

Performance of bone cements

Are current preclinical specifications adequate?

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Background Current specifications (standards) for pre-clinical testing of bone cements (ISO 5833: 2002, ASTM F451-99a) require simple mechanical testing after ageing for 24 h under dry conditions at 23°C. Some bone cements have fulfilled the requirements in the specifications, and yet had inferior clinical results. Clinically, bone cements are subjected to complex loading patterns in a moist or wet environment at 37°C. Thus, both the validity and the robustness of current standard testing protocols can be questioned.

Methods We examined the influence of temperature and storage medium on the properties of bone cement. We also compared the results of storage and testing under standard conditions of 23°C in dry air, with the results obtained at 37°C in water or plasma.

Results The dry specimens showed an increase in strength and elastic modulus with time, while the values of the wet ones decreased. There was no difference between specimens stored in water or in plasma. Ultimate compressive strength of dry specimens after 24 h was 1.16 times higher than that of the ones stored wet, increasing to 1.34 times after 1 month, and 1.46 times after 6 months ($p < 0.001$ for all comparisons).

Interpretation Testing under dry conditions—always gave higher values for mechanical properties than did storage and testing under more physiological conditions. The sensitivity of test values to different environments implies that testing conditions for bone cements should be scru-

tinized in order to develop more relevant testing protocols that reflect the *in vivo* environment more closely. ■

Bone cements are used routinely (Havelin et al. 1993, Malchau et al. 2002, 2005) for fixation of a variety of implants with different designs. The materials are polymeric materials usually based on methylmetacrylate (MMA) monomer and a prepolymer powder, mainly poly(methyl methacrylate) (PMMA). The arthroplasties will subject the cement to a variety of loading conditions. The selection of bone cements plays a critical role for the clinical outcome (Espehaug et al. 2002). The mechanical properties of bone cements are known to influence the survival of arthroplasties (Gruen et al. 1979), together with the surface preparation of the implant itself (Howell et al. 2004, Perez et al. 2006, Smailys et al. 2007).

Bone cements as materials are influenced by environmental factors such as moisture (Akashi et al. 1999) and temperature (Baleani et al. 2001), but they are also dependent on how the components of the cement have been prepared (Dunne and Orr 2001). Moreover, cements are technique-sensitive materials that require standardized handling in order to achieve reproducible results (Lewis and Austin 1994, Lewis et al. 2005, Nottrott et al. 2007).

With preclinical testing, the intention is to predict the clinical behavior of bone cements. Past experience has shown that bone cements that had adequate mechanical values according to existing specifications actually performed poorly in hip arthroplasties, as revealed by registries of implant survival (Thanner et al. 1995, Nilsen and Wiig 1996, Furnes et al. 1997, Carlsson 1998). Thus, it can be questioned whether standard preclinical testing is adequate for making a meaningful prediction about the clinical performance of bone cements. If not, then clinical trials may be required. Advanced preclinical in vitro testing such as fatigue testing has been described as a method for determination of the long-term survival of bone cements (Lewis 2003). There are still many areas of disagreement, which makes it necessary to standardize these test methods and conditions.

Current specifications for bone cements (Demian and McDermott 1998) are ISO 5833: 2002 (ISO 2002) and ASTM F451-99a (American Society for Testing and Materials 1999). According to these specifications, it is sufficient to perform simple static compressive mechanical tests after aging for 24 h under dry conditions at 23°C, which are also the recommended test conditions. Compressive strength should be at least 70 MPa. In addition, bending modulus and bending strength should be determined. Additionally, the standards define doughing time, setting time, maximum curing temperature, packaging, and labeling.

We compared the mechanical properties of a bone cement stored up to 6 months under 3 sets of conditions: (1) standard conditions (storage and testing at 23°C in air), (2) in water (storage and testing at 37°C), and (3) in plasma (storage in plasma 37°C and testing at 37°C in water).

