Differential blood contamination levels and powder–liquid ratios can affect the compressive strength of calcium phosphate cement (CPC): a study using a transpedicular vertebroplasty model

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Abstract

Purpose Calcium phosphate cement (CPC) is a potentially useful alternative to polymethylmethacrylate (PMMA) for transpedicular injection into osteoporotic vertebral fractures. Unlike PMMA, CPC is both biocompatible and osteoconductive without producing heat from polymerization, but it has lower compressive strength compared to PMMA. This in vitro model experiment analyzed how different CPC powder–liquid ratios (P/L ratios) and injection methods may minimize blood contamination in the CPC and, thereby its reduction in compressive strength.

Methods (1) CPC of different P/L ratios of 4.0, 3.5, and 3.2 was equally mixed with different amounts of freshly obtained human venous blood, producing cylindrically shaped CPC samples. (2) Using a transpedicular vertebroplasty model containing blood in the bottom, CPC pastes of different P/L ratios were injected with the nozzle of an injection gun affixed either to the bottom (Bottom method) or to the top of the container (Top method). All cylindrical CPC samples thus obtained were immersed in simulated body fluid and then underwent compressive strength tests at 3 h–7 days post-immersion.

Results In CPC equally mixed with blood, lower P/L ratios and a larger amount of blood contamination reduced compressive strength more significantly. Of the two methods of CPC injection, the ‘Bottom method’ produced significantly greater compressive strength values than the ‘Top method’.

Conclusions When performing CPC-assisted vertebroplasty, a greater load bearing-support can be obtained by injecting CPC paste of a high P/L ratio of 4.0 into the deepest part of the space inside the vertebral body to minimize blood contamination.

Keywords Calcium phosphate cement · Biomechanical study · Compressive strength · Blood contamination · P/L ratio

Introduction

Transpedicular kyphoplasty and vertebroplasty for osteoporotic vertebral fractures by injecting polymethylmethacrylate (PMMA) into fractures are minimally invasive surgical strategies providing rapid pain relief [1–3]. Calcium phosphate cement (CPC) (Biopex-R; HOYA Co., Ltd, Tokyo, Japan) has also been used for this purpose as a potentially useful alternative to PMMA [4–9]. Unlike PMMA, CPC is both biocompatible and osteoconductive and does not generate heat from polymerization [10–15]. However, CPC has lower compressive strength and requires longer time to reach its maximum strength compared to PMMA [12, 16, 17]. Therefore, CPC-assisted vertebroplasty through bilateral transpedicular access needs special care not to further reduce the CPC strength during injection [7–9].

Many studies in the past have explored the compressive strength of CPC in vitro and in cadavers [18–22], but to date there has been no study on the possible effect of blood contamination on compressive strength. This study analyzed how different CPC P/L ratios (ratios of mixed powder to liquid) and injection methods may affect blood contamination in the CPC and, thereby its compressive strength, using our vertebroplasty model.

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Materials and methods

Experiment 1: compressive strength of an equal mix of CPC and blood

Three different types of CPC paste were prepared by kneading for 1 min; 12 g of CPC powder mixed with a liquid solution of 3.0 ml (P/L ratio = 4.0), 3.4 ml (P/L ratio = 3.5), and 3.8 ml (P/L ratio = 3.2), respectively (Blood (–) group). We also prepared pastes of the same respective P/L ratios that were equally mixed with freshly obtained human venous blood of 1.0, 2.5, and 4.0 ml (Blood (+) group). These CPC pastes were then placed in plastic cylindrical containers 7 mm in diameter and 14 mm high. They were hardened at 37 °C in an incubator and then extracted from the containers. The cylindrical CPC samples were then immersed in simulated body fluid at a temperature of 37 °C and compressive strength was measured at 3, 12 h, 1, 3, 5, and 7 days post-immersion, respectively. In both the Blood (–) and Blood (+) groups, six CPC pastes were made for each respective post-immersion follow-up time. The density of the hardened paste (g/cm³) was calculated by measuring the weight and volume of the cement samples at day 7.

