time curves were recorded, from which the permeability was calculated using Darcy's law as [15]:

$$Q = \kappa A (P_b - P_0) / \mu L$$

where Q was the unit of flowing volume per second, κ was the permeability of the intertrabecular bone, A was the cross-sectional area to flow, and $P_b - P_0$ was the pressure drop, μ was the cement viscosity, and L was the length of the core. The bovine core samples had an average diameter of 13.3 ± 0.2 mm, a height of 20.2 ± 3.1 mm, a dry weight of 0.90 ± 0.32 g, a wet weight of 3.26 ± 0.56 g and porosity of 0.85 ± 0.03 .

The biomechanical tests performed on the Instron E10000 mechanical testing system included both a compressive test and a three-point bending test. The PMMA and gelatin micro-particle mixture were prepared as those used in the permeability test. In the compressive test, the samples of 6.0 ± 0.1 mm in diameter and 13.0 ± 0.1 mm in height were prepared in a plastic mold. Each cement

block was secured between the two compressive arms of the mechanical test system. The compression was at a speed of 5 mm/min, and the compressive force was documented until the deformation reached 4 mm. In the bending test, rectangular cement blocks were prepared (75 ± 0.1 mm in length, 3.3 ± 0.1 mm in thickness and 10 ± 0.1 mm in width). Each block was placed between the mounting apparatus for three-point bending. The loading rate was 4 mm/min. The three-point bending load was recorded until the block reached failure. The flexural strength of the test specimen S was calculated as:

$$S = 3 FL/2bh^2$$

where F was the load at a given point on the load deflection curve, L was the support span, b was the width of test specimen, and h was the depth of the specimen. The elastic modulus of the test specimen was calculated as:

$$E = L^3 \Delta P / 4bh^3 \Delta F$$

where $\Delta P/\Delta F$ was the gradient of the initial straight-line portion of the load deflection curve.

Scanning electron microscope (SEM) was used to examine the cement/gelatin mixture. The specimens were sputter-coated with gold for 40 s at 100 mA using a sputter coater and observed under SEM (Hitachi Co., Japan) at an accelerating voltage of 15 kV.

The mixtures were prepared in seven groups: control without particles; particle density of 1, 2 and 3 % with a particle size 0–125 μm ; 1, 2 % with a particle size of 125–250, and 250–500 μm with a density of 1 %. There were seven samples in each group. Data in each group were calculated by the mean and standard deviation. Analysis of variance with post hoc Tukey's honestly significant difference test was used to analyze the difference among the tested groups ($p < 0.05$).

Results

Addition of gelatin micro-particles increased the viscosity (Figs. 1, 2). Viscosity was significantly affected by the size of gelatin micro-particles, and the largest size tested (250–500 μm) had the highest viscosity, and the difference was significant among the largest size group and the other three groups ($p < 0.001$). In the density testing group, the 3 % gelatin particle cement showed the highest viscosity, and the difference was statistically significant after 4 min between the PMMA control and the other three particle density groups ($p < 0.001$).

The permeability depended on the size of micro-particles (Fig. 3): the 250–500 μm particles reduced the permeability from the $327.0 \pm 32.4 \text{ mm}^2$ in control to $136.2 \pm 14.4 \text{ mm}^2$, and the differences between 250–500 μm and control and between 125–250 μm and control were significant ($p < 0.05$). Similarly, the permeability was regulated by the density of the particle (Fig. 4). For the highest density of 3 %, the permeability dropped to $117.4 \pm 8.0 \text{ mm}^2$. The difference was significant among the PMMA control and 2 and 3 % density groups ($p < 0.001$).

Compressive strength changed with neither particle size nor density ($p > 0.05$) although increase of particle size and density had a tendency to decrease strength (Figs. 5, 6). For the bending test, cement strength did decrease with the increase of particle size and density. The highest density led to 20 % decrease in the bending strength, while the largest particle size had 15 % decrease in the bending strength, and only 1 %, one with 250–500 μm had significant difference with PMMA control ($p < 0.001$). The elastic modulus did not significantly change with the increase of the gelatin particle density and diameter ($p > 0.05$) (Figs. 7, 8). Structurally, the tested samples achieved uniform mixture as examined by SEM (Fig. 9).

Fig. 1 The effect of gelatin micro-particle size in PMMA viscosity

Fig. 2 The effect of gelatin micro-particle density in PMMA viscosity

Fig. 3 The effect of gelatin micro-particle size in PMMA permeability and injection pressure

Discussion

This study evaluated the viscosity, permeability and bio-mechanical strength of the PMMA and gelatin micro-particle mixtures. Overall, the addition of the gelatin micro-particles into PMMA effectively increases the viscosity, and reduces the permeability.

