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Bioactive glass S53P4 as bone graft substitute in treatment of osteomyelitis

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ABSTRACT

Bioactive glass (BAG)-S53P4 is an osteoconductive bone substitute with proven antibacterial and bone bonding properties. In a multicentre study 11 patients with verified chronic osteomyelitis in the lower extremity and the spine were treated with BAG-S53P4 as a bone substitute. The cavitary bone defect and the surrounding of a spinal implant were filled with BAG-S53P4. The most common pathogen causing the infection was *Staphylococcus aureus*. The mean follow-up was 24 months (range 10–38). BAG-S53P4 was well tolerated. Nine patients healed without complications. One patient who achieved good bone formation sustained a superficial wound infection due to vascular problems in the muscle flap, and one patient had an infection due to a deep haematoma. This study shows that BAG-S53P4 is a good and well-tolerated bone substitute, and can be used in treatment of osteomyelitis with good primary results.

Introduction

Osteomyelitis, first described by Chassaignac in 1852, is caused by infecting micro-organisms and defines a destructive inflammatory process in bone that is often accompanied by bone destruction [1]. The infection can arise from a variety of aetiologies [2]. Most often it is caused by trauma, but any kind of bone or soft tissue surgery where pathogens can enter the bone, may cause the infection. In diabetic patients, osteomyelitis may appear as a secondary manifestation due to vascular insufficiency and soft tissue infection [3]. Haematogenous osteomyelitis has been found in children, as well as in elderly patients [4].

Acute osteomyelitis is an infection characterized by oedema, locally decreased blood supply and pus formation. Untreated or due to treatment failure, the infection can progress to a more chronic phase, with formation of a large area of devascularized dead bone, a sequestrum. In treatment of chronic osteomyelitis, adequate debridement is mandatory. Unfortunately, this treatment often results in a poorly vascularized large bone defect, a dead space. Bacterial infection can also cause local acidosis, leading to dissolution of bone matrix mineral [5]. Many different methods have been used to treat the bone defect and the infection, including free vascularized bone grafts, local muscle flaps, antibiotic-impregnated polymethyl methacrylate (PMMA) beads, granulation formation according to the technique of Papineau and the Masquelet technique [6] or bone reconstruction based on Ilizarov technology [7].

Staphylococcus aureus and Gram-negative bacilli are the pathogens most commonly involved [7]. The bacterial colonization of host tissue or implanted materials is promoted by the ability of the bacteria to produce protein-specific adhesins on their surfaces, which is followed by interactions with host protein components, such as fibrinogen, fibronectin and collagen. Bacteria also have sophisticated methods for communication through hormone-like compounds in biofilms, making treatment with antimicrobial agents difficult [2]. Use of synthetic bone graft substitutes in treating osteomyelitis is, therefore, generally not recommended.

Bioactive glasses (BAGs) are synthetic biocompatible osteoconductive bone substitutes, with bone bonding capacity and documented antibacterial and angiogenesis-promoting properties [8–16]. Previous studies on atrophic rhinitis, a chronic purulent disorder often caused by *Klebsiella ozaenae* and difficult to treat, have shown that BAG-S53P4 does not favour adhesion or colonization of *K. ozaenae* on its surface. In addition, *K. ozaenae* cannot form biofilms on BAG-S53P4 [17].

The aim of this study was to apply the experimentally known antibacterial properties of BAG-S53P4 to clinical practice, evaluating the operative outcome using BAG-S53P4 as a bone graft substitute in treating osteomyelitis.

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Patients and methods

This is a multicentre study on patients with verified osteomyelitis in 2007–2009. Eleven patients (nine males, two females) with a radiologically diagnosed osteomyelitis participated. Osteomyelitis was verified on MRI (nine patients), or on CT scans (two patients). Osteomyelitis was localized in the lower extremity in ten cases and in the spine in one case (Figs. 1A, 2A–B). Seven of the patients had sustained a fracture: in the distal tibia (three patients), in the calcaneus (two patients), in the distal fibula (one patient) and in the distal femur (one patient). Nine patients had undergone previous operative treatments, including revisions, osteotomies and artrodesis. Autologous bone grafts had been used in two patients and a bone substitute (Norian®) in one patient. Kanamycin granules had been used in one patient and Garamycin granules (Septocol®) in two patients. Antibiotic therapies had been given to all patients. One patient had been treated for osteomyelitis for 64 years, four patients for 7–16 years and six patients for ~ 1–2 years. Data including the predominating aetiology of osteomyelitis, previous treatments and methods for verification of osteomyelitis are shown in Table 1.

In 2007–2009, all of the patients were operated on due to chronic infection and verified osteomyelitis. In the operation, the infected bone and the soft tissue were removed, and the cavitary bone defects were filled with BAG-S53P4 (BonAlive^{R}, Bonalive Biomaterials Ltd., Finland). The whole cavitary defect was filled and, therefore, the amount of glass used was depending on the size of the cavity. In four patients, muscle flaps were used as part of the treatment. A patient with verified spondylitis was treated using a metal implant which was covered with BAG-S53P4. The most common pathogen causing the infection was *S. aureus* (six patients). The outcome of the treatment was evaluated by the surgeon as excellent (no complications), good (a small complication) or a temporary stable situation.