Material and methods

Cement and preparation

We used Palacos R cum gentamicin bone cement (Schering-Plough) (Table). The cement was pre-chilled to 4°C prior to mixing, and prepared at 23°C according to the manufacturer's instructions. The polymer powder was placed in a cartridge (Optivac S; ScandiMed Implant AB, Sjöbo, Sweden) into which the monomer was added. The

Chemical composition of Palacos cum Gentamicin bone cement (Schering-Plough). Information from the manufacturer

<i>Powder sachet</i>	40.8 g
Palacos R-40 cum Gentamicin powder	
Lot no.: 1-NFBA-20/9430	
Methylmethacrylate/methylacrylate copolymer	82.84%
Benzoyl peroxide (initiator)	0.49%
Zirconium dioxide (X-ray contrast)	14.71%
Chlorophyll (coloring agent)	0.002%
Gentamicin (antibiotic)	1.96%
<i>Liquid in glass cartridge</i>	18.8 g
Palacos R-40 cum Gentamicin liquid	
Lot no.: 0-RDCA-67/3264	
Methylmethacrylate (MMA) (with 60 ppm hydroquinone as stabilizer)	97.87%
N,N-dimethyl-p-toluidine (activator)	2.13%
Chlorophyll (coloring agent)	0.002%

components were mixed under vacuum conditions below 0.15 bar for about 40 s. At dough time, usually after 3.5 min approximately, the cement was injected into a Teflon mold (NIOM, Oslo, Norway) which was produced according to ISO 5833 (2002) (ISO 2002). The cement was allowed to cure for 15 min. The test specimens (6 × 12 mm) were removed from the mold and wet-ground (DAP-V; Struers, Copenhagen, Denmark) to ensure that the end-faces of the specimens were perpendicular to the long axis.

Samples were aged unloaded, in 3 different environments, until testing. Group A was aged in air at 23°C, group B in water at 37°C, and group C in fresh frozen plasma (Octaplas; Octapharma AS, Hurdal, Norway) at 37°C. Test specimens were mounted singly. In groups B and C, 4 mL of the respective fluid was used. In group B, the water was changed every second week. There were no visual signs of bacterial growth. In group C, plasma was changed every week; fungal growth was observed twice and sodium azide was then added to the plasma.

Test specimens were obtained from 3 different mixing procedures and were randomly assigned to the testing groups. All test specimens were from the same lot (batch) (Table).

Time protocol

Groups A and B were mechanically tested after 24 h, 1 month, and 6 months. 10 samples were tested at each time point in each group. The zero point

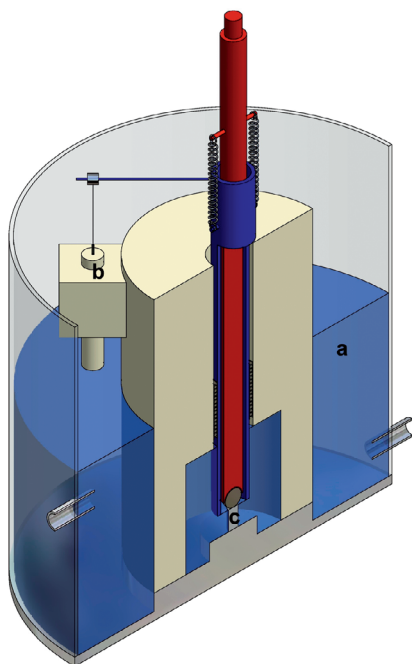


Figure 1. Schematic diagram of the experimental configuration: (a) water at 37°C, (b) strain transducer, (c) test specimen.

was defined as the start of mixing of the components.

Group C was tested after 1 week and at 3 months; 9 samples were tested at each time point and compared to results at the same time points in a former study (Nottrott et al. 2007).

Mechanical testing

Cement specimens were tested in compression with a servo-hydraulic testing machine (Material Test System 810, model no. 318.10; MTS Systems Corp., Eden Prairie, MN) with a compression jig and strain transducer (custom-made by NIOM, Oslo, Norway).

The test set-up (Figure 1) made it possible to measure small strains in the specimens, being unaffected by overall mechanical compliance of the testing system.

In group A, testing was performed in air at 23°C. In groups B and C, the jig was placed in a water-bath (custom-made by NIOM, Oslo, Norway) where the water temperature was kept constant at 37°C ± 0.5°C.

