Medical Hypotheses 105 (2017) 63–68

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

An intramedullary nail coated with antibiotic and growth factor nanoparticles: An individualized state-of-the-art treatment for chronic osteomyelitis with bone defects

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ARTICLE INFO

Article history:
Received 16 February 2017
Accepted 28 June 2017

Keywords:
Osteomyelitis
Nanoparticles
Bone morphogenetic protein
Insulin-like growth factor I
Polymer
Intramedullary nail
Individualized medicine

ABSTRACT

Among various infections, chronic osteomyelitis is one of the most challenging in terms of treatment. This infection is more common among patients with open fractures and those who have undergone elective orthopedic procedures. The treatment of osteomyelitis requires high antibiotic doses and an aggressive and multifaceted surgical approach. The use of parenteral antibiotics alone, without debridement, is not sufficiently effective, due to the formation of sequestra and the low vascularity of the affected area. The surgical options available for patients with chronic osteomyelitis include sequestrectomy, curettage, and intramedullary reaming, although these procedures usually result in bone defects that require further surgical intervention. Polymethyl methacrylate or calcium phosphate beads, impregnated with antibiotics, are commonly placed in such cases; however, this option has several disadvantages, including the need for future removal of cement, uncontrollable local release of antibiotics, and the need for broad-spectrum agents. The resulting bone defects also require additional treatments involving vascularized fibula grafting, intramedullary nails, use of techniques like Masquelet and Ilizarov, and even soft tissue transfers. All of these methods have certain limitations, such as the eventual requirement of more than one surgical event. Certain growth factors aid in the development and vascularization of new bone, such as bone morphogenetic proteins (BMPs) and insulin-like growth factor I (IGF-1). We propose that nanoparticles of BMPs, IGL-1, and microorganism-specific antibiotics can be placed on the surface of intramedullary nails. These nanoparticles can be attached to various different polymeric materials such as poly(D,L-lactide), which is a biocompatible and biodegradable polymer, and can be positioned in several layers, to ensure controlled and systematic release. The placement of nanoparticles at the infection site alone will also ensure local delivery of the drugs only to the required areas. Moreover, these intramedullary nails will be useful for both infected non-unions and mal-unions. Over time, the nanoparticles will eradicate the infection and stimulate new healthy bone formation, whereas the intramedullary nail itself will provide constant stability and immobilization. This model provides new and revolutionary ideas for the development of individualized technologies in medicine.

Introduction

Osteomyelitis has been one of the most challenging and problematic conditions encountered by orthopedic surgeons and infectious disease specialists over the past several years. The incidence of osteomyelitis after elective orthopedic surgery ranges from 0.7% to 4.2% [1]. The incidence of osteomyelitis is greater in trauma patients, particularly in cases with open fractures; this incidence can reach approximately 1% following surgical osteosynthesis of closed low-energy fractures and may increase to >30% in cases of complicated open tibia fractures [1,2]. Up to 5% of cases with fractures of the lower extremity experience delayed healing or non-union [3,4].

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http://dx.doi.org/10.1016/j.mehy.2017.06.023
0306-9877/

The bone is well protected against external pathogens. However, this feature may represent a double-edge sword from a clinical standpoint, as it may not only resist infection to some extent, but may also resist the therapy administered for these infections. Early diagnosis is vital for successful management of osteomyelitis, along with the use of appropriate antimicrobial and surgical treatments based on the principles described by Cierny in 1983 [5,6].

Osteomyelitis is characterized by inflammation of the bone, induced by an infecting organism. This infection can be restricted to a particular section of the bone or it may comprise several segments including the bone marrow, cortex, periosteum, and the adjacent soft tissues. The most common causative agents are *Staphylococcus aureus* and *S. epidermidis*; however, other bacteria, fungus, viruses, and mycobacteria can also cause osteomyelitis [5]. The condition is classified as acute, subacute, or chronic [5]; acute and subacute osteomyelitis can be successfully treated with antibiotics alone, whereas chronic osteomyelitis requires surgical treatment and oral and parenteral antibiotic therapy for several weeks or months to successfully eradicate the infection [5–8].

One of the problems with chronic osteomyelitis is the formation of sequestra, which are areas of dead infected bone contained by a compromised envelope of soft tissue. The infected foci in the bone are delimited by sclerotic and somewhat avascular bone that is enclosed by thickened periosteum, muscle, and subcutaneous tissue. This scar tissue cover, which is avascular, reduces the effectiveness of systemic antibiotics (Fig. 1) [5,9].