The surfaces of the top and bottom sides of the cylindrical CPC samples were smoothed by gently removing tiny CPC projections using an Isomet (ML-210, Sakai Machine Tool Co., Ltd., Japan). This maneuver of fine adjustment does not affect the strength of the cement. The maximum compressive strength (MCS) of each sample was then measured by applying compression at a cross-head speed of 0.5 mm/min using an Instron Universal Testing Machine (Type 4466, Instron Corp., Kanagawa, Japan). In addition, the state of crystallization in the CPC paste fragments was examined using scanning electron microscopy (SEM) after the compressive strength test at day 7.

Experiment 2: compressive strength of CPC injected with the ‘Bottom method’ or the ‘Top method’

A cylindrical PVC container, 16 mm in diameter and 32 mm high, was used with both ends sealed with vinyl tape with two hole perforations 5 mm in diameter made on the upper side of the container (vertebroplasty model) (Fig. 1a). First, we injected freshly obtained human venous blood of 3 ml into our model, in which the blood occupied approximately half the volume of the container. The blood-open space ratio of 1:1 was chosen arbitrarily, since the amount of blood contained in the created void during vertebroplasty varies depending on the balance between bleeding and suction. We then injected CPC into the container using a specially designed Biopex injection gun with a nozzle 3.7 mm in internal diameter (HOYA Corp.,

Tokyo, Japan) (Blood (+) group). In order to keep the P/L ratios consistent with those used in Experiment 1, CPC pastes with three different P/L ratios of 4.0, 3.5, and 3.2 were prepared for the ‘Bottom method’, and those with two different P/L ratios of 4.0 and 3.2 for the ‘Top method’. The pastes were then injected at 1 min. 45 s. after commencement of kneading at a delivery rate of 0.8 ml/s.

In the ‘Bottom method’, the nozzle of the injection gun was fitted onto the bottom of the container (Fig. 1b). As the container filled with CPC, blood extruded from the other hole on the upper side of the container. The CPC continued to be injected as the nozzle was withdrawn. This injection technique follows actual clinical procedures with particular care to ensure that as little blood as possible mixed with the cement [7–9]. In the ‘Top method’, CPC paste was injected attaching the nozzle above the layer of accumulated blood, which resulted in air coming into contact with the CPC paste prior to its flowing into the accumulated blood (Fig. 1c). We repeated each method of injection into the containers without blood (Blood (–) group).

The same procedure used in Experiment 1 was followed to prepare cylindrical CPC samples for measuring MCS of CPC at 3, 12 h, 1, 2, 3, 5, and 7 days post-immersion in the ‘Bottom method’ and, at 3, 12 h, 1, 3, and 7 days post-immersion in the ‘Top method’. We examined each P/L ratio type using 5 CPC paste samples in the Blood (+) group and four CPC paste samples in the Blood (–) group at each of the aforementioned time stages.

Data analysis

For statistical analysis, the Mann–Whitney *U* test for comparing data between the groups, the Kruskal–Wallis test for comparing values over time within each group, and Pearson’s correlation coefficient for interrelation analysis were used. Values were expressed as mean ± SD with a significance of $p < 0.05$.

Results

Experiment 1

The MCS of three different P/L ratio CPCs in the blood (–) group increased significantly up until day 7 ($p < 0.05$). In contrast, the compressive strength in the blood (+) group increased significantly up until day 3 ($p < 0.05$), but the values plateaued thereafter (Fig. 2). In both the blood (–) and blood (+) groups, the MCS at day 7 decreased significantly as the P/L ratio decreased ($p < 0.05$) (Table 1). With the same P/L ratio, the MCS was significantly lower in the blood (+) group than in the blood (–) group ($p < 0.0001$) and the larger the amount of blood

Fig. 1 The injection methods of CPC paste used in our vertebroplasty model. **a** The vertebroplasty model used in the experiments was a cylindrical PVC container. Both ends were sealed with vinyl tape and two perforations were made on the upper side of the container (*a*). CPC paste was injected into the model using a specially designed Biopex injection gun (*b*). The CPC paste was hardened and then extracted from the container as a cylindrical CPC sample (*c*). The maximum compressive strength of the CPC sample was measured using an Instron Universal Testing Machine (*d*). **b** CPC paste was injected into the model containing blood with the nozzle of the injection gun affixed to the *bottom* of the container (*Bottom method*). As the container was filled with CPC, blood was extruded from the other hole. CPC continued to be injected as the nozzle was withdrawn. **c** CPC paste was injected with the nozzle of the injection gun affixed to the *top* of the container (*Top method*)

contamination, the lower the MCS of the cement ($p < 0.0001$) (Fig. 2; Table 1). Lower P/L ratios and a larger amount of blood contamination not only reduced MCS but also, as expected, the density of the CPC (Table 1), resulting in a significant correlation between MCS and density ($r = 0.949$, $p < 0.001$).