Data for operative treatment, BAG-S53P4 used, pathogens, postoperative treatment and complications are provided in Table 2.

Patients were seen at the outpatient departments at 1, 2, 3–4, and 6–15 months postoperatively. Five patients had a follow-up of 2–6 months and six patients of 8–15 months. Patient data were also obtained from hospital patient records until March 2010, resulting in a mean follow-up period of 24 months (range 10–38).

Results

BAG-S53P4 was well tolerated; no BAG-related adverse effects were seen in any patient. The use of BAG-S53P4 as a bone graft substitute resulted in a fast recovery, i.e. patients that had been treated with long-lasting therapies responded well to the treatment. Clinical outcome was good or excellent in nine of eleven patients. The clinical and radiological findings are summarized in Table 3.

Postoperative complications needing treatment were seen in two patients. In one patient, vascular problems occurred in the muscle flap, with a subsequent wound infection. No sign of osteomyelitis was, however, observed on X-rays. The BAG was well incorporated into the bone and the bone cavity healed well.

In another patient, a postoperative complication was observed one month after treatment. This patient had been in the Second World War in 1944, where he had a shell splinter accident and sustained a mutilated tibial fracture. Over the years, he had undergone numerous treatments. Postoperative X-ray verified that the evacuated cavity had not been properly filled with BAG. During arthroscopic revision the empty part of the treated cavity was observed to be filled with a haematoma, which was considered to be the cause of the re-infection.

According to patients' records, no relapses or other complications were observed.

The postoperative radiological appearance of the treated bone cavity and the spine is shown in Figs. 1B–C and 2C.

Discussion

Despite advances in antibiotic therapies and operative techniques, treatment of osteomyelitis remains challenging, expensive and time-consuming for both the doctor and the patient.

Debridement in combination with local administration of antibiotics, e.g. gentamicin-loaded PMMA beads, has for years been the method of choice in treating osteomyelitis. However, in a long-term follow-up study of 100 patients treated with gentamicin-PMMA beads, relapses were observed for 8.8% of patients with acute osteomyelitis and for 21.2% of patients with chronic osteomyelitis [18]. PMMA is also known to provide a favourable environment for proliferation of bacteria [19].

Biodegradable antibiotic-impregnated implants have also been used to treat chronic osteomyelitis. Five patients treated with calcium sulphate tobramycin impregnated pellets and one patient treated with calcium sulphate tobramycin–vancomycin impregnated pellets have shown excellent osseous repair [20]. However, an increase in antibiotic-resistant bacteria, such as gentamicin- or methicilline-resistant *S. aureus,* has been observed [21].

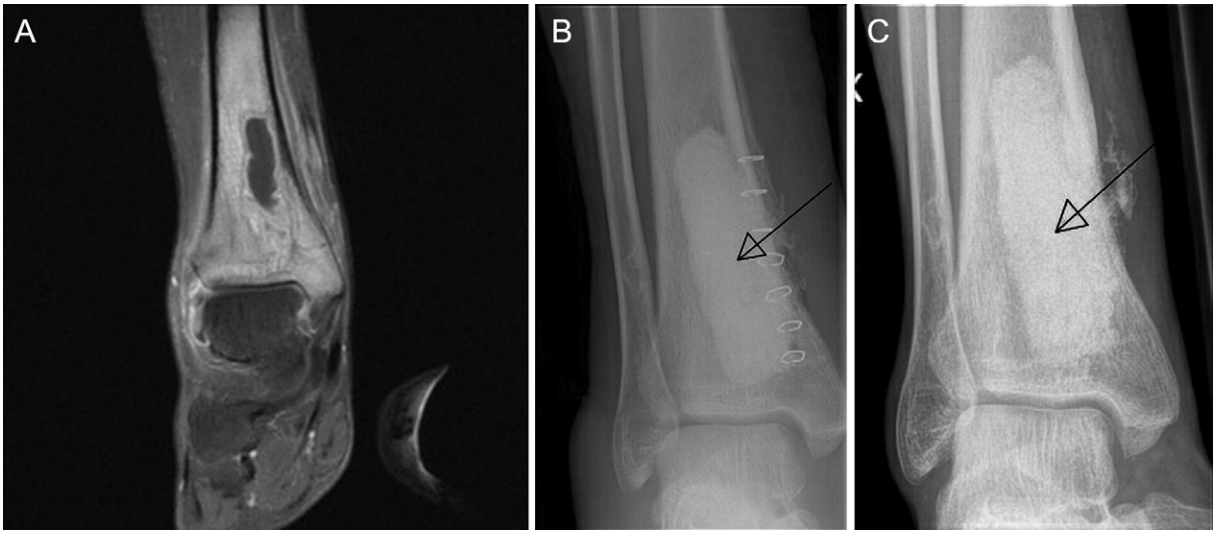

Fig. 1. (A–C) Osteomyelitis caused by *S. aureus* in distal tibia treated with BAG-S53P4 as bone graft substitute: (A) preoperative MRI showing osteomyelitis in tibia, (B) postoperative X-ray showing BAG-S53P4 in the treated bone cavity (arrow), and (C) X-ray at five months follow-up showing the treated region (arrow).