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Review

Review: Emerging developments in the use of bioactive glasses for treating infected prosthetic joints

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ABSTRACT

Bacterial contamination of implanted orthopedic prostheses is a serious complication that requires prolonged systemic antibiotic therapy, major surgery to remove infected implants, bone reconstruction, and considerable morbidity. Local delivery of high doses of antibiotics using poly(methyl methacrylate) (PMMA) cement as the carrier, along with systemic antibiotics, is the standard treatment. However, PMMA is not biodegradable, and it can present a surface on which secondary bacterial infection can occur. PMMA spacers used to treat deep implant infections must be removed after resolution of the infection. Alternative carrier materials for antibiotics that could also restore deficient bone are therefore of interest. In this article, the development of bioactive glass-based materials as a delivery system for antibiotics is reviewed. Bioactive glass is osteoconductive, converts to hydroxyapatite, and heals to hard and soft tissues in vivo. Consequently, bioactive glass-based carriers can provide the combined functions of controlled local antibiotic delivery and bone restoration. Recently-developed borate bioactive glasses are of particular interest since they have controllable degradation rates coupled with desirable properties related to osteogenesis and angiogenesis. Such glasses have the potential for providing a new class of biomaterials, as substitutes for PMMA, in the treatment of deep bone infections.

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1. Introduction

Bacterial infection of articular prosthetic implants is a serious complication. Currently, there are more than 1 million prosthetic hip and knee replacement surgeries performed each year worldwide. With modern aseptic techniques and antibiotics, the incidence of prosthetic joint infections can be controlled at 1.5–2.5% for primary total hip arthroplasty (THA) or total knee arthroplasty (TKA), and 3.2–5.6% for revision THA or TKA [1]. Deep infection, one of the most challenging infections, occurs at rate of 0.3–4.0% for primary THA [2–5] and 0.4–4.0% for primary TKA [1,6–9]. The most common organism responsible for infections in orthopedic implants is *Staphylococcus aureus* (*S. aureus*) or

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coagulase-negative *Staphylococci* [10,11]. Bacterial cells can generally adhere and grow on implant surfaces and produce biofilms that contain complex communities of tightly attached bacteria to resist antimicrobial agents and host defenses [12,13]. Persistent antibiotic therapy or surgical intervention is generally used to cure infection. Most prosthetic implants infected by *S. aureus* require surgical removal [14]. Surgical removal of infected implants that are secured to periarticular bone results in skeletal deficiency and attendant difficulty in subsequent reconstruction [15]. The economic burden to healthcare systems associated with infected prosthetic joints is high, as the cost associated with revision surgery is estimated as 5–7 times higher than for primary operations [2,14,16].

Two major operations are usually required to treat infected prosthetic hips and knees. First, the infected implants and all infected tissue must be excised. The joint space is maintained with static or articulating spacers made of PMMA loaded with a high dose of antibiotics, while the patient is treated with systemic intravenous antibiotic therapy for several weeks. Upon resolution of the infection, removal of PMMA spacers and reconstruction of the joint with a new prosthesis can be performed. This so-called two-stage reimplantation technique is the current standard of care for infected joint replacements, and it is associated with prolonged antibiotic therapy, two major operations, and related morbidity and expense. Local delivery of high doses of antibiotics is desirable in treating implant-related bone infections. High local concentrations of antibiotics can facilitate the delivery of antibiotics by diffusion to avascular areas that are inaccessible by systemic antibiotics [17]. In some cases, infecting organisms that are resistant to drug concentrations achieved by systemic antibiotics are susceptible to the higher drug concentrations provided by local antibiotic delivery.

An ideal system for local delivery of antibiotics should provide controlled delivery of higher concentrations of antibiotics to the site of infection and yet minimize the risks of systemic toxicity associated with traditional methods of intravenous delivery. The delivery system should also provide a matrix for supporting bone regeneration. This is particularly advantageous in osteomyelitis associated with infected prosthetic implants in which bone loss is inevitable when well-fixed infected metal implants are removed.

A widely-used method for treating bacterial infection in orthopedic surgery has been to use poly(methyl methacrylate) (PMMA) cement as a carrier material for the antibiotics [17,18]. However, PMMA is not biodegradable, and provides a surface upon which secondary bacterial infection can occur [19,20]. Also, PMMA must be removed upon completion of antibiotic treatment at which time, assuming control of the infection, surgeons usually reimplant a new prosthesis. This so-called two stage resection and reimplantation strategy of treating deep bone infections in which the implants are contaminated with bacteria is complicated by bone loss related to the infection and to the removal of implants that are well-fixed to the skeleton [21].