Elastic modulus of CPC in the blood (–) group, calculated from the slope of the load–displacement curves in the linear elastic region, decreased progressively with a lower P/L ratio, although the trend was not statistically significant ($p = 0.16$); 5.6 ± 0.3 GPa for P/L of 4.0, 5.4 ± 0.1 GPa for P/L of 3.5 and 5.3 ± 0.2 GPa for P/L of 3.2.

Scanning electron microscopy (SEM) of CPC cross-sections

Low magnification views revealed a uniform electron density in the blood (–) group (Fig. 3a) in contrast to an uneven density with many low density areas in the blood (+) group (Fig. 3c). With a high magnification, there were plenty of needle-like crystals and large plate-like crystals formed in the blood (–) group (Fig. 3b) in contrast to finer needle-like crystals and reduced plate-like crystal growth with some crystal cracks in the blood (+) group (Fig. 3d).

Experiment 2

Either with the ‘Bottom method’ (Fig. 4) or with the ‘Top method’ (Fig. 5), as expected from the results of Experiment 1, the higher the P/L ratio of the CPC, the greater the MCS value recorded in both the blood (–) and blood (+) groups ($p < 0.05$). The MCS for all P/L ratio samples increased over time, with values approaching maximum at around day 3 (Figs. 4, 5). Comparing same P/L ratio samples, the values were lower in the blood (+) group than in the blood (–) group, which was statistically significant only for the low P/L ratio samples (P/L = 3.2) ($p < 0.0005$) at day 7, but not for the high (P/L = 4.0) and the medium P/L ratio (P/L = 3.5) samples, with the ‘Bottom method’ (Table 2) suggesting that the lower the P/L ratio of the cement, the greater the decrease in MCS in the blood (+) group versus the blood (–) group. In contrast, this trend was statistically significant for both the low and high P/L ratio samples ($p < 0.02$) with the ‘Top method’.

Comparing the two methods of CPC injection, MCS values at day 7 were significantly greater in the ‘Bottom method’ than in the ‘Top method’ in both the blood (–) group (see Fig. 5a; Table 3) and the blood (+) group (see Fig. 5b; Table 3).

Fig. 2 Changes in compressive strength in the equal blood contamination model (*Experiment 1*) as a function of the duration of immersion in simulated body fluid (abscissa) for P/L = 4.0 in (a), for P/L = 3.5 in (b) and for P/L = 3.2 in (c). Compressive strength decreased as the volume of blood contamination increased. Strength also decreased as the P/L ratio of the cement decreased

Table 1 Experiment 1: maximum compressive strength of an equal mix of CPC and blood

	Amount of blood						
	0 ml Mean $\pm$ SD	1.0 ml Mean $\pm$ SD	<i>p</i> value	2.5 ml Mean $\pm$ SD	<i>p</i> value	4.0 ml Mean $\pm$ SD	<i>p</i> value
P/L = 4.0							
MCS (MPa)	76.7 $\pm$ 8.3	37.3 $\pm$ 8.5	<0.0001	13.2 $\pm$ 2.6	<0.0001	7.3 $\pm$ 0.8	<0.0001
Density (g/cm ³)	1.8 $\pm$ 0.5	1.6 $\pm$ 0.2		1.4 $\pm$ 0.3		1.1 $\pm$ 0.2	
P/L = 3.5							
MCS (MPa)	65.3 $\pm$ 7.1	30.4 $\pm$ 7.4	<0.0001	13.2 $\pm$ 1.1	<0.0001	6.5 $\pm$ 1.4	<0.0001
Density (g/cm ³)	1.7 $\pm$ 0.1	1.5 $\pm$ 0.2		1.3 $\pm$ 0.3		1.1 $\pm$ 0.1	
P/L = 3.2							
MCS (MPa)	57.5 $\pm$ 3.0	24.2 $\pm$ 2.4	<0.0001	9.2 $\pm$ 1.2	<0.0001	6.3 $\pm$ 0.4	<0.0001
Density (g/cm ³)	1.6 $\pm$ 0.2	1.4 $\pm$ 0.6		1.2 $\pm$ 0.2		1.1 $\pm$ 0.2	

