Residual gentamicin-release from antibiotic-loaded polymethylmethacrylate beads after 5 years of implantation

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Abstract

In infected joint arthroplasty, high local levels of antibiotics are achieved through temporary implantation of non-biodegradable gentamicin-loaded polymethylmethacrylate beads. Despite their antibiotic release, these beads act as a biomaterial surface to which bacteria preferentially adhere, grow and potentially develop antibiotic resistance. In routine clinical practice, these beads are removed after 14 days, but for a variety of reasons, we were confronted with a patient in which these beads were left in situ for 5 years. Retrieval of gentamicin-loaded beads from this patient constituted an exceptional case to study the effects of long-term implantation on potentially colonizing microflora and gentamicin release. Gentamicin-release test revealed residual antibiotic release after being 5 years in situ and extensive microbiological sampling resulted in recovery of a gentamicin-resistant staphylococcal strain from the bead surface. This case emphasizes the importance of developing biodegradable antibiotic-loaded beads as an antibiotic delivery system.

1. Introduction

Gentamicin-loaded polymethylmethacrylate (PMMA) beads constitute an effective drug delivery system for local antibiotic therapy in bone and soft-tissue infections, as they enable gentamicin concentrations at the site of the infection to become much higher than can be achieved with systemic application. The release of gentamicin from the beads is a diffusion process as in all antibiotic-loaded bone cements [1]. Gentamicin-loaded PMMA beads, however, release much more gentamicin than solid bone cement plugs, mainly due to the greatly increased surface area of the many, relatively small beads (see Fig. 1).

Patients are treated with gentamicin-loaded beads during approximately 14 days, after which 20–70% of the total amount of gentamicin incorporated in the beads is released into the body and gentamicin concentrations drop greatly [2]. The main effect of gentamicin is therefore immediately after implantation of the beads and long-term implantation of the beads is of no value in combating infection. In clinical practice, the gentamicin-loaded beads are usually removed after 14 days, although permanent implantation is not absolutely contra-indicated. Removal must be weighed against the risk of leaving the beads in the human body. The gentamicin-loaded beads can act as a biomaterial surface to which bacteria preferentially adhere and grow. If a relapse occurs, the beads will form a biomaterial center of infection [3]. Likely, the slow release of gentamicin from the cement matrix into the local environment is an efficient way to induce and/or select for resistant small colony variants [4], as the onset to the development of overall antibiotic resistance of a strain.

Recently, we were confronted with a patient in whom these beads were left in situ for 5 years. Retrieval of gentamicin-loaded beads from this patient constituted an exceptional case to study the effects of long-term implantation on potentially colonizing microflora and gentamicin release.
2. Materials and methods

2.1. Retrieval of the gentamicin-loaded beads

Recently, a 70-year-old male patient of the orthopedic clinic of the Streekziekenhuis Coevorden-Hardenberg complained of pain, associated with his right hip prosthesis that was implanted 5 years earlier. Immediately after implantation of the hip prosthesis a hematoma occurred, with signs of inflammation. To prevent infection of the hip prosthesis, a chain of 30 gentamicin-loaded PMMA beads (Septopal; Merck Darmstadt; each bead contained 4.5 mg of gentamicin) was inserted in the soft tissue, without removal of the implant. For unknown reasons, however, the beads were never removed until causing problems recently. X-rays showed loosening of the right hip prosthesis and breakage of the chain with gentamicin-loaded beads. Consequently, the hip prosthesis and the gentamicin-loaded PMMA beads were removed. Loosing of the hip prosthesis was suspected to be septic, although routine hospital culturing of excised tissue revealed no bacteria.

2.2. Examination of the retrieved gentamicin-loaded beads

This case provided an opportunity to study beads after 5-year implantation. Residual gentamicin release was established using fluorescence polarization immunoassay and extensive microbiological culturing of the retrieved beads [5] was done to isolate infecting bacterial strains. Finally, the gentamicin sensitivity of the isolated strains was measured by a broth dilution test.

3. Results and discussion

Gentamicin-loaded PMMA beads implanted for treatment of orthopedic infections in patients for 3–36 weeks have been demonstrated to release high levels of antibiotic after retrieval [6]. This case shows that even after implantation for 5 years, PMMA beads remain able to release measurable amounts of gentamicin. Approximately 0.4 mg of gentamicin per bead was released after retrieval, as measured without breaking the cement matrix. This prolonged release of sub-inhibitory concentration of antibiotics is worrisome in the clinical application of antibiotic-loaded bone cement, as it stimulates the introduction of gentamicin-resistant strains. Previously, growth of a gentamicin-resistant staphylococcal strain on an infected total hip arthroplasty, fixed with gentamicin-loaded bone cement was described [7]. Also, in vivo studies have shown bacterial survival on gentamicin-loaded bone cement beads after two-stage revision surgery [5]. In this case, infectious bacteria were recovered from the surface of
the explanted beads, that were identified as gentamicin-resistant coagulase-negative staphylococci, CNS with a MIC equal to 10 \( \mu \)g/ml, well above the limit for gentamicin resistance, i.e. 4 \( \mu \)g/ml [8].

The presented observations raise the question whether infection in this patient, with gentamicin-resistant bacteria, could have been prevented when in the course of the past 5 years the beads would have been removed. Any biomaterial left in the human body must be considered as a potential focus for infection [9]. In this respect, biodegradable beads as carriers for antibiotics may be preferred, as they do not show long-term release of sub-inhibitory antibiotic concentrations. Moreover, no biomaterial is left in situ to act as a potential focus for infection. In vitro results have already shown that polycaprolactone beads, made of a bioresorbable polymer, have superior antibiotic elution characteristics compared with PMMA beads [10]. Also, hemihydrate of calcium sulfate, commonly known as plaster of paris, is a biodegradable antibiotic carrier that does not require removal and releases its entire antibiotic load on resorption [11]. Although such biodegradable antibiotic delivery systems are still in experimental stages, further development of biodegradable antibiotic-loaded beads will provide a novel approach in the future for the eradication of infection in joint arthroplasty.

In conclusion, the present case is a strong plea for the development of biodegradable antibiotic-loaded beads as an antibiotic delivery system.

References