Strontium-containing hydroxyapatite bioactive bone cement in revision hip arthroplasty


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Abstract

Clinical outcome of cemented implants to revision total hip replacement (THR) is not as satisfactory as primary THR, due to the loss of bone stock and normal trabecular pattern. This study evaluated a bioactive bone cement, strontium-containing hydroxyapatite (Sr-HA) bone cement, in a goat revision hip hemi-arthroplasty model, and compared outcomes with polymethylmethacrylate (PMMA) bone cement. Nine months after operation, significantly higher bonding strength was found in the Sr-HA group (3.36 ± 1.84 MPa) than in the PMMA bone cement group (1.23 ± 0.73 MPa). After detached from the femoral component, the surface of PMMA bone cement mantle was shown relatively smooth, whereas the surface of the Sr-HA bioactive bone cement mantle was uneven, by SEM observation. EDX analysis detected little calcium and no phosphorus on the surface of PMMA bone cement mantle, while high content of calcium (14.03%) and phosphorus (10.37%) was found on the surface of the Sr-HA bone cement mantle. Even higher content of calcium (17.37%) and phosphorus (10.84%) were detected in the concave area. Intimate contact between Sr-HA bioactive bone cement and bone was demonstrated by histological and SEM observation. New bone bonded to the surface of Sr-HA cement and grew along its surface. However, fibrous tissue was observed between PMMA bone cement and bone. The results showed good bioactivity of Sr-HA bioactive bone cement in this revision hip replacement model using goats. This in vivo study also suggested that Sr-HA bioactive bone cement was superior to PMMA bone cement in terms of bone-bonding strength. Use of bioactive bone cement may be a possible solution overcoming problems associated with the use of PMMA bone cement in revision hip replacement.

1. Introduction

Although primary total hip replacement (THR) is a very effective and successful treatment for serious disabilities or illnesses, the failure rate is on the order of 10–30% worldwide [1–5]. Revision surgery without substantial bone loss may work rather well clinically with the conventional polymethylmethacrylate (PMMA) bone cement [6]. However, there are other publications suggesting that clinical outcome of cemented implants for revision hip replacement could be unsatisfactory [7–10]. PMMA bone cement relies on mechanical interlocking with bone rather than adhesive chemical bonding to form a stable cement–bone interface [11]. However, THR with PMMA bone cement can lead to loss of bone stock and normal trabecular pattern, especially in the femur. Therefore, the smooth bone surface encountered in revision cases leads to poor interference fit, as there are fewer crevices available for mechanical interlocking with cement [12]. An in vitro study showed the maximum interface shear strength between cement and bone after revision surgery sharply reduced to only 20.6% of the strength achieved at primary THR, and weakened further to 6.8% of primary strength following a second revision [13].

The cement–bone interface is crucial to the stability of the cemented femoral component. Nevertheless, due to the non-adhesiveness of PMMA bone cement to
bone—namely formation of a fibrous layer between bone surface and cement [14]—it is difficult to achieve a stable cemented femoral component, especially on a smooth bone surface in the revision procedure. Bioactive bone cements are developed to overcome the problems of conventional PMMA bone cement [15]. Unlike PMMA bone cement, bioactive bone cements can react in a variety of ways with living tissue, rapidly forming chemical bonds [16–18]. A bioactive bone cement containing glass-ceramic powder and silica glass powder for filling particles was evaluated for total hip arthroplasty in an earlier study on a canine model, and was found to bond directly to bone, with fixation stronger than PMMA at different time points [18]. More recently, a morselized graft–calcium phosphate cement composite was evaluated in vitro for revision hip arthroplasty, with results showing that addition of the calcium phosphate cement to the allograft layer may improve its mechanical properties, preventing early subsidence and therefore improving the clinical results [19].

