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Influence of a novel radiopacifier on the properties of an injectable calcium phosphate cement

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Abstract

An injectable calcium phosphate cement (CPC) with excellent radiopacity was proposed by introducing a novel radiopacifier, strontium carbonate, into the powder phase of CPC. The results showed that the cement showed improved radiopacity even when the content of strontium carbonate was only 8 or 12 wt.%. The addition of 8 or 12 wt.% strontium carbonate clearly improved the injectability and compressive strength of the cement. Furthermore, the addition of strontium carbonate influenced the pore distribution in the cement. An injectable CPC containing 8 or 12 wt.% strontium carbonate has the potential for use in procedures such as vertebroplasty and kyphoplasty.

Keywords: Radiopacifier; Calcium phosphate cement; Rheological properties; Strontium carbonate; Pore distribution

1. Introduction

Due to population ageing, osteoporosis is becoming an increasingly common medical problem [1]. Osteoporosis leads to a remarkable increase in the incidence of bone fracture. It has been showed that using minimally invasive bone cement injection for stabilizing osteoporosis or treating vertebral body fracture has significant clinical potential [2]. At present, the use of cement augmentation techniques (vertebroplasty and kyphoplasty) to treat persistently painful vertebral compression fractures is on the rise [3,4].

However, during surgical operations, cement leakage outside the surgical site often occurs and can cause serious problems. For instance, although vertebroplasty is usually well tolerated, serious neurological complications have been reported in a few patients [5]. Extravertebral cement extrusion is another common problem and can also lead to complications. The most common adverse event is nerve root pain, usually caused by leakage of the cement into the intervertebral foramen [5]. Reducing cement leakage should lessen the morbidity associated with the procedure. If cement leaks outside the surgical site the injection should be stopped and the physician should perform a neurological examination postoperatively [6–9].

In order to avoid cement leakage outside the vertebral body, the procedure must be guided by close fluoroscopic monitoring [10]. The cement itself needs to be radiopaque, so that any leakage outside the vertebral body can be detected at an early stage [11,12] by enabling the surgeon to delineate between the cement border and bone marrow on X-ray images. At present, in order to improve the radiopacity of polymethylmethacrylate, researchers have advocated the addition of a radiopacifier to enhance the visualization of the cement paste flow during injection and to monitor and prevent leakage beyond the confines of the vertebral body [13]. Barium sulfate and zirconium dioxide are the two most common radiopacifiers used in contemporary bone cements, and usually comprise about

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10–15 wt.% of the formulation [14]. However, the implantation of millions of non-resorble particles in a matrix that is likely to be resorbed over time is concerning. And the addition of such particulate additives can be detrimental to some of the physical, mechanical and biological properties [15–19].

Calcium phosphate cement (CPC) has been regarded as a promising material to realize minimal invasive surgery for bone defect repair, because it shows excellent biocompatibility, bioactivity and osteotransductivity, i.e. after implantation it is rapidly integrated into the bone structure and transformed into new bone. Although CPC is intrinsically radiopaque, there is room for improvement. Therefore, strontium carbonate was introduced as a novel radiopacifier in this work. Strontium carbonate is thought to be innocuous. Studies have shown that both carbonate and strontium are components of bone minerals, and have a significant effect in the body. Recently, great attention had been paid to the effect of CO_3^{2-} and Sr^{2+} on the properties of CPC [20–22]. Many studies have shown that CO_3^{2-} and Sr^{2+} favor the dissolution, and therefore the resorption, of the implant [23].

Among the trace elements present in bone cells, strontium was found to exert beneficial effects on the osteoblastic activity [24]. Studies have shown that strontium can enhance the cell viability and differentiation [25]. Grynpa et al. [26] observed that treatment with low doses of strontium increases the number of bone-forming sites and vertebral bone volume in rats and shows no adverse effects on the mineral profile, bone mineral chemistry or bone matrix mineralization. Ni et al. [21,27,28] also reported that Sr-containing CPC was biocompatible.

The objective of the study was to study the influence of additions of $SrCO_3$ on various properties of a CPC. To the best of our knowledge, this is the first report about the influence of the content of strontium carbonate on the radiopacity, mechanical properties, setting time, rheological properties, injectability, phase evolution and pore distribution of CPC.

2. Materials and methods

2.1. Materials and preparation

The CPC powder (median diameter: 3.0 μm) used in this study was prepared by mixing 50 wt.% amorphous calcium phosphate (ACP) and 50 wt.% dicalcium phosphate dihydrate (DCPD), as described in our previous work [29]. The Ca/P ratio of the ACP was 1.5. ACP was synthesized from an aqueous solution of $Ca(NO_3)_2 \cdot 4H_2O$ and $(NH_4)_2HPO_4 \cdot 12H_2O$ by chemical precipitation in our laboratory. The deposit was then separated by centrifugation, freeze-dried and ball-milled. Commercial DCPD was obtained from Shanghai No. 4 Reagent & H.V. Chemical Co. Ltd., China. Commercial strontium carbonate powders (median diameter 2.5 μm, AR grade pure) were obtained from Shanghai Zhenxin Reagent Factory, China. The CPC powder was uniformly mixed with 0, 4, 8, 12, 16 and 20 wt.% strontium carbonate by dry-grinding in a ball mill for 24 h, respectively. The jar used for milling was 90 mm in diameter and 150 mm in length. During grinding, 50 g of balls and 50 g of CPC powder were added to the jar. The grinding speed or rotation speed of the jar was 50 rpm. The blended CPC powders were homogeneously mixed with de-ionized water at a liquid to powder ratio of 0.5 ml g^{-1} for 1 min. The suspension was then transferred to the cylinder. The rheological and injectability tests always started 2 min after mixing was initiated. All preparation steps were carried out in laboratory air, at 25 ± 2 °C. The labels 0, 4, 8, 12, 16 and 20 in the figures indicate blended cements with the addition of 0, 4, 8, 12, 16 and 20 wt.% strontium carbonate, respectively.

2.2. Radiographic assessment of the cement

A radiographic study was carried out with a standard clinical GE Medical Systems (set to 60 kV and 250 mA). The relative X-ray opacity was determined visually by comparison of the cements containing 0, 4, 8, 12, 16 and 20 wt.% strontium carbonate with cortical bone. The samples for radiographic assessment were prepared in the same way as for the compressive test, except the height of the samples was 5 mm – the same thickness as the cortical bone used.

The image process software Photoshop was used to measure the grayscale of the specimens averaged over an area of 5×5 pixels, as introduced by Kjellson et al. [30]. Ten measurements were performed for each specimen and the average contrast and standard deviation calculated. One-way analysis of variance (ANOVA) was used for statistical analysis of the measured image contrast.

2.3. Rheological properties tests

The rheological properties (zero shear rate viscosity) of the injectable pastes were tested with a rheometer (MCR301, Germany). The as-prepared paste was poured onto the measuring plate (plate number: PP50), and the tests were carried out under shear rate control mode. Specially, shear rate increased linearly from 0.0001 to 0.1 s^{-1} within 10 min.

2.4. Injectability tests

The injectability of the calcium phosphate bone substitute material was tested with commercial equipment (mini MIIG™, Wright Medical Technology, Inc., USA). In particular, the injectability was tested with a syringe (12 mm in diameter and 60 mm in length) fitted with a cannula of 2.2 mm inner diameter and 100 mm in length. Two minutes after mixing the cement powder and liquid, the as-prepared paste was poured into the syringe and a 1 kg compressive load was mounted vertically on top of the plunger. Then, 2 min later, the volume of the paste expelled from the

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