There has been a considerable effort over the last three decades to develop local antibiotic delivery vehicles as alternatives to PMMA bone cement [17,18,22–25]. The main carrier materials used or under research and development for treating bacterial infection in orthopedic surgery are summarized in Table 1. Biodegradable materials have attractive characteristics as carriers for antibiotics because of the potential for reducing the risk of secondary infection and the avoidance of a second surgical procedure to remove foreign material. Some biodegradable carrier materials also provide the ability to vary the magnitude and duration of the antibiotic delivery through compositional and size control of the carrier material. Biodegradable polymers, whether synthetic or natural, have received considerable attention as potential carrier materials. Collagen sponge (or fleece) is the most widely used biodegradable polymer carrier material. However, studies have shown rapid antibiotic release rates in vitro [26,27] and conflicting results for its use as a carrier material [22]. Consequently, there has been interest in developing biodegradable polymer carrier materials with longer-lasting release rates. The synthetic biodegradable polymers, such as poly(lactic acid), PLA, poly(glycolic acid), PGA, and their copolymers, poly(lactic-co-glycolic acid), PLGA, with proven biocompatibility and controllable antibiotic release rates, have been widely studied [22–24].

Inorganic materials that are compatible with bone or promote bone formation have also been studied as alternative carrier materials to PMMA [22–24]. Calcium sulfate, $CaSO_4$, has been used as a biodegradable ceramic carrier material in the treatment of osteomyelitis [28]. The calcium phosphate biomaterials such as beta-tricalcium phosphate (β-TCP), $Ca_3(PO_4)_2$, and hydroxyapatite (HA), $Ca_{10}(PO_4)_6(OH)_2$, composed of the same ions as bone, are non-toxic and they do not elicit any immune reactions [29]. More recently, bioactive glass-based materials have shown promise as carrier systems for inhibiting bacterial growth in vitro and in eradicating osteomyelitis in animals and humans. In addition to providing a controlled delivery function, bioactive glass converts to an HA in vivo, bonds firmly to hard and soft tissues, and releases ions during the conversion process which have been shown to enhance bone formation [30–32].

The objective of this article is to review emerging developments in the use of bioactive glass-based materials as carriers for local delivery of antibiotics in the treatment of bone infection. After summarizing the biodegradable polymers and inorganic materials currently used or under development, this article provides a review of recent studies related to the development of bioactive glass-based carrier materials. Future directions in advancing the use of bioactive glass-based technology to clinical applications are discussed.

2. Biodegradable polymeric delivery systems

While other natural polymers such as chitosan and alginates have been studied [33–35], collagen sponge is the most widely used biodegradable polymer carrier material [24,36]. The material is produced as a three-dimensional (3D) porous carrier from Type I collagen, typically from sterilized animal skin or tendon. As a major component of connective tissues, collagen sponge has several desirable biological properties, such as biocompatibility and non-toxicity. Studies have shown rapid release rates from antibiotic-loaded collagen sponge, as well as conflicting results for the use of collagen as a carrier material. In vitro studies have shown that antibiotic release is rapid, with 95% of gentamicin released from collagen sponge in the first 1.5 h [27], and the release of gentamicin and vancomycin completed within 4 days [26]. It has been suggested that collagen sponge is not a suitable carrier material for the treatment of osteomyelitis because of its rapid antibiotic release rate [37]. In comparison, other studies have concluded that collagen sponge is an effective carrier material for up to 28 days in a rabbit model [38], and that it is more effective than PMMA clinically [39–41].

Biodegradable synthetic polymers have received interest because of the need for a carrier material with longer antibiotic release times than collagen. While several polymers have been studied, including polyanhydride and polycaprolactone [42], the biodegradable polyesters such as PLA, PGA and PLGA, with their proven biocompatibility, have received the most attention [43]. These polymers degrade into their monomeric forms (lactic or glycolic acid) and, in the process, they release the encapsulated antibiotics. Techniques for encapsulating antibiotics in these polyester carriers, such as the formation of microspheres, beads, or discs, have been investigated [44–48]. Manipulation of the polymer composition (e.g., ratio of PLA to PGA in the copolymer) and the material properties (e.g., molecular weight of the polymer, radius of microsphere carrier, porosity and geometry of the carrier) can lead to a wide range of clinically desirable release rates. In vitro elution studies have shown sustained release of high concentration of antibiotics for more than 32 days from compression-molded PLGA beads [44–46]. In addition, the effectiveness of antibiotic-loaded PLA, PGA and PLGA beads and rods for treating osteomyelitis in animal models has been shown [43,44,47,49,50].