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Introduction

Vertebral augmentation procedures such as percutaneous vertebroplasty (PV) or kyphoplasty (KP) are used for the treatment of chronic pain resulting from vertebral fractures which are caused by osteoporosis and other skeletal pathology such as spinal metastasis or multiple myeloma. Patients typically present with axial back pain at the site of the fractured vertebra. This pain is exacerbated with weight-bearing and simple daily living activities such as rising from a chair or getting out of bed. [1-3] During the augmentation procedure, bone cement is injected through a cannula into the cancellous bone of the vertebral body with the goal of relieving pain and restoring mechanical stability. The bone cements used are chemically complex, multi-component and significantly non-Newtonian with their viscosity having differing degrees of time and shear-rate dependency. These cements also interact with other fluids present within the porous media and with the porous structures through which they flow. [4] The most widely used cement, poly(methyl methacrylate) (PMMA), is generally assumed insoluble in any biofluid (bone marrow) it comes into contact with, thus the cement-marrow displacement is characterized as a two-phase immiscible flow in porous media. This is mainly due to the nonzero cement-marrow surface tension, resulting in a distinct fluid-fluid interface which separates the fluids within each pore. [5, 6]

Cement leakage during vertebral augmentation procedures is frequent and may cause serious clinical complications such as nerve root or spinal cord compression as

well as pulmonary embolism.[7-10] The cement may leak into various anatomical structures including the paravertebral soft tissue (52.5% [11]), the surrounding vasculature (5% [11] to 16.5% [12]), the spinal canal (37.5% [11]) and the intervertebral discs (25% [13]). Due to the high frequency of cement leakage and the potential cause for serious clinical complications, in-vitro studies have been designed to elucidate the fundamental mechanisms underlying cement leakage. [14-18] However, this is just one part of a wider requirement to understand how the cement flows within cancellous bone and accurately predict the cement placement within the vertebral body, which has been identified as a critical parameter in the biomechanical behaviour of the construct post-augmentation. [19, 20]

The rheological properties play a crucial role in the cement flow behaviour during injection and within a porous structure such as cancellous bone. Although the cement viscosity has been identified as a key determinant of the cement flow patterns, [17, 18, 21] other factors, including the intrinsic cement-marrow surface tension, influence the injection biomechanics, making the scientific understanding of cement flow in cancellous bone particularly challenging. While new cement formulations are continuously being developed, there is no standardized methodology for assessing their flow behaviour in cancellous bone. We propose a novel method using reproducible and pathologically representative flow models to help study the influence of cement properties on injection behaviour.

Materials and methods

Flow models were developed to represent a cross-section of the vertebral body. Each model was placed in a specimen holder (Removable Cage Plate, Thorlabs, New Jersey, USA) with its pattern facing up. A circular glass window (Ø= 50 mm) was placed on top of the model and a threaded ring was used to press the window against the model creating a tight seal (Figure 1). The use of flow models has a key advantage over previously used three-dimensional open-porous foams in terms of monitoring the cement spreading during the injection, which is performed using a camera instead of a fluoroscope. This simplifies the experimental set-up and avoids exposure to x-rays. An aqueous solution of carboxymethyl cellulose (2.5% w/w) was used as the bone marrow substitute with a nominal viscosity of 0.4 Pa·s which has been reported for red bovine marrow. [22] A syringe containing the marrow substitute was screwed into the corresponding threaded hole of the specimen holder and manually injected until the entire flow model was filled. This simulates the rheological environment of the vertebral body in terms of bone marrow present within the bony channels. Once the marrow substitute was injected, the syringe was removed and the threaded hole was further filled with the marrow substitute to prevent air bubbles within the flow system. Following this, a 3mL syringe containing the bone cement was screwed into the same threaded hole and both the syringe and the specimen holder were placed into the experimental set-up (Figure 2).