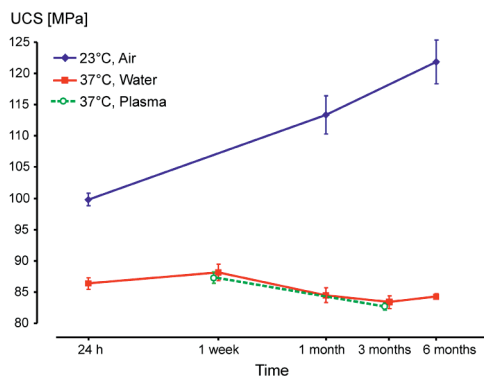


Figure 2. Mean ultimate compressive strength (UCS) with 95% confidence intervals (CIs), on a logarithmic time scale.

In all groups, a constant cross-head speed of 24 mm/min (ISO 2002) was employed until the cylinder fractured. Deformation and load were recorded continuously. Ultimate compressive strength, UCS (in MPa), maximum strain (in %) and E-modulus (E, in GPa), were calculated.

Statistics

We used a generalized linear model (GLM) to model an ANOVA to determine differences between the different groups, and also for the different time points in any particular group. The group differences were tested at each time point in the GLM using a categorical variable defined with an interaction of time. All p-values less than 0.05 were considered statistically significant. SPSS release 13.0 was used for the statistical analysis.

Results

Specimens in group A showed a continuous increase in ultimate compressive strength (UCS) while UCS decreased slightly in group B (Figure 2). There were statistically significant differences in UCS in group A between 24 h and 1 month ($p < 0.001$), and also between 1 month and 6 months ($p = 0.001$). In group B, the differences in UCS between 1 week and 1, 3, and 6 months were statistically significant ($p \leq 0.001$). UCS in group A after 24 h was 1.16 times higher than in group B, increasing to 1.34 times after 1 month and to 1.46 times after 6 months. The respective differences between groups A and B at each time point

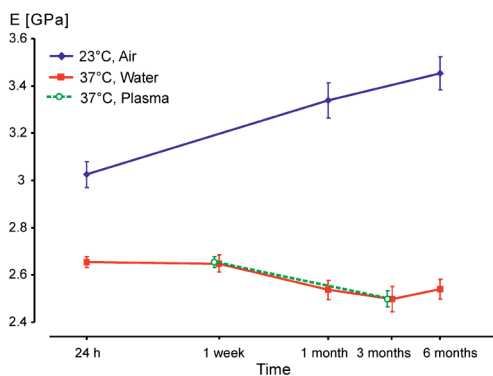


Figure 3. Mean E-modulus with 95% confidence intervals, on a logarithmic time scale.

of testing were always statistically significant ($p < 0.001$).

The same behavior was detected in elastic modulus (E), which increased continuously in group A whereas we observed a decrease in group B (Figure 3). In group A, the differences in E between 24 h and 1 month, and between 24 h and 6 months were statistically significant ($p < 0.001$), but those between 1 and 6 months were not ($p = 0.07$). In group B, the differences in E between 1 week and 1, 3, and 6 months were statistically significant ($p \leq 0.02$). In group A, E after 24 h was 1.1 times higher than that in Group B, increasing to 1.31 times after 1 month and to 1.4 times after 6 months. Also here, the respective differences between groups A and B at each time point of testing were always statistically significant ($p < 0.001$).

Maximum strain values increased in both groups but the differences were statistically significant only in group A between 24 h and 6 months ($p < 0.001$). However, no statistically significant differences were detected between the groups ($p = 0.7$ at 24 h, $p = 0.5$ at 1 month, and $p = 0.2$ at 6 months) (Figure 4).

Storage in plasma resulted in approximately identical values of ultimate compressive strength, modulus, and maximum strain to those for storage and testing in water at 37°C. The changes (decreases) in UCS (Figure 2) and E-modulus (Figure 3) were statistically significant ($p < 0.001$), but this was not the case for changes in maximum strain values ($p = 0.5$) (Figure 4).

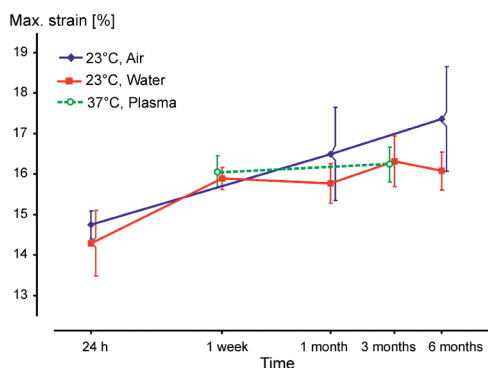


Figure 4. Mean maximum strain with 95% confidence intervals, on a logarithmic time scale.

