Osteomyelitis Treated with Antibiotic Impregnated Polymethyl Methacrylate

Hsueh-Yu Li, Kyu-Ho Yoon, Kwan-Soo Park, Jeong-Kwon Cheong, Jung-Ho Bae, Jung-Gil Han, Hyung-Koo Park, Jae-Myung Shin¹, Ji-Sun Baik¹

Department of Oral and Maxillofacial Surgery, Inje University Sanggye Paik Hospital,

¹Department of Oral and Maxillofacial Surgery, Inje University Ilsan Paik Hospital

Abstract

Chronic osteomyelitis is an infection and inflammation of the bone or bone marrow, causing ischemia in bone marrow due to lack of blood, nutrients, and oxygen supply to the bone marrow, eventually leading to necrosis of bone marrow. A current method for treatment of chronic osteomyelitis is administration of systemic antibiotics followed by removal of the infected bone and tissues. Because infected tissue of chronic osteomyelitis is surrounded by avascular necrotic bone, supply of blood and antibiotics to the infected area is diminished. For effective treatment, high plasma concentrations of antibiotics should be provided for a prolonged period. However, long term high serum level of antibiotics may result in undesirable adverse effects. For delivery of a sufficient concentration of antibiotic to the infected area while avoiding the adverse effect, implantation of a local antibiotic delivery system is suggested. One of the implantation systems that has been utilized is antibiotic impregnated polymethyl methacrylate.

Key words: Polymethyl methacrylate, Drug delivery system, Osteomyelitis, Mandible, Infection

Introduction

Chronic osteomyelitis is an infection and inflammation of bone or bone marrow, causing ischemia in bone marrow due to lack of blood, nutrients, and oxygen supply to the bone marrow, eventually leading to necrosis of bone marrow. A current method for treatment of chronic osteomyelitis is administration of systemic antibiotics followed by removal of infected bone and tissues. Because infected tissue of chronic osteomyelitis is surrounded by avascular necrotic bone, supply of blood and antibiotics to the infected area is diminished. For effective treatment, high plas-

ma concentrations of antibiotic should be provided for a prolonged period. However, long term high serum level of antibiotics may result in undesirable adverse effects, such as nephrotoxicity, neurotoxicity, and hepatotoxicity. For delivery of a sufficient antibiotics concentration of antibiotic to the infected area while avoiding the adverse effect, implantation of a local antibiotic delivery system is suggested. One of the implantation systems that has been utilized is antibiotic impregnated polymethyl methacrylate (PMMA).

The original successful use of antibiotic impregnated PMMA was reported in 1970 by Buchholz and Engelbrecht[1]

RECEIVED August 2, 2013, REVISED October 3, 2013, ACCEPTED November 26, 2013

Correspondence to Jung-Ho Bae

Department of Oral and Maxillofacial Surgery, Inje University Sanggye Paik Hospital

1342 Dongil-ro, Nowon-gu, Seoul 139-707, Korea

Tel: 82-2-950-1161, Fax: 82-2-950-1167, E-mail: bgeneral@paik.ac.kr

© This is an open access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

in their treatment of an infected hip prosthesis. In 1976, Klemm[2] introduced a method for treatment of osteomyelitis by means of gentamicin impregnated PMMA. In 2007, Coviello and Stevens[3] successfully used antibiotic impregnated PMMA in treatment of chronic osteomyelitis of the mandible. We experienced favorable results with antibiotic impregnated PMMA for treatment of chronic osteomyelitis on the mandible. Therefore, we report this case with a review of the literature.

Case Report

A 70-year-old male patient was referred to the Department of Oral and Maxillofacial Surgery in Sanggye Paik Hospital with a history of sustained gingival swelling and pain on the left mandible after extraction of the left mandibular second premolar. At the first visit, a pus draining intraoral fistula, which had existed for 14 days, was observed in the left mandible. Panoramic radiograph and computed

tomography showed an osteolytic appearance from the first molar to the third molar in the left mandible (Fig. 1, 2).

Under the diagnosis of osteomyelitis, tooth extraction and surgical curettage were performed (Fig. 3). Severe destructed cancellous bone, which extended widely to the ramus, was observed during surgery. Therefore, the surgeon decided to cease the operation after surgical curettage (Fig. 4). Although it could be regarded as an indication of mandibulectomy, the surgeon decided to try a conservative method first.

The surgery team searched for other treatment methods for conservative management of the wide lesion of the mandible. In the process of searching, a treatment option using antibiotic impregnated PMMA was found. In the field of orthopedics, implantation of local antibiotic delivery system has been used for treatment of osteomyelitis of iliac, hip, and patella since the 1970s. Antibiotic impregnated PMMA is one of the mentioned implantation systems. Some journal of oral and maxillofacial surgery have reported suc-

Fig. 1. Panoramic radiograph from the first visit: shows loss of alveolar bone on the left mandible and loss of teeth on the left mandibular second premolar and second molar.