MCS maximum compressive strength of CPC at day 7

p value: comparisons between the group of 0 ml blood and the groups of various amount of blood contaminations

Discussion

CPC vs. PMMA

Of the injectable cements, PMMA hardens approximately 10 min after kneading reaching a MCS of 91.6 MPa, whereas CPC achieves its MCS of 80–90 MPa at day 3 after kneading in vitro [16]. After injecting PMMA and CPC into a canine vertebral body, Turner et al. [23] observed thin fibrous membranes surrounding the PMMA cement whereas biological bonding was documented between CPC and the surrounding bone with evidence of resorption of CPC

materials on its periphery with bone remodeling and bone ingrowth. Clinically, Blatter et al. [4] reported that PMMA showed better results than CPC when performing balloon kyphoplasty, because there have been instances of CPC leakage and correction loss in AO type A3 burst fractures. On the other hand, Grafe et al. [5] found no difference in clinical results between PMMA and CPC materials after kyphoplasty. Furthermore, there was no difference found in the compressive strength between PMMA and CPC in cadavers [18, 20, 22], implying that particular care should be taken in minimizing blood contamination during CPC-assisted vertebraloplasty to maintain CPC strength [7–9].

Fig. 3 CPC cement cross-sections observed by scanning electron microscopy after the compressive strength test at day 7. In the blood (–) group of $P/L = 4.0$ (a, b), there was evidence of not only needle-like crystallization (→), but also large plate-like crystals (*asterisk*). In the blood (+) group of $P/L = 3.4$ with 4.0 ml blood (c, d), there was little evidence of plate-like crystallization and cracks were confirmed inside the plate-like crystals present. Needle-like crystals in the blood (+) group were thinner than those in the blood (–) group

Fig. 4 Compressive strength of CPC samples from the ‘Bottom method’ as a function of the duration of immersion in simulated body fluid (abscissa) for three different P/L ratios. Compressive strength for all P/L ratio samples approached maximum levels at day 3. The higher the P/L ratio of the cement sample, the greater the compressive strength. Note the higher values in the blood (–) groups than in the blood (+) groups. This tendency was, however, significant only in the samples of $P/L = 3.2$ at day 7

The effect of the P/L ratio on CPC strength

In the CPC samples not contaminated with blood, MCS diminished as the P/L ratio decreased, which corroborates

the findings of Hirano and Takeuchi [12]. This reduction in MCS with lower P/L ratios is probably due to higher porosity [20]. Much of the liquid in CPC paste evaporates after the paste hardens, forming pores in the cement. In fact, Experiment 1 showed a progressively lower cement density as the P/L ratio decreased.

The effect of blood contamination on CPC strength

In Experiment 1, the MCS of the CPC sample decreased as the volume of blood mixed into the substance increased. In addition, blood contamination arrested the increase of CPC strength at day 3 unlike CPC without blood in which its strength progressively increased up until day 7. The SEM findings of the CPC materials contaminated with blood revealed poor levels of crystallization and many low electron density parts. Taken together, two possible mechanisms combined seem to account for the reduction of CPC strength with blood contamination. First, the blood itself may act on the cement, causing changes in the CPC properties by inhibiting crystallization in CPC [24]. Other researchers also indicated that the blood cells and protein content in blood can inhibit the hydration reaction by covering the surface of the paste [12]. Second, blood contamination results in a higher volume of liquid content, which, as mentioned above, may lead to a larger number of pores not filled with crystals. Our results of Experiment 1 support this view; i.e., the density of the cement decreased as the amount of blood contamination increased.

