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Research Paper

Compressive mechanical properties and cytocompatibility of bone-compliant, linoleic acid-modified bone cement in a bovine model

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ABSTRACT

Adjacent vertebral fractures are a common complication experienced by osteoporosis patients shortly after vertebroplasty. Whether these fractures are due to the bone cement properties, the cement filling characteristics or to the natural course of the disease is still unclear. However, some data suggests that such fractures might occur because of an imbalance in the load distribution due to a mismatch between the elastic modulus (E) of the bone–cement composite, and that of the vertebral cancellous bone. In this study, the properties of bone-compliant linoleic acid-modified bone cements were assessed using a bovine vertebroplasty model. Two groups of specimens (cement-only and bone–cement composites), and four subgroups comprising bone cements with elastic moduli in the range of 870–3500 MPa were tested to failure in uniaxial compression. In addition, monomer release as well as time and concentration-dependent cytocompatibility was assessed through the cement extracts using a Saos-2 cell model. Composites augmented with bone-compliant cements exhibited a reduction in E despite their relatively high bone volume fraction (BVF). Moreover, a significant positive correlation between the BVF and the E for the composites augmented with 870 MPa modulus cements was found. This was attributed to the increased relative contribution of the bone to the mechanical properties of the composites with a decrease in E of the bone cement. The use of linoleic acid reduced monomer conversion resulting in six times more monomer released after 24 h. However, the cytocompatibility of the bone-compliant cements was comparable to that of the unmodified cements after the extracts were diluted four times. This study represents an important step towards introducing viable bone-compliant bone cements into vertebroplasty practice.

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1. Introduction

Poly(methyl methacrylate) (PMMA)-based cements have gained and kept an important place as orthopaedic biomaterials ever since their first use for prosthesis fixation in 1958 and later for vertebroplasty in the 1980s (Charnley, 1960; Galibert et al., 1987). Vertebroplasty refers to the percutaneous injection of bone cement into a vertebral body and is typically prescribed for patients with vertebral compression fractures (O'Brien et al., 2000). These fractures can be caused by different pathologies such as hemangioma (Vinay et al., 2011), multiple myeloma (Angtuaco et al., 2004), osteolytic metastases (Georgy, 2008) and primary or secondary osteoporosis (Freedman et al., 2008). Acrylic bone cements have succeeded as orthopaedic biomaterials since vertebroplasty in patients with vertebral compression fractures has shown good results (McGraw et al., 2002; Evans et al., 2003; Diamond et al., 2003). Acrylic bone cements are non-degradable and hydrophobic making it difficult for the implant to integrate with the surrounding tissue. A fully hardened PMMA-based implant can be considered as bioinert since it does not chemically interact with the host tissue (Blokhuis et al., 2000) or induces a negative host response (Jäger and Wilke, 2003). Moreover, high strength and non-degradability permit the incorporation of relatively high amounts of insoluble inorganic radiopacifiers, which are required to monitor the delivery and positioning of the implant, without significantly compromising its mechanical integrity or risking a release of the radiopacifier.

