One stage uncemented revision of infected total hip replacement using cancellous allograft bone impregnated with antibiotics

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Infection of a total hip replacement (THR) requires component removal and thorough local debridement. Usually, long-term antibiotic treatment in conjunction with a two-stage revision is required. This may take several months. One-stage revision using antibiotic-loaded cement has not gained widespread use, although the clinical and economic advantages are obvious. Allograft bone may be impregnated with high levels of antibiotics, and in revision of infected THR, act as a carrier providing a sustained high local concentration.

We performed 37 one-stage revision of infected THRs, without the use of cement. There were three hips which required further revision because of recurrent infection, the remaining 34 hips (92%) stayed free from infection and stable at a mean follow-up of 4.4 years (2 to 8). No adverse effects were identified. Incorporation of bone graft was comparable with unimpregnated grafts.

Antibiotic-impregnated allograft bone may enable reconstruction of bone stock, insertion of an uncemented implant and control of infection in a single operation in revision THR for infection.

The treatment of an infected total hip replacement (THR) commonly requires removal of the implant, radical debridement, and long-term antimicrobial treatment. Eradication of infection is difficult because of the high resistance of bacteria to antibiotics, adhering to foreign bodies within biofilms[1,2] and the poor penetration of antibiotics into infected bone.[3,4] Local administration of high-dose antibiotics has been used to overcome the problems with systemic antibiotic delivery. In order to optimise local antibiotic administration a carrier with good biocompatibility and storage capacity is needed. Buchholz and Engelbrecht[5] have used polymethylmethacrylate (PMMA) cement impregnated with various antibiotics since 1970 and subsequently developed a technique of cemented one-stage revision of infected THRs.[6] However, this technique had several disadvantages and acceptance was low among the orthopaedic community, but the principles of local antimicrobial delivery gained widespread use, in the form of spacers in two-stage revisions. Unfortunately, even antibiotic-loaded PMMA may act as a bed for colonisation with selected bacteria[7] and a novel approach is necessary.

At revision of an infected THR, after removal of implants and debridement of necrotic bone, bony defects remain. Impacted cancellous allograft bone is commonly used to restore bone stock and give mechanical support, but only after a period of systemic antibiotic therapy, while signs of infection decline and blood indices return to normal. Otherwise, the allograft is likely to become re-colonised with any remaining bacteria. Allograft bone has previously been used as a delivery vehicle for antibiotics. Witso et al[8] used netilmicin-impregnated allografts for reconstruction in revision hip or knee surgery and found no adverse effects. Buttaro, Russo and Piccaluga[9] and Buttaro et al[10] favourably used vancomycin-supplemented cancellous grafts for reconstruction after infected THR. Michalak et al[11] and Khoo et al[12] impregnated segmental allografts with gentamicin and flucloxacillin, respectively. However, all those groups have used antibiotic-impregnated grafts only in the second stage of a two-stage revision, after resolution of clinical and laboratory evidence of infection. Uncemented reconstruction of failed THR has been recommended by several authors.[13-15] However, all of them have excluded its use in cases with florid infection. Our own studies, using a proprietary impregnation technique, revealed markedly higher concentrations of antibiotics inside processed bone grafts with a further prolonged release for

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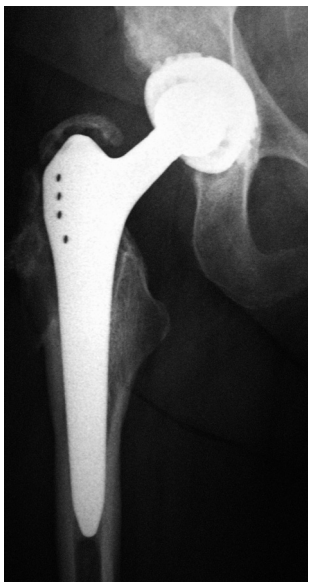