Discussion

We found a difference in the development of mechanical properties of a bone cement between storage in air (group A) and in water (group B), whereas there were no differences between storage in water (group B) and storage in plasma (group C). Moreover, we found that testing as recommended by the specifications (group A) always gave higher values than storage and testing under more physiological conditions (groups B and C).

The increase in strength and E-modulus in group A can be explained as being the result of ongoing polymerization and crosslinking, and the onset of physical ageing (Struik 1978, Hay 1995). For groups B and C, we assume that the slight decrease in strength and modulus between 1 week and 1 month was caused by water uptake in the cement (Ruyter and Svendsen 1980, Schmitt et al. 2004), which has a plasticizing effect (Deb et al. 1995, Akashi et al. 1999, Unemori et al. 2003). Thus, storage and testing at room temperature in the dry state, as recommended in specifications for bone cements, produces unrealistically high values compared with storage and testing under simulated body conditions.

Multiphase poly(methyl methacrylate) (PMMA) is sensitive to environmental temperature (Hailey et al. 1994, Arnold and Venditti 2001). This is supported by our finding that the values for 23°C were higher than those for 37°C, as also demonstrated earlier (Nottrott et al. 2007). The glass transition temperature (T_g) of PMMA is of importance: the T_g is about 100°C in pure PMMA but in bone

cement it is in the range of 60–70°C (Kuehn 2000, Kühn 2005), which is not far from the 37°C testing temperature. The low T_g of bone cements is caused by residual monomer of about 2–6% (Hailey et al. 1994, Kühn 2005). Residual monomer has a plasticizing effect on the cement, leading to reduced mechanical strength. Moreover, the effect of a difference of 14°C in testing temperature may be enhanced in the presence of water (Hailey et al. 1994, Arnold and Venditti 2001). Comparing the results of our present study with those of our former study (Nottrott et al. 2007), the effect of temperature on a bone cement in air appears to be less important.

After storage for 1 month in water at 37°C, the cement is nearly saturated with water and has reached stable values of strength and modulus, whereas there is a continuous increase in strength and E-modulus for cements stored under dry conditions. The change in maximum strain values, indicating brittleness, suggests that there are continuous internal or external processes influencing the material.

The results of the present study confirm the recommendations given in our previous study of testing bone cements in a physiological environment after storage for at least 5 weeks (Nottrott et al. 2007). The use of plasma solutions seems unnecessary, as the values correspond closely with those obtained in water.

The current standards for bone cements—being reference documents for product evaluation and approval—do not mimic the conditions or environment in which the material is used clinically.

The current study investigated a single bone cement that is considered to be representative for PMMA-based materials, and which is commonly used (Havelin et al. 1993, Furnes et al. 2007, Kärholm et al. 2007). We used a quasistatic compressive test, which represents a simplified test configuration. Still, differences were demonstrated, due to environmental factors and time span. Other test procedures may be relevant, e.g. tension, torsion, bending, and determination of viscoelastic properties and fatigue. Standardization of testing is necessary for meaningful comparison of test results (Lewis and Nyman 2000). The present study has addressed some basic properties of a well-established material. Considering that new

materials often appear, the selection of test method could be crucial for preclinical approval.

In the absence of appropriate preclinical test methods for new bone cements, we still have to rely on data from randomized trials and registry studies, where the outcomes have a considerable lag time from product launch. Our results extend our understanding of the material behavior of bone cements, and may contribute to the development of more clinically relevant preclinical evaluation procedures.

All authors contributed to the conception and design of the study and manuscript preparation.

In addition, individual authors contributed as follows. MN: data collection, data processing, statistical analysis, interpretation of results, and writing of the manuscript. AOM: statistical analysis, interpretation of results, and writing of the manuscript. IOM: data collection and data processing. NRG: data collection, data processing, interpretation of results, and writing of the manuscript. WRW: interpretation of results and writing of the manuscript.

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No competing interests declared.

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