Previous studies indicated several factors related to cement leakage: the bone permeability, the marrow viscosity, the bone porosity, the size of the injection cavity, the diameter of the leakage path, the bone pore size and the cement viscosity [21]. Among these factors, the cement viscosity is the only one not determined by the bony structure, suggesting that the adjustment of cement viscosity may be used as an independent approach to control the bone cement leakage. Viscosity is affected by a number of factors: polymer particle parameters, composition of the polymer particles, molecular weight distribution of the polymer component, storage conditions and room temperature [22–25]. Two processes might contribute to rise of

Fig. 4 The effect of gelatin micro-particle density in PMMA permeability and injection pressure

viscosity of bone cement: swelling of the polymer in the early phase and polymerization of the monomer in the later phase [26].

Clinically, PMMA with low and medium viscosity was identified as a risk factor for the occurrence of cement leakage in the percutaneous vertebroplasty [27]. High-viscosity PMMA, on the other hand, effectively stabilized vertebral compression fractures, while minimizing the risk of cement leakage and associated complications in vitro [28]. The present study also demonstrated that the inclusion of gelatin micro-particles could regulate cement viscosity through particle size and density. This finding, however, should be further verified more systematically before the mixture could be used safely and effectively in clinical practice.

Permeability is affected by the cancellous bone structure. Cancellous bone is a sponge-like structure consisting of a continuous three-dimensional network of trabecular connectivity, plates and a pore space filled by various tissues such as marrow, fat and vein. Our data suggested that PMMA mixed with micro-particles of a size slightly

Fig. 5 The effect of gelatin micro-particle size in PMMA compressive and flexural strength

Fig. 6 The effect of gelatin micro-particle density in PMMA compressive and flexural strength

Fig. 7 The effect of gelatin micro-particle size in PMMA elastic modulus

Fig. 8 The effect of gelatin micro-particle density in PMMA elastic modulus

greater than the cancellous pore could effectively reduce the cement permeability in the cancellous bone. In addition, cancellous bone is highly anisotropic although the

permeability is not demonstrated to have significant differences in three orthogonal directions (superior–inferior, anterior–posterior and medial–lateral) [29]. In this study,

Fig. 9 Structure of cement/gelatin micro-particle (arrows) mixture (a) in comparison to the control of PMMA (b)

the cylindrical core samples were taken along the superior/inferior direction to avoid the difference caused by the direction [15].

The addition of the gelatin micro-particles did not change the surgical procedure, specifically, the cement injection time. In practice, the injection started 6–7 min after initial mixture, and completed in a 2–3 min window before the rapid cement solidification began. Our data did not show that the addition of gelatin micro-particles significantly changed the solidification time except for the particles of 250–500 µm size or 3 % density. However, the permeability of the gelatin mixed cement was significantly reduced except for 1 % density with 0–125 µm. This finding suggested that the particles of 2 % in density and 125–250 µm in size could be a suitable addition to the PMMA.

Although the addition of gelatin into the cement increases permeability, it is equally critical to ensure sufficient mechanical strength of the modified cement. When PMMA is mixed with gelatin particles, factors such as density of gelatin micro-particles and degree of cross-

linking of the polymer, gelatin distribution in the cement need to be considered; and a direct outcome is looser PMMA with increasing porosity. Our biomechanical data demonstrated that gelatin addition did not lead to a decline in the compressive strength. However, the bending strength was significantly decreased. As bending is a combination of compression and tension, it is deduced that gelatin micro-particles might cause weakening in the PMMA tensile strength. Our finding was also supported by previous studies of PMMA/gelatin/antibiotic constructs used for craniofacial tissue materials [20]. It should also be noted that the decrease of the bending strength was detected within a relatively narrower range of particle density and size than what was reported in the literature as our cement mixture was designed to be injectable [20, 30, 31].

Limitations of this study included only the initial phase of cement fixation that was considered. It is expected that biodegradation of the gelatin should affect the mechanical properties and bony ingrowth. Tissue ingrowth into the pores also creates a stable interface anchoring the implant to the host tissues. This, however, requires further investigation in vivo. The other issue was the temperature. The test was performed at the room temperature simulating the temperature condition in the operation room where the PMMA was mixed and injected. However, during the surgery, once the cement was injected into the vertebral body, it would reach the body temperature of 37 °C. The focus of this study was on the particle effects; the cement viscosity and permeability were compared among groups under the same temperature. Finally, the test should further be performed on a cadaveric model or animal model in vivo to directly evaluate the permeability and leakage, especially in the situation of fracture clefts and possible intravascular leakage. This may help to address any possible correlation between the permeability and fissure leakage, or between the permeability and intravascular leakage. These are the studies currently undergoing in the laboratory.

Conclusions

The study investigated the mechanical properties of PMMA/gelatin micro-particle mixture used in vertebral cement augmentation. Addition of gelatin micro-particles increased the viscosity. All groups except for 0–125 µm in size and 1 % in density could significantly decrease the cement permeability in the cancellous bone. Micro-particles of 2 % in density and 125–250 µm in size offered reduced permeability without significantly change in the compressive strength. However, the bending strength was significantly decreased by up to 20 %. The test should be

further verified on a cadaveric model or an animal model before the mixture could be used safely and effectively in the clinical treatment.

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Conflict of interest None.

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