Fig. 1a

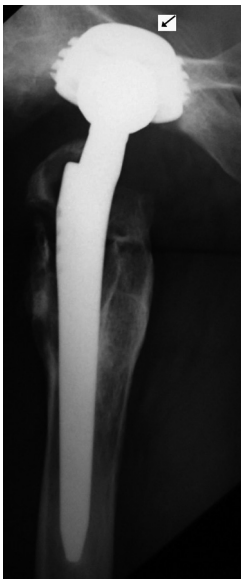

Fig. 1b

a) Anteroposterior and b) lateral radiographs of a 57-year-old woman taken four years after primary total hip replacement for osteoarthritis secondary to dysplasia. An aspirate of an abscess at the anterior aspect of the joint grew coagulase-negative staphylococcus. There is no sign of implant loosening but marked osteolysis around the proximal third of the stem and a type 2c acetabular defect is seen (arrow).

several weeks compared with the unprocessed grafts used by other groups.[16] Based on these experiences we have developed a technique using antibiotic-impregnated allograft in one-stage revision of infected THR, using exclusively cementless components.

Patients and Methods

Between 1998 and 2004 we treated 37 patients with an infected THR. Operations were performed in the index clinic (Weinviertelklinikum Mistelbach) (20 hips) and various other hospitals (17 hips) by the senior author (HW). Follow-up of these 17 hips was in our Osteitis Center (Vienna, Austria).

There were 17 men and 20 women with a mean age at revision of 68.5 years (42 to 83). Infections were classified according to the Mayo Clinic classification[17] as early (acute) in 12, low-grade (chronic) in nine and late (hematogenous) in 16 hips, respectively.

This study included all patients undergoing one-stage revision THR with culture-proven deep-infection. Bone defects not exceeding type 2 according to Paprosky, Perona and Lawrence[18] on the acetabular side (Fig. 1) and any defects on the femoral side were included. In all hips a lateral transgluteal approach was used. All the acetabular implants were removed, even when they were well fixed, but five uncemented femoral implants were retained as they were completely integrated. The remainder were removed with minimal damage to the remaining bone. Meticulous excision of all cement, granulation and necrotic tissue was performed. Debridement was completed using saline pulsed lavage. The extent of the bone defects was evaluated and the defect then filled with antibiotic-impregnated allograft. The allograft was from tibial and femoral metaphyses of cadaver donors, procured according to the standards of the European Association of Tissue Banks.[19] The retrieved cancellous bone was morsellised to granules with a diameter of between 2 mm and 8 mm and lavaged with ether and alcohol to remove fat, marrow and adhering soft tissue. After lyophilisation and packaging, sterilisation was performed by gamma irradiation. The allograft was stored at room temperature. Immediately preceding surgery, the allograft was impregnated with antibiotic, using a specific incubation technique.[16] The choice of antibiotic, vancomycin or tobramycin, depended upon the causative pathogen. Vancomycin was used in all cases, but tobramycin was added in cases of mixed infections. The impregnation procedure produced an antibiotic-bone compound with high levels of antibiotic inside the graft; vancomycin levels were in the range of 100 mg/cc of bone and; tobramycin levels were in the range of 75 mg/cc of bone. The mean amount of antibiotic-bone compound used per case was 75 cc (30 to 150). On the acetabular side, this was impacted into the defects using a modification of the technique described by Schreurs et al.[20] The choice of implant depended upon the size of the bony defects; in cases with minor defects (Paprosky type 2) a threaded conical acetabular component (Alloclassic Zweymueller; Zimmer, Warsaw, Indiana) was used, while larger defects (Paprosky type 2) required a hemispherical acetabular component with or without additional screw fixation (Allofit, Zimmer). On the femoral side we routinely used a rectangular-diameter titanium stem (Alloclassic Zweymueller, Zimmer); a standard SL component where there was good femoral bone stock, and the oblong SLL component where there was marked metaphyseal bone loss. If a lateral osteotomy was required, it was secured with one or two titanium cerclage bands. All components were inserted using a press-fit technique without the use of cement. Fixation intra-operatively was regarded as stable in all cases. Additional antibiotic-bone compound was placed around any uncovered parts of the implants and impacted for stability. In general, this was implanted on the medial wall of the acetabulum, in the femoral medullary cavity and around the proximal half of the Zweymueller component (dorsally and ventrally) (Fig. 2). It was important that the fixation of the implant mainly relied on the original bone, around the distal third of the component and the rim of the acetabulum. Wounds were drained and closed and rehabilitation was commenced as per a routine revision operation.[21] Peri-operative intravenous antibiotic treatment was according to susceptibility testing for two weeks, usually with second-generation cephalosporins or, in cases with methicillin resistant *Staphylococcus aureus* (MRSA), with fusidic acid. Post-operatively, levels of vancomycin were monitored both in the drainage fluid and in serum for two to three days.