Fig. 5 Compressive strength of CPC samples from the two methods of CPC injection into the containers without blood (blood (–) group) in **a** or with blood (blood (+) group) in **b** as a function of the duration of immersion in simulated body fluid (abscissa) for two different P/L

Table 2 Experiment 2: maximum compressive strength of CPC injected with the “Bottom method”

	Blood (–) group Mean ± SD	Blood (+) group Mean ± SD	<i>p</i> value
P/L = 4.0			
MCS (MPa)	69.9 ± 2.8	65.6 ± 4.8	0.16
P/L = 3.5			
MCS (MPa)	63.2 ± 3.0	57.4 ± 4.8	0.08
P/L = 3.2			
MCS (MPa)	56.9 ± 1.5	47.4 ± 2.7	<0.0005

MCS maximum compressive strength of CPC at day 7

The effect of injection method on CPC strength

In Experiment 2 with the ‘Bottom method’, which simulated actual clinical procedures using a transpedicular vertebroplasty model, CPC was injected at the deepest point possible to minimize blood contamination. As a result, only in the low P/L ratio group (P/L = 3.2), but not in the other two groups with higher P/L ratios, the ultimate MCS was significantly lower in the blood (+) group than in the blood (–) group, albeit the difference was slight. This is probably because CPC with a low level of viscosity mixes more readily with blood and CPC is made to be hydrophilic to improve its biocompatibility [25].

In Experiment 2 with the ‘Top method’, injecting from the superior surface is likely to lead to more contamination with blood and air bubbles, further weakening CPC strength. In a study by Yamamoto et al. [15], CPC strength in vivo was reduced by half its strength in vitro, which was attributed to contamination with air bubbles and blood in vivo. We infer from the results of Experiment 2 that in

clinical settings, the MCS of CPC can be reduced to 49 % (69.9 → 34.0 MPa) when injected with the worst procedure (i.e., ‘Top method’ injection using low P/L ratio CPC into an area with blood) as compared to when injected with the best procedure (i.e., ‘Bottom method’ injection using high P/L ratio CPC into an area without blood) (see Table 3).

In an actual transpedicular vertebroplasty with the patient prone, blood from the fractured vertebral body tends to collect anteriorly first by gravitation in the space created within the cancellous bone. Immediately before CPC paste injection, it is important to minimize the amount of blood contained in the space within the vertebral body by suction and also to inject a high P/L ratio CPC paste into the deepest part of the anterior vertebral body to prevent compromising the CPC strength [7–9]. In this case, injection of the paste under excessive pressure should be avoided to decrease the risk of it leaking outside of the vertebral body. The high P/L ratio of 4.0 chosen in this study is what we are using clinically in transpedicular vertebral augmentation procedures without any difficulty. Higher P/L ratios, however, could make CPC paste too hard to be injected through the nozzle of an injection gun.

There are several limitations to our study. First, we used simulated body fluid of 37 °C to simulate the actual hardening process of CPC paste in human patients, but it does not completely reproduce actual internal biological conditions. Second, we did not make any long-term follow-up observations after 7 days of kneading the CPC. Third, we only tested the ultimate static strength of the CPC, but not its tendency to fail in cyclic loading relevant to actual vertebroplasty practice. Nevertheless, the data provided by this study will be clinically more relevant than those from previous studies conducted in vitro and in cadavers.

Table 3 Maximum compressive strength of CPC injected with the Bottom vs. Top methods

	Blood (–) group			Blood (+) group		
	Bottom method Mean $\pm$ SD	Top method Mean $\pm$ SD	<i>p</i> value	Bottom method Mean $\pm$ SD	Top method Mean $\pm$ SD	<i>p</i> value
P/L = 4.0						
MCS (MPa)	69.9 $\pm$ 2.8	50.2 $\pm$ 5.7	<0.02	65.6 $\pm$ 4.8	41.1 $\pm$ 6.0	<0.002
P/L = 3.2						
MCS (MPa)	56.9 $\pm$ 1.5	41.0 $\pm$ 4.2	<0.02	47.4 $\pm$ 2.7	34.0 $\pm$ 3.2	<0.002

MCS maximum compressive strength of CPC at day 7

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Conflict of interest None.

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