Bone Surrogate Development

The structure of the flow models was tailored to mimic three different skeletal conditions: osteoporosis (Osteo), spinal metastasis (Lesion) and vertebral fracture (Fracture) (Figure 1). The trabeculae were represented as solid columns (Ø= 0.25 mm; h= 0.5 mm) with a 1 mm intercolumnar spacing to simulate the trabecular separation that has been reported for human vertebral osteoporotic bone. [23, 24] The external shape was circular with a solid boundary to mimic the vertebral shell. A flow exit point (Ø= 2.5 mm) was applied at the outer boundary to simulate a breach through the cortex due to a fracture or a blood vessel supplying blood in and out of the vertebral body. The flow models were first designed in a graphic suite (CorelDRAW, Corel Corporation, Ontario, Canada) then manufactured via flexography (AFP-SH/DSH, Asahi Photoproducts Europe, Brussels, Belgium), a technology used extensively within the print industry where a high degree of reproducibility is required. Once the models were manufactured, inter- and intra-variability in the model geometry was assessed. Left and right cuts were consistently performed through the sagittal plane close to the centre of three osteoporosis type models. A profile projector (Model V-16D, Nikon Corporation, Tokyo, Japan) was used to visualize the cuts from a lateral perspective and test the geometrical variations in terms of valley-to-valley and edge-to-edge distances as well as the total height of the profiles (Figure 1). The profile projector was also used to measure the porosity of the flow models. Furthermore, contact angle measurements were

performed on the material to compare the surface wettability to that of cortical bone from a dry human femur and a fresh ovine vertebra.

Powder Imaging and Cement Preparation

Four brands of commercially available acrylic bone cements were tested (Table 1): Opacity+ (OC, Teknimed S.A.S, Bigorre, France), Osteopal V (OP, Heraeus Medical GmbH, Hanau, Germany), Parallax (PL, ArthroCare Corporation, Austin, TX, USA), and Simplex P (SP, Stryker Corporation, Kalamazoo, MI, USA). Due to its known contribution to the flow behaviour,[25] the morphology of the powder components was assessed through Scanning Electron Microscopy (SEM). The specimens were sputter-coated with palladium prior to image acquisition. The images (Figure 4) were acquired on a LEO 1550/EVO MA15 (Carl Zeiss AG, Oberkochen, Germany) microscope, operated at an acceleration voltage of 2 kV with a secondary electron detector to achieve topographic contrast.

All cements, except for Simplex P, are specifically formulated with a high radiopacifier concentration for use in vertebral augmentation procedures such as PV. However, commercially available brands used in cemented arthroplasties (mainly Simplex P) have been used in PV with an extra amount of radiopacifier added by the surgeon to bring the concentration to 20–30% w/w of the powder and increase the radiopacity of the cement. [26, 27] For this reason, a modified formulation for Simplex P

was used in this study. Each batch of cement was prepared according to the liquid-to-powder (L/P) ratio recommended by the manufacturer. For Simplex P, an additional L/P ratio (SP1:1) was also tested to assess its effect on the flow behaviour. [28] All powders were weighed in vials with an accuracy of ± 0.01 g and all liquids were measured using micropipettes with an accuracy of ± 2 μL. The timer on a stopwatch was started as the liquid monomer was added to the powder. Subsequently, the vial was capped and vigorously shaken for 30 s to uniformly distribute the liquid monomer throughout the powder. A metal spatula was then used to further mix the components for another 30 s ensuring no dry powder areas were visible in the vial. The times for which the cements were mixed and handled are summarized in Table 2. A standard protocol was adopted in all the experiments and involved mixing the cement for 1 min (shaking and stirring) then allowing the mixing vial to rest on its side for 1.5 min before the cement was transferred into a 3 mL luer-lok syringe.

Testing Protocol

As the flow models represent a cross-section of the vertebral body, a maximum volume of 1 mL of cement was injected into each model. The injections were performed at a constant flow rate of 3 mL/min and stopped when the cement had reached the boundary of the models. The same 3 mL syringe was used to test the effect of three different injection time points (4, 6, and 8 min from the addition of the liquid to the powder) on