In this study, a bioactive bone cement, strontium-containing hydroxyapatite (Sr-HA) bone cement was developed, consisting of Sr-HA powder and Bis-GMA-based resin [20,21]. Strontium reportedly stimulates bone formation and was recently used to treat osteoporotic spinal fractures and other related osteoporosis [22]. Our previous in vivo studies with small animals demonstrated bone mineralization and osseo-integration with cancellous bone under both non-weight-bearing and weight-bearing conditions [23–26]. However, bioactive bone cement in revision hip replacement has not been evaluated before. Therefore, in this study, we used a goat revision hip hemiarthroplasty model performed with Sr-HA bioactive bone cement to investigate the mechanical properties and morphology of bone–cement interface up to 9 months after implantation. The outcomes were compared with the results of PMMA bone cement. Goats, being larger animals, were used in this study because they more closely resemble the physical dimensions of humans.

2. Materials and methods

2.1. Preparation of the bone cements

The Sr-HA bone cement contains a filler blend and a resin blend. The filler blend contains Sr-HA (97.0 wt%), fumed silica (2.5 wt%), and benzoyl peroxide (BPO) (0.5 wt%). In Sr-HA powder, 10% calcium ions were substituted by strontium ions. The resin blend consists of biphenol A diglycidylether dimethacrylate (Bis-GMA, 50 wt%), triethylene glycol dimethacrylate (40 wt%), poly(ethylene glycol) methacrylate (9.75 wt%), and N,N-dimethyl-p-toluidine (DMPT) (0.25 wt%). Sr-HA was synthesized and characterized in the author's laboratory as previously reported [20,21]. Commercially available PMMA bone cement (Surgical Simplex P, from Howmedica, Ireland) was chosen as the control. Both cements were injected into the femoral canal with a syringe for fixation of the femoral component.

2.2. Animal model

A total of 17 goats with a mean age of 9.6 years (age range, 7–13) were used. The institution’s guide for the care and use of laboratory animals was followed. The mean weight of the goats was 37.5 kg (range, 35–43 kg). Both the rearing of these goats, and the experiments, were carried out according to guidelines for animal experiments of the University of Hong Kong. Unilateral cemented revision hip replacement model was created by the same experienced orthopaedic surgeon with 11 goats performed with Sr-HA bioactive bone cement and six others with PMMA bone cement.

An established ovine hemiarthroplasty model [27] was used in this study. Goats were chosen for the revision hip arthroplasty model because the goat femur has a wide medullary cavity with relatively thin cortical walls and relatively little trabecular bone in the proximal femoral metaphysis, allowing adequate volume for cement and implant [28]. All the surgeries were performed under general anaesthesia using aseptic techniques. A cranialateral approach was used involving the transection of only the deep gluteal muscle. Combined with suturing the joint capsule after insertion of the prosthesis, this provides good stability and precluded post-operative dislocations.

Following a cranial incision over the junction of the tensor fascia lata and glutoeobiceps, the tendon of the deep gluteal was exposed by blunt dissection. This tendon was transected close to its insertion on the greater trochanter, exposing the underlying joint capsule. The capsule was opened using a T incision along the femoral neck, preserving the femoral attachment. Following transection of the ligamentum teres (round ligament), the hip joint was dislocated and the femoral head removed, using an oscillating saw to cut along the intertrochanteric line. The remnants of the ligamentum teres were cleaned from the acetabulum and this was packed with a sterile gauze swab. The medullary cavity of the proximal femur was rasped to remove all cancellous bone to create a revision hip replacement model [27,29,30], and then the cavity was cleaned and dried. Afterwards, PMMA cement or Sr-HA cement was prepared and injected into the canal through a syringe. Next, the custom-made hip prosthesis was inserted into the femur at a suitable position, and maintained until the cement was set. Finally, the joint was reduced slowly by external rotation until the prosthesis was located in the acetabulum. The range of movement was checked before the joint capsule was sutured and the tendon of the deep gluteal re-attached. The subcutaneous tissues and skin were closed and the animal recovered in a pen with a non-slip floor.

2.3. Histological preparation and examination

All the goats were sacrificed at 9 months after implantation by intravenous overdose of pentobarbital, and their femurs were removed. The part of the femur containing the femoral component and the cement was cut into parallel sections of 10-mm thickness, from proximal to distal, axial normal to the long axis of the femur, using a high speed, water-cooled saw with a fine diamond coating (EXAKT 300 CP Band System, Norderstedt, Germany). This yielded five sections for each femur. The most proximal part of the femur, including the femoral component and the femoral canal, was excluded from the analysis because of the variable shapes of the femoral canal. The most distal section was used for the histological analysis and others were subjected to mechanical testing.