Fig. 3. First post-operation panoramic radiograph: tooth extraction and surgical curettage were performed.

Fig. 2. Facial bone computed tomography from the first visit: shows an osteolytic lesion on the left mandible (A, B).

successful cure of osteomyelitis using antibiotic impregnated PMMA in the mandible. With the patient's consent, the second operation was performed six days after the first operation. The surgeon performed the second operation so that the antibiotic impregnated PMMA beads were inserted on the infected focus for application of high concentrations of antibiotics locally.

Antibiotic impregnated PMMA is molded in the shape of a bead during the operation. The bead manufacturing method is as follows: After mixing monomer with 1 g of Vancomycin and 20 g of PMMA powder containing gentamicin, an operator made several 7 mm-diameter beads in dough stage and strung some of those on 26-gauge steel wires. During the second surgery, via an intraoral approach, the operator removed the infected cancellous bone, then inserted some strings of beads into the dead

space, and finally closed the wound tightly (Fig. 5, 6).

At postoperative follow-up one week later, dehiscence had occurred at the operative site; however, epithelization was observed. Considering the period for the maintenance of an effective concentration of the antibiotics and promotion of wound healing, our team planned removal of the antibiotic impregnated beads four weeks after the operation under local anesthesia (Fig. 7). It was observed that fibrous tissue filled the area (Fig. 8, 9). The anterior part was sutured; however, the posterior part was packed with Vaseline-gauze (Fig. 10). At follow-up six months later, our team did not observe recurrence of the lesion, and favorable healing was observed (Fig. 11, 12).

Fig. 4. Intra-operation intraoral photograph. Severely destructed cancellous bone on the mandibular body and ramus is observed.

Fig. 5. Second post-operation panoramic radiograph. Saucerization and antibiotic impregnated polymethyl methacrylate insertion are performed.

Fig. 6. Antibiotic impregnated polymethyl methacrylates are inserted into dead space (A) and the wound is closed (B).

Fig. 7. Post-operation intraoral photograph (after 30 days). Antibiotic impregnated polymethyl methacrylates are partially exposed due to excessive tension.

Fig. 8. Inner aspect after removal of antibiotic impregnated polymethyl methacrylate.

Fig. 9. Antibiotics impregnated polymethyl methacrylate with wire.

Fig. 10. The wound was closed and vaseline gauze was inserted.

Fig. 11. Six months after panoramic radiograph.

Fig. 12. Six months after intraoral photograph.

Discussion

Osteomyelitis (OM) is infection and inflammation of bone or bone marrow. It can be classified according to some subtypes by the presence of suppuration, length of disease, and area of the skeleton (for example, suppurative and sclerosis, acute and chronic). Chronic OM is defined as the presence of OM for more than one month, and could present at any age, more commonly in females, with pain and local swelling, which may or may not be accompanied by diffuse sclerosis or an area of irregular radiolucency with loss of a trabecular pattern may appear. In histological examination, a chronic inflammatory response within bone, predominantly involving plasma cells, with osteoblast proliferation and new bone formation is seen.

Chronic OM causes ischemia in bone marrow by diminishing blood supply and eventually leads to necrosis of bone and bone marrow. The necrotic bone and tissues not only decrease vascularity but also provide a good substrate for bacterial proliferation and colony formation,

There are some treatment options: 1) removal of the infected bone and tissues, 2) long-term high concentration of parenteral antibiotic therapy, 3) systemic steroid therapy, and 4) hyperbaric oxygen therapy. Each treatment option has its own merits and limits[4].

Removal of affected bone has the following merits: 1) Reduction of necrotic and avascular bone. 2) Reduction of bacterial counts. 3) Promotion of revascularization by bringing well vascularized soft tissue into contact with the exposed surface of the diseased bone[4]. However, it alone cannot remove microorganisms. In cases of systemic antibiotic therapy, it is not easy to maintain minimum inhibitory concentration (MIC) level at the infected site. In addition, there is a chance of side effects, such as nephrotoxicity, neurotoxicity, hepatotoxicity, etc. Although treatment with systemic steroids can result in dramatic reduction of symptoms, these recur rapidly upon cessation of therapy. Use of hyperbaric oxygen is impractical, requiring access to a hyperbaric chamber and periods of treatment ranging between 10 and 320 hours[4].

Local antibiotic delivery systems must provide high concentration of antibiotics in a localized site for extended periods of time, while simultaneously maintaining low serum concentrations in order to avoid systemic deleterious effects. Characteristics of the drug carrier include stability, nontoxic, and easily formed, and of such a consistency as to allow its easy placement and removal from the surgical site[5]. The antibiotic impregnated PMMA beads system has the characteristics mentioned above. It has been used successfully in the department of orthopedics for more than 40 years. Originally, in 1970, Buchholz and Engelbrecht[1] used PMMA antibiotic-impregnated bone cement in their treatment of an infected hip prosthesis. Klemm[2] first applied gentamicin impregnated PMMA beads for treatment of osteomyelitis in 1976.