the flow behaviour. All injections were performed at room temperature (19.0 ± 1.4ºC) into separate models. The flow behaviour of each cement was tested in each structure and all injections were repeated three times. A constant flow rate was established by controlling the testing machine's cross-head speed which controls the displacement of the syringe plunger. LabVIEW software (2010 SP1, National Instruments, Austin, TX, USA) was used to acquire video and load cell data. The data acquisition was tested and validated to ensure that the load cell and video data were synchronized and saved simultaneously such that the number of load cell data points corresponds to the number of video frames. The load cell was used to measure the force (N) applied on the syringe plunger, thus calculate the peak pressure (MPa) in the system. The force measurements were calculated based on previously determined calibration curves. In order to quantitatively describe the resulting flow patterns, the video data were analyzed in Matlab (R2009b, MathWorks, Massachusetts, USA). A custom Matlab script was developed to allow automated segmentation of the flow distribution by subtracting the first frame of the video sequence, which shows the flow models with no fluid injected, from the remaining frames. The following parameters were calculated when the cement had reached the boundary of the flow models: i) the time to reach the boundary, which is determined directly from the video sequences, ii) the filled area, which is a measure of the number of pixels in the segmented region converted to squared-millimeters (mm^2) using a conversion factor then presented as a percent of the total area on the basis

of a flow model with an inner diameter of 38 mm, and (iii) the roundness (Equation 1), which is a shape descriptor most sensitive to elongation, calculated by comparing the area A_s of a shape S to the maximum caliper diameter L_s of that shape measured for all orientations. [29] A perfect circular pattern has a roundness of one, whereas the value approaches zero for increasingly elongated contours.

$$\text{roundness} = \frac{4A_s}{\pi L_s^{\ 2}} \qquad (1)$$

Statistical Analysis

All data were presented as mean ± standard deviation. The influence of the model structure (Osteo, Lesion and Fracture), the cement formulation (OC, OP, PL, SP1:2 and SP1:1), and the injection time point (4, 6 and 8 min) on the peak pressure, the time to reach the boundary, the filled area, and the roundness was evaluated using a multivariate general linear model (GLM) with a significance level set at $\alpha = 0.05$.

Results

Lateral visualization of the osteoporosis models revealed that the structure was conical rather than cylindrical in shape. The edge-to-edge and valley-to-valley distances were 934 ± 4.4 and 1251 ± 3.0 µm, respectively. The total height of the profiles was 431 ±

6.1 µm. The measured porosity of the osteoporosis models was 88.2%. The surface wettability was comparable between all materials with a range of contact angles from 60 to 74º for the photopolymer used to manufacture the flow models, 60 to 75º for bone from a dry human femur, and 58 to 69º for bone from a damp ovine vertebra. Qualitative SEM analysis of the powder components (Figure 4) showed that OC and OP have similar as well as more uniform particle size and distribution (~19–69 and 18–55 µm, respectively) when compared to PL and SP, which have the largest and widest range of particle sizes (~11–105 and 7–83 µm, respectively). The non-circular particles in the images are the radiopacifiers, which appear to be large in OC and OP (both containing 45% w/w ZrO_2) and more granular in PL and SP (containing 30 and 10% w/w $BaSO_4$, respectively). Also, the angular-shaped particles observed in the OC powder are hydroxyapatite crystals.

Figure 5 illustrates the resulting flow contours and Table 3 summarizes the results of the GLM. The peak pressure significantly increased with injection time and was generally independent of the model structure. The cement formulation significantly affected the peak pressure with SP1:1 and SP1:2 generally showing the lowest and highest recorded pressures, respectively. Furthermore, the injection pressure for OP significantly decreased in both lesion and fracture models, equally (Figure 6). The early injection time point (4 min) as well as the presence of lesion or fracture significantly decreased the time it took the cements to reach the boundary. PL and SP1:1 were the

fastest cements to reach the boundary, however the behaviour of PL was improved in both lesion and fracture models as evident in the significant increase in its time to reach the boundary (Figure 7). The percent filled area was generally independent of the injection time, except for SP1:1 and OP which showed a significant decrease in filled area when injected at 4 min after cement mixing. The structure, however, significantly affected the filled area with the presence of fracture causing a more significant decrease compared to the presence of lesion. SP1:2 had the highest percent filled area for all structures, whereas PL had the lowest for the Osteo model and SP1:1 had the lowest for both lesion and fracture models (Figure 8). The roundness significantly decreased in the presence of fracture only and was generally independent of the injection time. Similar to the filled area results, SP1:2 showed the highest roundness in all structures, whereas PL had the lowest in the Osteo model and SP1:1 had the lowest in both lesion and fracture models (Figure 9).