The treatment of chronic osteomyelitis usually requires comprehensive aggressive surgical procedures, including the debridement of infected and dead bone, sequestrectomy, curettage, and dead-space management [5,10]. If the surgical treatment is not sufficiently aggressive, the infection will persist and recurrence may develop. However, extensive debridement can also lead to the formation of a considerable large area in the bone that requires multiple procedures to fill (Fig. 1) [5,8]. Polymethyl methacrylate (PMMA) beads impregnated with antibiotics are usually used to fill such defects, although this approach has several clinical limitations, including their non-biodegradable nature, the need for a second surgical intervention to remove the cement, insufficient antibiotic release following an initial burst, and the lack of mechanical stability [9–14]. Moreover, this method can result in antibiotic resistance, proneness to biofilm formation, and a moderate toxicity resulting from the absorption of methyl methacrylate (MMA) monomers via the carboxylesterase-mediated conversion of MMA to methacylic acid [10]. Studies have found that the released antibiotics from the cement fall under the detection threshold following 1 week of implantation, and that merely 4–17% of the incorporated antibiotic (gentamicin) is effectively liberated [14,15]. One encouraging technique to reduce the release rate and suppress the primary flare is to encapsulate the drug-loaded nanoparticles within thin polymer layers [5,7,16]. Another alternative method for reducing the rapid discharge of growth factors involves the use of heparin-based liberation methods. As a greatly negatively charged linear polysaccharide, heparin has a great binding affinity for many growth factors, including bone morphogenetic proteins (BMPs) [17]. In addition to treatment with PMMA, calcium sulfate cements represent another option for ensuring sustained release.

However, these alternatives are also associated with disadvantages such as the rapid degradation time scale (weeks), which is shorter than the bone in-growth rate. This limits the capacity of the material to release substantial amounts of drugs for an extended period of time [7]. These alternatives can also lead to severe inflammation, secondary to the overabundance of calcium ions; accordingly, the material would resist the encapsulation of drugs due to intercalation. Furthermore, when using such material, it has been found that 80–90% of the drug is desorbed within the first minutes of contact with saline solution or blood [7].

Several surgical options are available for the treatment of chronic osteomyelitis, including sequestrectomy, curettage, antibiotic bead pouch use, intramedullary antibiotic cement nail use,

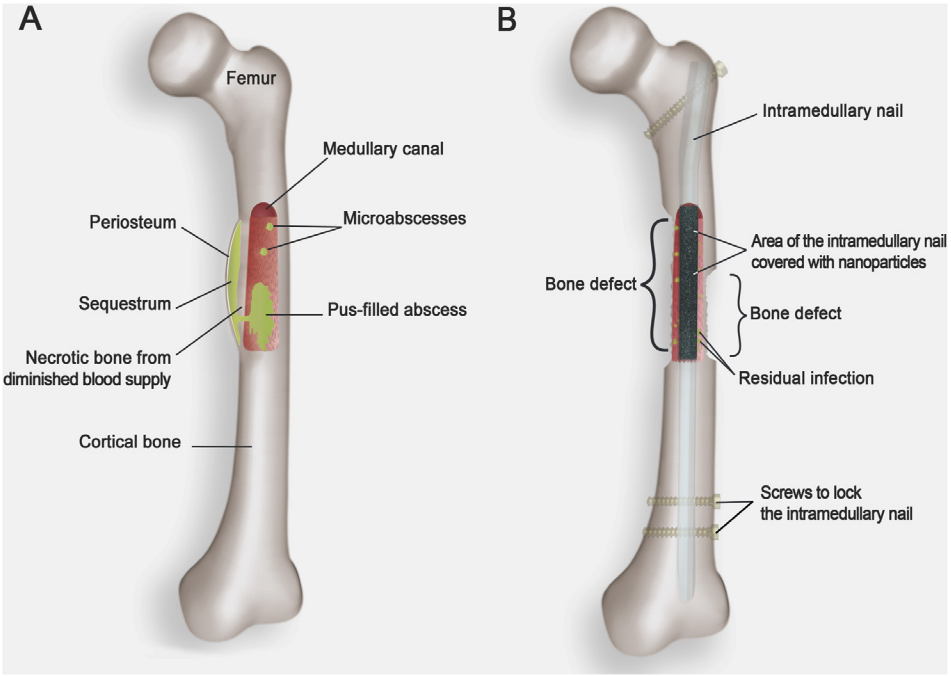

Fig. 1. (A) Chronic osteomyelitis of the femoral shaft. The infection starts with the formation of an intramedullary abscess, which then penetrates into the cortical bone to form a sequestrum (an area of necrotic bone within a compromised soft tissue envelope [periosteum]). Note the formation of multiple satellite microabscesses. (B) Image of the femur after extensive surgical debridement, curettage, and sequestrectomy is performed. The surgery involves the removal of large quantities of bone, which can affect bone stability. Moreover, it is impossible to remove all the infected tissue. The placement of a locked intramedullary nail is required to ensure bone stability. Note that only the nail surface in contact with the infected area is covered with nanoparticles.