Sections for histological analysis were fixed in 4% neutral-buffered formaldehyde (pH 7.2) for 3 days, and then rinsed for 1 h under tap water. They were dehydrated in successive alcohol concentrations (70% to absolute) and cleared with xylene before being embedded in PMMA. After hardening, normal to the long axis of the femur, the sections were cut using a cutting machine (EXAKT 300 CP Band System, Norderstedt, Germany) to make two 500- to 600-μm thick sections. The sections were ground down to 100–120 μm thickness using a grinding machine (EXAKT 400 CP Micro Grinding System, Norderstedt, Germany), and the surface was polished with number 4000 garnet paper. Finally, one cut section was examined by scanning electron microscopy (SEM). The other was stained with giemsa and eosiin solution for histological observation under a Nikon H600L microscope and image analysis system (Japan). Based on the findings by Srikumaran et al. [31], histological preparation and embedding process would dissolve some of the PMMA. However, enough cement, such as the residual barium, remained to enable study of the interface between the PMMA cement and adjacent tissue.
2.4. SEM and energy dispersive X-ray microanalyzer

Representative sections were ground further with alumina-coated sandpaper to remove the surface staining, and then sputter coated with a 100 Å layer of carbon. These sections were analysed using Leo 1530 field emission scanning electron microscope, a high-resolution FESEM which, together with an energy dispersive X-ray analysis (EDX system from Oxford2), enables visualization and analysis of surface features of material as small as 0.3 μm in diameter. This makes SEM/EDX ideal for analysis of materials, minerals, contaminant particles and particles collected by filtration.

2.5. Biomechanical testing

A method of the push-out test was described previously [18]. Briefly, the cement and femoral component were pushed together with a 6 mm diameter metal rod at a crosshead speed of 0.5 mm per minute, using a servo-hydraulic materials testing machine (MTS 858 Bionix machine, MTS System Inc., Minneapolis, MN, USA). The pushing direction was invariably from the smaller inlet to the larger inlet. The bonding strength at the interface was calculated by dividing the failure load by the total area of bone–cement interface. After detachment, the gross surface of the cement mantle was examined by SEM.

2.6. Statistical analysis

Values were expressed as the mean ± standard deviation. Values from the mechanical properties for bone cements were compared using one-way analysis of variance (ANOVA). P-values less than 0.05 were considered to be statistically significant.

3. Results

All goats were able to bear their body weight within 1 week of surgery, and walked without a limp by 3 weeks. There was no postoperative hip dislocation. Three deep infections (two goats in the Sr-HA cement group and one goat in the PMMA bone cement group) were shown on gross examination at the time of sacrifice 9 months after implantation. These three goats were excluded from the present study. In the other 14 goats, neither infection nor abnormal inflammatory reaction of the hip was shown on gross examination, and all the implants appeared to be fixed securely to the skeletons. Radiographs of both groups showed neither loosening of the hip prosthesis nor abnormal bone resorption around the cement mantle at 9 months (Fig. 1).

Significantly higher bonding strength was found in the Sr-HA group (3.36 ± 1.84 MPa) than on the PMMA bone cement group (1.23 ± 0.73 MPa) (P < 0.01). Detachments occurred consistently at the bone–cement interface. Fibrous tissue can be clearly observed attached to bone in the PMMA bone cement group (Fig. 2a), indicating that a fibrous tissue layer had been formed between PMMA bone cement and bone. However, no such phenomenon was found in the Sr-HA bone cement group (Fig. 2b).