Discussion

Researchers have tended to avoid the use of cadaveric tissues due to their inherent uniqueness and variability, which render the experiments irreproducible and make the scientific understanding of how the cement flows within cancellous bone difficult. [14, 17] The use of bone surrogates allows researchers to focus on the importance of geometry when the variability in the biological tissue is eliminated. Therefore, the relative

importance of different geometrical or structural variations within the bone can be highlighted and evaluated through varying the structural geometry within the surrogates. [30] Furthermore, bone surrogates have advantages in terms of health and safety, cost and limited ethical issues associated with their usage.

As the inter- and intra-variability in model geometry was very low, the developed flow models can be assumed constant in geometrical structure. This is crucial to reduce the variability, render the experiments reproducible and shift the focus onto understanding the influence of cement properties on the injection behaviour. This also allows for the injections to be performed at various time intervals after cement mixing into separate models while assuming that the injections are being performed into the same structure. Although the structure was conical in shape instead of cylindrical, the porosity of the osteoporosis models (88.2 %) was similar to that reported by Lochmuller et al. (89.3 %) [24] and Hulme et al. (87.5 %) [23] for human osteoporotic vertebral cancellous bone. Another key advantage is that the models have a boundary to simulate the vertebral shell which confines the flow and controls the intravertebral pressure, significantly affecting the filling pattern. [31] The opening in the boundary simulates a breach through the cortex due to a fracture or a vessel supplying blood in and out of the vertebral body. This is crucial as such breaches create paths of least resistance providing means for leakage into the surrounding structures. The models also simulate the rheological environment within the vertebral body. Based on contact angle

measurements, the surface wettability of the models matches that of bone. Furthermore, the presence of the marrow substitute simulates the two-phase flow that occurs within the vertebral body. A true representation of the rheological properties of red bone marrow is extremely important as such properties significantly affect the cement flow behaviour [18]. Although there has been data in the literature that describes the rheological properties of human yellow bone marrow,[32, 33] there is still a need to test the rheological properties of human red bone marrow which is found within the bony channels of the vertebral body. The cement rheological properties also play a crucial role in the flow behaviour during injection and within a porous structure such as cancellous bone. [17]

This study highlights the influence of cement formulations on the spreading behaviour. We were able to show that varying the L/P ratio drastically alters the cement injection behaviour. This is evident in all the measured parameters for SP1:1 compared to SP1:2. Furthermore, we were able to show that OP and OC have similar injection behaviour, which is not surprising as these two cements have very similar composition and particle size (Table 1, Figure 4). There are two processes that contribute to the rise in viscosity as a function of time: swelling of the polymer particles in the monomer and polymerization of the monomer itself. This implies that the rate of viscosity rise is affected by various factors including particle size (surface area), shape, and distribution as well as the composition of the polymer particles and molecular weight distribution of the polymer components. [25]

The peak injection pressure recorded in this study was comparable to that reported during clinical PV and showed a similar increase with injection time. [34] However, our results showed that the peak pressure was independent of structure. This may be due to the pressure required to inject the cement through the inlet (Ø2.4 mm) dominating over that required to distribute the cement into the structure. This finding highlights the role of syringe tip diameter and needle gauge in controlling the pressure required to deliver the cement into porous structures such as cancellous bone, although the choice of needle gauge is mainly dictated by the vertebral level being augmented. Filled area and roundness were used to quantitatively describe the resulting flow contours. Both indicators were needed as roundness is a shape descriptor invariant of size. Mean spreading distance and circularity have been previously used, [16] however we found that areal measurements (compared to point measurements) reduced the error associated with irregular shapes, while roundness was most sensitive to elongation, with a high roundness value signifying a more circular pattern which is an indication of uniform spreading. Contrary to data reported by Loeffel et al. [16], our results showed that increasing the elapsed time from mixing, thus cement viscosity, generally did not have a significant effect on both indicators, especially roundness. This may be due to the cements used in our study having a high starting viscosity at the early injection time point of 4 min compared to the range reported by Loeffel et al. (50 to 100 Pa·s). The filled area significantly decreased when SP1:1 was injected at 4 min after cement

mixing, however this cement formulation has a viscosity in the range reported by Loeffel et al. (based on data presented by Widmer et al. [28]). Our results showed that the presence of a fracture significantly decreases the filled area compared to the presence of lesion and is more likely to cause irregular flow patterns, emphasizing the influence of structure on the cement spreading. In this study, there was a high leakage rate at the early injection time point (4 min) independent of structure and cement formulation, which is consistent with the study performed by Baroud et al.[17] who also reported immediate leakage when the cement was injected at 5 min after cement mixing. This suggests that there is a critical injection point at which the risk of leakage can be significantly reduced. Our results also emphasized the influence of structure on the time to reach the boundary and showed that the presence of lesion or fracture increases the risk of leakage.