Antibiotics mixed with PMMA should not only be effective against OM pathogens, but also sufficiently stable in the face of high temperatures in order to prevent degradation during the curing process of the cement[5]. Regarding drugs of choice, gentamicin and tobramycin are the antibiotics most commonly used for treatment of OM at the department of orthopedics[5]. They are aminoglycosides, possess a broad spectrum of activity against gram-negative and some gram-positive organisms, and have thermal

stability. In addition to the two antibiotics mentioned above, beta-lactam and clindamycin are also appropriate[6,7].

Recently, two different antibiotics have been used more frequently in treatment of orthopedic infections[8,9]. Vancomycin is used primarily with aminoglycoside. There is a synergistic effect between aminoglycosides and glycopeptides with regard to antimicrobial properties and pharmacokinetics of bone cement[10]. *In vivo* studies conducted in 1998 showed that the elution of vancomycin was enhanced by the presence of tobramycin[9].

Elution of antibiotics from antibiotic impregnated PMMA beads is highest on post-operative day 1, and the concentrations show constant decay at a similar rate over the following days[11]. The period of time in which PMMA beads cannot elute enough antibiotics and local concentration is below MIC is controversial. However, journals have recently recommended approximately two weeks for the time of bead removal in case of gentamicin and vancomycin use, assuming that they are not to be used as space maintainers for subsequent reconstruction[5,11]. One study reported that gentamicin- and vancomycin-loaded beads and hip spacers appear to be capable of releasing sufficient concentrations over the first 7 to 13 postoperative days *in vivo*[11]. Another journal reported formation of a dense fibrous capsule around the beads. This, it seems, would in time lead to a significant reduction in the ability of the antibiotics, from day 8 to day 14[5].

In addition to local implantation of antibiotic impregnated PMMA beads, systemic antibiotic is still necessary, over the first 4 to 6 postoperative weeks, in order to avoid not only spread of the infection, but also persistence of the infection locally[11].

In the case of antibiotic impregnated PMMA bead implantation, the dose of the parenteral antibiotic could be reduced over the first two postoperative weeks due to sufficiency of local antibiotic therapy; however, after this time period, a re-adjustment of the dose might be necessary in order to prevent the emergence of resistant bacterial strains. One report recommends use of systemic antibiotics for at least the first four postoperative weeks.

Not surprisingly, the successful treatment advocated includes antibiotic therapy, curettage, and local resection. Patients would benefit from application of antibiotic im-

pregnated PMMA. Although the results of our treatment are encouraging in the short term, we await long-term follow-up, appreciating the limitations of our presentation.

References

1. Buchholz HW, Engelbrecht H. Depot effects of various antibiotics mixed with Palacos resins. *Chirurg* 1970;41:511-5.
2. Klemm K. Treatment of chronic bone infections with gentamicin-PMMA chains and beads. *Accid Surg* 1976;1:20-5.
3. Coviello V, Stevens MR. Contemporary concepts in the treatment of chronic osteomyelitis. *Oral Maxillofac Surg Clin North Am* 2007;19:523-34.
4. Grime PD, Bowerman JE, Weller PJ. Gentamicin impregnated polymethyl methacrylate (PMMA) beads in the treatment of primary chronic osteomyelitis of the mandible. *Br J Oral Maxillofac Surg* 1990;28:367-74.
5. Chisholm BB, Lew D, Sadasivan K. The use of tobramycin-impregnated polymethyl methacrylate beads in the treatment of osteomyelitis of the mandible: report of three cases. *J Oral Maxillofac Surg* 1993;51:444-9.
6. Levin PD. The effectiveness of various antibiotics in methyl methacrylate. *J Bone Joint Surg Br* 1975;57:234-7.
7. Picknell B, Mizen L, Sutherland R. Antibacterial activity of antibiotics in acrylic bone cement. *J Bone Joint Surg Br* 1977;59:302-7.
8. Anagnostakos K, Fürst O, Kelm J. Antibiotic-impregnated PMMA hip spacers: Current status. *Acta Orthop* 2006;77:628-37.
9. Masri BA, Duncan CP, Beauchamp CP. Long-term elution of antibiotics from bone-cement: an in vivo study using the prosthesis of antibiotic-loaded acrylic cement (PROSTALAC) system. *J Arthroplasty* 1998;13:331-8.
10. Anagnostakos K, Kelm J, Regitz T, Schmitt E, Jung W. In vitro evaluation of antibiotic release from and bacteria growth inhibition by antibiotic-loaded acrylic bone cement spacers. *J Biomed Mater Res B Appl Biomater* 2005;72:373-8.
11. Anagnostakos K, Wilmes P, Schmitt E, Kelm J. Elution of gentamicin and vancomycin from polymethyl methacrylate beads and hip spacers in vivo. *Acta Orthop* 2009;80:193-7.