Remarkable contrast was observed on the surfaces of cement mantle after detached from the femoral component (Figs. 2a and b). The surface of PMMA bone cement was somewhat smooth. However, the surface of the Sr-HA bone cement was uneven. SEM micrographs displayed this contrast clearer. The surface of PMMA bone cement was intact and even, except for some voids created by bubbles (Fig. 3a). However, a number of concave areas appeared on the surface of the Sr-HA bone cement (Fig. 3b). Only 0.02% (at%) calcium and no phosphorus at all were detected by EDX analysis on the surface of the PMMA bone cement mantle (Fig. 4). In contrast, high content of calcium (14.03%) and phosphorus (10.37%) was found on the surface of the Sr-HA bone cement mantle, and even higher content of calcium (17.37%) and phosphorus (10.84%) were in the concave areas.

The bone cement–bone interfaces were observed histologically. Intimate contact between the Sr-HA bioactive bone cement and bone without any intervening fibrous layer was indicated (Fig. 5b). However, residual barium was present within the cement space, and a fibrous tissue layer about 10 μm thick can be observed between bone and PMMA bone cement (Fig. 5a). Fibrous tissue stains blue with Giemsa stain [32]).

SEM observation was taken of an area including Sr-HA bone cement and bone (Fig. 6). A relatively radiolucent interface about 2–5 μm thick was found between Sr-HA bone cement and bone. EDX analysis revealed that the content of calcium and phosphorus was lower at the interface than either bone or Sr-HA bioactive bone cement (Fig. 6-1). However, new bone was observed to grow through this low calcium/phosphorus interface, bond to the surface of Sr-HA bone cement, and grow along the surface of bone cement subsequently (Fig. 6-2). By EDX analysis, the content of calcium and phosphorus of the newly formed bone was higher than the cement.

4. Discussion

Mid-term evaluation of Sr-HA bioactive bone cement conducted in a goat revision hip arthroplasty model showed it had significantly higher bonding strength with bone (3.36 ± 1.84 MPa) than PMMA bone cement...
After 9 months implantation. Direct bonding of the Sr-HA bone cement with bone without intervening fibrous tissue layer was confirmed by microscopy and SEM observation. In contrast, fibrous tissue was found formed between the PMMA bone cement and bone, and the surface of the PMMA bone cement mantle was intact and even. Overall, intimate contact between the Sr-HA bone cement and bone was demonstrated in this goat revision hip arthroplasty model, implying high bioactivity of Sr-HA bioactive bone cement and indicating adequate initial fixation after 9 months implantation.

Results of this study were consistent with our previous studies showing that Sr-HA bioactive bone cement can bond directly to adjacent bony tissue under both non- and weight-bearing conditions [24–26]. In this study, intimate contact between Sr-HA bone cement and bone was demonstrated by histological and SEM observation. SEM observation further revealed that new bone bonded to Sr-HA bone cement and grew along its surface, indicating good osteoconductivity of Sr-HA bioactive bone cement. EDX analysis revealed that the content of calcium and phosphorus were higher in the concave areas than other areas of the Sr-HA bone cement surface because bone tissue was left at the concave areas after push-out testing. This is also in line with the results of bonding zone with bone reported in some other studies [24,33]. In addition, the uneven surface of the Sr-HA bone cement mantle after the push-out testing made it possible for mechanical interlock with bone. This, combined with the chemical bonding, contributed to the high bonding strength shown in this study.