An important limitation of this study is that the flow rate was kept constant at 3 mL/min and the effect of varying flow rates was not considered. This is significant as acrylic cements are known to exhibit shear thinning behaviour. A second limitation is that the models only allow fluid flow in one plane and do not simulate a three-dimensional flow, which occurs in the vertebral body. However, these models represent an alternative simulated environment to quickly and effectively study the flow behaviour of different bone cement formulations without the use of ex-vivo models. The parameters measured in this study can be translated into parameters of interest to help in

the design of new injectable biomaterials. Peak injection pressure can be used as an indication for the ease of injectability. Our results showed that, as expected, the injectability seems to increase with L/P ratio as the recorded pressure was lowest for SP1:1, which has the highest L/P ratio (Table 1). The pressure was generally highest for SP1:2 and PL indicating that the injectability was lowest for these two cement formulations, which differ from OP and OC in terms of powder composition, wider range of particle sizes, and radiopacifier composition and concentration. A relatively high amount of small-sized polymer beads has been found to increase the polymerization rate, while a high amount of large-sized beads prolongs the onset of curing. [35, 36] Our results suggest that the injectability was lower for cements containing $BaSO_4$; these also had a lower filler concentration (19 and 29.4% w/w for SP1:2 and PL, respectively) than those containing ZrO_2 (both OC and OP contained 45% w/w). Hernández et al. [37] showed that a PMMA cement with 10% w/w $BaSO_4$ has a similar viscosity-time curve but a much earlier onset of viscosity rise compared to the same cement with no radiopacifier. Their results also showed that the same PMMA cement with 10% w/w bismuth salicylate as the radiopacifier had a significantly lower viscosity and much longer onset of viscosity rise compared to the cement with 10% w/w $BaSO_4$. This highlights the effect of varying the radiopacifier composition on the viscosity of the cement, thus the injection behaviour of that cement suspension. However, further research is needed to elucidate the effect of varying the concentration of the

radiopacifier on the injection behaviour of the cement. Our results also suggest that the injectability seems to decrease with an increase in the DMPT concentration. OC and OP have very similar powder composition and particle size, however the injectability was lower for OP, which has a DMPT concentration twice higher compared to OC (Table 1). This is consistent with the study performed by Pascual et al. [38] who reported that the cement setting time was lowered as the DMPT and BPO concentrations increased. The roundness and time to reach the boundary can be used to predict the uniformity of the cement spreading and the risk of leakage. High values for these parameters indicate a more uniform spreading pattern and a reduced risk of leakage. Due to boundary we are imposing (i.e. flow exit point, fracture plane, and lesion), a high filled area would also signify that the cement is less affected by the structure. A low viscosity cement (such as SP1:1) would have a low filled area as it will follow the path of least resistance and reach the boundary quicker. Based on our results, cement formulations with a high L/P ratio (such as SP1:1) should be avoided in the presence of a large lytic lesion or fracture.

Conclusion

In the present study, we comparatively assessed five cement formulations by examining the influence of structure and injection time on the peak pressure, the time to reach the boundary, the filled area, and the roundness. It is extremely important to control the

surrogate environment, as bone cement precursors are heterogeneous, especially their powder component which varies in composition, size and molecular weight of the pre-polymerized polymer beads as well as morphology of the radiopacifier particles. All these factors have a significant effect on the interaction between the liquid and the powder components during mixing and injection, consequently resulting in different flow behaviours for different cement formulations. While new injectable bone cements are continuously being developed, there is no standardized methodology for assessing the cement flow behaviour in cancellous bone. The presented methodology provides a novel tool for quick, robust differentiation between various cement formulations through the visualization and quantitative analysis of the cement spreading at various time intervals. This will help study cement-fluid interaction to better understand how rheological properties, other than viscosity alone, affect the cement flow within cancellous bone and ultimately provide a better prediction of the cement placement.

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