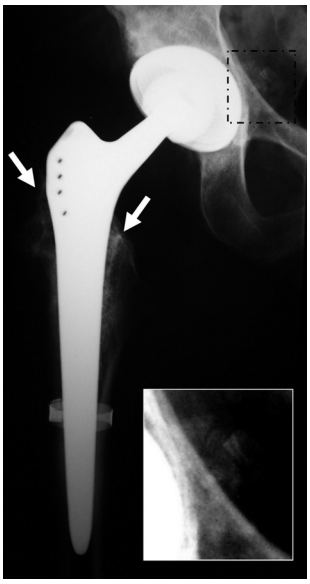

Fig. 2

Anteroposterior radiograph of same patient taken post-operatively. The implants were exchanged to an Alloclassic SLL stem and Allofit acetabular component. The femoral osteotomy, needed for removal of the stem, is secured with one titanium cerclage band. Antibiotic-bone-compound is impacted into defects in the proximal femur (arrows) and the acetabular floor. Some chips have protruded into the pelvis during impaction (magnified).

Intra-operative cultures grew coagulase-negative staphylococci in 19 hips, *Staph. aureus* in 11, MRSA in five, enterococci in eight, and other gram-positive pathogens in six. In eight hips gram-negative organisms were also identified. All organisms were susceptible to vancomycin, tobramycin, or both. Patients were reviewed at two weeks, six weeks, three months, six months and one year after surgery. Follow-up included clinical and radiological examination, and blood tests including C-reactive protein, erythrocyte sedimentation rate, white blood cell count, urea and creatinine. A successful outcome was defined as a stable implant without clinical, radiological or laboratory evidence of infection.

Results

The mean vancomycin level in the drainage fluid was 535.6 μg/ml (43 to 854) on the first post-operative day declining to 400.5 μg/ml (8 to 1717) on the third post-operative day. The mean post-operative serum level of vancomycin was 0.2 μg/ml (0.0 to 1.8) on the first post-operative day. Wound healing was uneventful in all cases. No adverse side effects were observed during the follow-up period. Specifically, renal-function did not show any remarkable changes. The mean hospital stay was 16 days (10 to 32). Post-operative rehabilitation in patients with a short history of infection (up to three months) was similar to rehabilitation after an uncomplicated primary THR.21 However, lengthy rehabilitation was required in cases of prolonged infection.

The mean follow-up was 4.4 years (2 to 8). There was recurrence of infection in three hips, two of which were diagnosed between six and 12 weeks after operation. In one hip the well-fixed femoral component had not been exchanged, in the other a technical error during impregnation of the bone graft was noted. Both patients underwent successful revision using the same technique with complete removal of components and use of appropriately impregnated bone graft, and remain free of infection at the latest follow-up. In the third hip, infection recurred after six months; *Staph. aureus* was cultured as in the previous revision. This patient underwent resection arthroplasty in another hospital.