Concave areas on the surface of the Sr-HA bone cement mantle are assumed to be due to dissolution of this biomaterial. Our previous study [26] indicated that Sr-HA bioactive bone cement bonded to cancellous bone through a high calcium/phosphorus apatite layer, but to cortical bone through a low calcium/phosphorus interface. A similar low calcium/phosphorus interface was also observed in the present study between Sr-HA bioactive bone cement and cortical bone. However, newly formed bone was found to grow through this interface, bond to Sr-HA bioactive bone cement, and grow along its surface. This might be due to the differences in both animal model and implantation duration between these two studies. In the previous study, relatively young rabbits (aged 12–14 months) were used, and the Sr-HA bioactive bone cement was implanted for 6 months.
Conventional bone cement, PMMA bone cement, has been successfully used for prosthetic fixation for more than 40 years. However, there are several problems associated with the use of it. The most serious is its non-adhesiveness to bone—namely, formation of a fibrous layer between the bone surface and cement, which is one of the major contributions to loosening of cemented femoral components [11,14]. In the present study, fibrous tissue was formed between PMMA bone cement and bone, which was consistent with our previous study [25] and many other reports [11,14,31,34]. PMMA bone cement relies on mechanical interlocking with bone rather than adhesive chemical bonding to form a stable cement–bone interface [11]. Nevertheless, in the present study, the surface of PMMA bone cement mantle was found intact, even after detachment from the cemented femoral component. The smooth cement mantle surface, together with the smooth bone surface encountered in the revision case, leads to poor interference fit as well as inadequate mechanical interlock [12]. Hence, the maximum interface shear strength between cement and bone after revision surgery sharply decreased when compared to that after primary THR [13]. It is
Therefore not surprising that the bonding strength with bone shown in the present study was significantly lower in PMMA bone cement than Sr-HA bioactive bone cement. This intimate bonding between Sr-HA bioactive bone cement and bone was demonstrated by both our present and previous studies\[25,26\]. This indicates great clinical significance in hip surgery. Firstly, without intervening fibrous tissue there is better physiological stress transfer between the implant and host bone\[35\]. Secondly, the increase in bone ingrowth should increase sheer strength\[36\]. In addition, bonding with the bone may limit stress shielding and give the implant a potentially longer life.

<table>
<thead>
<tr>
<th>Element (At. %)</th>
<th>Oxygen</th>
<th>Calcium</th>
<th>Phosphorus</th>
<th>Strontium</th>
<th>Sodium</th>
<th>Chlorine</th>
<th>Sulphur</th>
<th>Barium</th>
</tr>
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<tbody>
<tr>
<td>A: Concave</td>
<td>71.14</td>
<td>17.37</td>
<td>10.84</td>
<td>0.65</td>
<td>1.32</td>
<td>1.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B: Sr-HA surface</td>
<td>72.16</td>
<td>14.03</td>
<td>10.37</td>
<td>1.11</td>
<td>1.32</td>
<td>1.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C: PMMA surface</td>
<td>82.28</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.84</td>
<td>8.86</td>
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![Fig. 4](image1.png) **EDX analysis on the concave (a), relative smooth areas (b) of the Sr-HA bone cement mantle, as well as the surface of PMMA bone cement mantle surface (c).**

![Fig. 5](image2.png) **Undecalcified sections with Giemsa and eosin staining: (a) an intervening soft tissue layer (white arrow) approximately 10 μm-thick was observed at the bone–PMMA bone cement interface (between black arrows). Residual barium was also present (white arrows); (b) intimate contact was found between the Sr-HA cement and bone without fibrous layer intervening. B: bone; C: Sr-HA bioactive bone cement; CS: PMMA bone cement space (Bar = 20 μm).**

![Fig. 6](image3.png) **SEM micrograph and EDX analysis of an area including bone, Sr-HA bone cement, and the interface. Two areas were chosen for EDX analysis. For area 1, an interface with about 2–4 μm-thick was shown, and its content of calcium and phosphorus was much lower than either bone or Sr-HA bone cement. For area 2, new bone (white arrow) was found to grow through the low calcium/phosphorus interface shown in area 1, bond to the surface of Sr-HA bone cement, and grow along its surface. The content of calcium and phosphorus of the newly formed bone was higher than Sr-HA bioactive bone cement.**
span. Finally, bonding directly with the bone may decrease the possibility of wear debris at the bone–cement interface, meaning osteolysis is less likely to occur [18]. Subsequently under investigation in this continuing study is the effect of the use of the Sr-HA bone cement on femoral bone loss using this goat revision hip replacement model.

5. Conclusion

The Sr-HA bioactive bone cement was evaluated in a goat revision hip replacement model morphologically and mechanically, good bioactivity and bone-bonding ability were suggested at the ninth month after implantation. Although promising results suggest possible clinical use of bioactive bone cement for revision hip replacement procedure, further investigations of long-term outcome are necessary before this bioactive bone cement can be applied for human total hip arthroplasty.

Acknowledgements

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References