Most commercial acrylic bone cements exhibit a compressive strength and elastic modulus in the range of 85–114 MPa and 1700–3700 MPa, respectively (Kurtz et al., 2005; Hernandez et al., 2008). The apparent compressive strength and elastic modulus of cancellous bone, on the other hand, are typically in the ranges of 0.1–15 MPa and 10–900 MPa (Nazarian et al., 2008; Morgan et al., 2003; Helgason et al., 2008), respectively, encompassing osteoporotic to healthy bone. Multiple experimental studies have shown that, upon curing, cement and bone form a bone–cement composite whose apparent mechanical properties are closer to that of the cement than to that of healthy cancellous bone (Williams and Johnson, 1989; Race et al., 2007; Helgason et al., 2012). This is a consequence of the much higher cement volume fraction than bone volume fraction (0–20% for vertebral cancellous bone) (Morgan et al., 2003; Fields et al., 2011), but the lack of bonding between bone and PMMA also results in a simple rule of mixture not being applicable for predicting the mechanical response of the composite (Helgason et al., 2012; Helgason et al., 2011). The mismatch of apparent properties between healthy cancellous bone and the bone–cement composite has raised concerns, since adjacent vertebral fractures occurring shortly after vertebroplasty have been reported (Grados et al., 2000; Uppin et al., 2003; Trout et al., 2006). Other causes of fractures may be related to bulging of the adjacent endplates, higher volume of injected cement, and cement leakage into the disc (Baroud et al., 2003; Baroud et al., 2003; Berlemann et al., 2002; Chen et al., 2010). However it is still debated, whether adjacent vertebral fractures can simply be attributed to the progression of the underlying disease or because of an altered load pattern in the spine after the augmentation (Klazen et al., 2010).

These concerns have stimulated material scientists to develop new bone cement formulations that more closely match the mechanical properties of cancellous bone, in an attempt to reduce the occurrence of adjacent vertebral fractures. Boger et al. (2008a, c) modified the macrostructure of acrylic bone cements by inducing macroporosity through the incorporation of a hydrogel phase into the cement; however, increased levels of particle release (Beck and Boger, 2009) seem to have prevented this formulation from further advance. Another approach consisted of physically modifying the cements by partially substituting the monomer with a lactam structure organic plasticizer (Boger et al., 2009) to reduce the elastic modulus of the cements. To the authors' knowledge, no further assessment of the cytocompatibility of this formulation was reported. Recently, we introduced the use of a triglyceride oil as a method of producing compliant bone cements; however, relatively high amounts of the additive were required to produce a significant reduction in the elastic modulus, and potential interference of the additive with the polymerization resulted in a negative cytocompatibility outcome (López et al., 2011). A similar outcome was reported by Lam et al. (2010), who modified cements intended for joint fixation with strontium-substituted hydroxyapatite-nanoparticles and linoleic acid (15 vol% of the liquid phase). In a previous study (data to be published), we evaluated different fatty acids and triglyceride oils as potential mechanical property modifiers for acrylic bone cements. We found that lower amounts of linoleic acid than those used by Lam et al. (~6 vol% of the liquid phase) could help to reduce the elastic modulus of bone cement for vertebroplasty, Osteopal®V, by 75%. Because of the relatively small amounts required to reach a Young's modulus in the range of cancellous bone and its low cytotoxicity according to our preliminary tests, linoleic acid was chosen for this study.

Small concentrations of linoleic acid (≤ 50 mM), which is naturally occurring in living organisms, might lack a cytotoxic effect on human osteoblast-like cells and have been suggested to be beneficial for bone formation (Cusack et al., 2005). The incorporation of linoleic acid to tailor the mechanical properties, however, requires an in vitro cytocompatibility assessment prior to any pre-clinical studies (Demian and McDermott, 1998). A consensual methodology to assess the cytocompatibility of acrylic bone cements for vertebroplasty is not established in the literature. The ISO-10993-11 standard "biological evaluation of medical devices" suggests a method to evaluate the biocompatibility of potential biomaterials through their extracts, namely, an extraction media in which the material is soaked for a certain period of time (ISO-10993-11, 1993). However, this standard does not establish the time that injectable cements should be cured prior to extraction. In addition, the cytocompatibility of cement extracts is highly dependent on the concentration of residual monomer and the critical monomer concentrations are not well defined. Therefore, if not neglected, different protocols are often reported in the literature (López et al., 2011; Ciapetti et al., 2000; Pepiol et al., 2011). To resemble in vivo conditions, regular medium changes and dilutions should be implemented in the protocols, since marrow transport would attenuate potential cytotoxic effects due to unreacted remnants.

In an attempt to assess the feasibility to use the material, we defined two aims for the present work: first, to test in