At latest follow-up 34 hips (92%) showed no signs of infection. C-reactive protein values remained normal and were not significantly different when compared with the findings after an uncomplicated THR.[22]

Radiological examination revealed partial resorption of allograft bone in non-weight-bearing areas, while in weight-bearing areas, increased density was observed. Parts of the allografts, especially in the femoral diaphysis remained unchanged at latest follow-up. In general, the allografts appeared to follow the established patterns of incorporation compared with normal allograft with uncemented implants.[15,23] There were no signs of loosening in any of the components during the period of follow-up (Fig. 3).

Discussion

One-stage revision of an infected THR is attractive because of reduced burden for the patient and economic advantages. However, this technique is rarely used and only ever with cemented components (with cement as the antibiotic carrier). Bone cement can provide local antibiotic levels which exceed levels achieved by parenteral delivery,[24] but the mechanical properties of cement are diminished, and *in vivo* levels are still estimated to be insufficient by many surgeons, leaving two-stage revision as the present technique of choice.[25-28] Antibiotic-bone compound is a powerful carrier, likely to outperform the properties of PMMA in most aspects. The mechanical properties of cement are not of relevance since fixation relies on press fit with original bone and as the local antibiotic concentration is increased both immediately after implantation and in the following weeks,[29] there should be less risk of the development bacterial resistance due to subinhibitory concentrations originating from old PMMA,[30] and there is a good chance of allograft integration into osseous defects. Uncemented implants, both on the femoral and the acetabular side, are likely to provide better long-term results in revision cases than cemented systems.[31] The technique of using antibiotic-bone compound in combination with uncemented implants

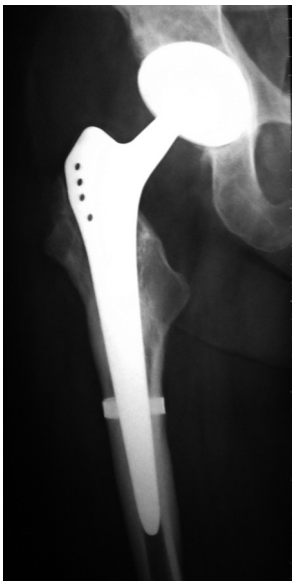

Fig. 3a

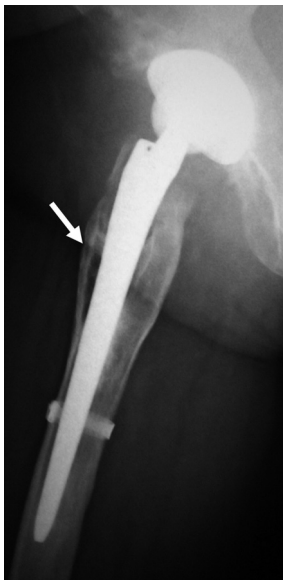

Fig. 3b

a) Anteroposterior radiograph taken of same patient as shown in Fig. 2 one year after the revision procedure. Complete restoration of bone stock on both the femoral and acetabular side is shown. Unloaded intrapelvic fragments have completely resorbed. b) The lateral radiograph shows some unincorporated parts of the grafts at the anterior aspect of the femoral stem, indicating stress shielding (arrow). No clinical or laboratory signs of infection or loosening were found.

has major advantages increased and prolonged local antibiotic concentrations for bacterial eradication, restoration of deficient bone stock and uncemented fixation for improved long-term results, all within a single revision procedure. It must be emphasised that antibiotic-bone compound can only be considered one tool within a complex treatment protocol, which follows the established principles of revision surgery for infection.

To date, impregnated bone grafts have been used by other groups as a prophylactic measure in patients with a high risk of infection but without any florid signs of infection. Buttaro's group added 500 mg of vancomycin powder to one morsellised femoral head,[9] which may be estimated to represent a volume equivalent to 50 cc of cancellous bone. Similar techniques and concentrations were used by Witso et al.[32,33] Both groups found comparable levels of antibiotic in the immediate post-operative drainage fluid, as we did in our series. However, we could show that with our impregnation technique, 5 g of vancomycin may be incorporated into the same volume of cancellous bone graft, which represents a tenfold concentration. We conclude that our impregnation technique is likely to provide a biphasic antibiotic release: the superficially-adhered antibiotic seems to be active immediately but this only represents approximately 10% of the total implanted dose. The additional nine times greater dose, bound to the osseous structures of the graft, is presumed to be released slowly between two and eight weeks after operation. The sustained release of antibiotic may protect both the graft and the implant from recolonisation, even in markedly contaminated areas, and simultaneously may eradicate the remaining bacterial colonies. We consider these kinetics to be a fundamental prerequisite for a one-stage revision.

Although extremely high concentrations of antibiotic were present at the operative site we did not see any adverse effects, confirming the results of similar studies.[34] The local wound healing and remodelling of the graft seem not to be impaired by these high concentrations of antibiotic. This may be because of the low cytotoxic property of vancomycin and tobramycin, respectively.[35-37] We did not observe any differences in the biological behaviour between our impregnated allografts and existing allograft described in the literature.[23] Both are well incorporated in regions where a physiological stress is present and are resorbed or remain static in unloaded areas.

Studies investigating the diffusion rates of vancomycin into biofilms were suggested that the minimum bactericidal concentration of vancomycin required to eliminate staphylococci embedded in biofilms is 200- to 600-fold greater than the minimum bactericidal concentration for freely floating planktonic cultures.[38,39] Such concentrations can never be reached by parenteral administration or by established carriers like PMMA. Therefore it has been considered mandatory to remove all implants for eradication of infection. Since antibiotic-bone compound can create and maintain local antibiotic concentrations more than 1000 times the minimum bactericidal concentration of relevant pathogens for several days,[16] it is possible that closely-adjacent antibiotic-bone compound might be sufficient to eliminate even biofilm-embedded bacteria. Such a possibility potentially avoids the need to remove well-incorporated implants. However, leaving an implant *in situ* makes it impossible to examine its whole surface. Hidden, or more distant colonies may be isolated from sufficient antibiotic diffusion and be the origin of later recurrence. In our series, five femoral components had been well fixed and were left in place, surrounded by antibiotic-bone compound. While four of the hips did not show any sign of recurrence, one re-infection occurred 12 weeks after operation. We believe that undetected colonies may explain the failure in this case and, therefore, still recommend removing well-incorporated implants. If removal is only feasible with destruction of original bone it is the surgeon who should calculate the risks of retention *versus* removal.

Deep infection with MRSA is considered a particular threat in THR surgery. Published treatment protocols include repeated surgery and markedly prolonged hospital stays[39] Positive results are infrequent with a success rate of approximately 50%. One reason for the poor outcome is the limited availability of effective antibiotics, most of which show unfavourable kinetics when administered systemically. Local application of vancomycin in sustained high concentrations may be a solution to this problem. In our series, five deep infections caused by MRSA were treated successfully with a one-stage revision.

To the best of our knowledge this is the first report in literature describing one-stage THR without the use of cement. Although numbers are small, it seems that one-stage uncemented revision, in combination with antibiotic-bone compound, provides an excellent tool in the treatment of infected THR. Further studies are needed to answer questions like possible retention of implants and the long-term behaviour of the reconstructions. The prescribed technique of uncemented reconstruction is applicable to all defects on the femoral side but restricted to acetabular defects of Paprosky type 1 and 2. In our opinion, infection-related type-3 defects still require the use of cement.

In conclusion, antibiotic-impregnated bone grafts may provide increased local antibiotic concentrations at the site of infection as well as simultaneous repair of osseous defects. Uncemented one-stage revisions for infection appear feasible. A success rate of 92% may be achieved, which is comparable with the results of two-stage exchange procedures but without the obvious disadvantages of two operations and the period of disability between them. For the patient there is a marked reduction of disability and pain with improvement of post-operative function; while for the treating team there is a markedly reduced burden of peri-operative care, and for society a significant cost-saving may be expected.

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