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Treatment of infected total knee arthroplasty by a local drug-delivery system with retention of the metal components

Jun Aikawa, Ken Urabe, Mamoru Fujita, Hiroaki Minehara, Kouji Naruse, Dai Iwase, Moritoshi Itoman, Masashi Takaso

Department of Orthopaedic Surgery, Kitasato University School of Medicine

Objectives: To evaluate the use of antibiotic-impregnated calcium phosphate cement (CPC) for the treatment of infected total knee arthroplasty while retaining the metal components.
Methods: Five infected knees in 5 patients (2 rheumatoid arthritis, 3 osteoarthritis; average age 71 years) were examined after an average postoperative follow-up period of 45 months. The causal bacteria were methicillin-sensitive *Staphylococcus aureus* in 1 case, *Staphylococcus sp.* in 2, *Staphylococcus epidermidis* in 1, and *Streptococcus agalactiae* in 1. Arthrotomy and anterior capsulectomy was performed. Infected bone lesions identified on radiographs and computed tomography were thoroughly removed by curettage. Bone defects caused by curettage were subsequently filled with antibiotic-impregnated CPC to allow retention of the metal components.
Results: Retention of the metal components was made possible when the infection subsided in 4 of the 5 cases. The Japanese Orthopaedic Association scores used to evaluate treatment were comparable before and after treatment in those 4 cases but not the one in which infection was not controlled by antibiotic treatment.
Conclusion: Arthrotomy, anterior capsulectomy, thorough debridement with curettage of any infected osseous lesion, and filling the defect with antibiotic-impregnated CPC allowing retention of the metal components proved to be a useful treatment for infected total knee arthroplasty.

Key words: total knee arthroplasty, infection, calcium phosphate cement, retention

Introduction

The incidence of infection after total knee arthroplasty (TKA) has declined as the medical environment has improved. However, infection as a complication of TKA is still a critical problem and has been reported to occur in approximately 1% of cases.[1] Administration of antibiotics, lavage, and debridement may allow retention of the metal components in cases of early postoperative infection or acute hematogenous infection.[2] In general, however, one-stage or two-stage exchange (of components), resection arthroplasty, arthrodesis, and amputation of the lower extremity are the treatment options.[3] Removal of the metal components is often required.

Two-stage reimplantation revision surgery has emerged as the standard method of care for a late chronic infection at the site of a TKA.[4] In the first stage, the components are removed by debridement and synovectomy, including resection of part of the articular capsule, and then an antibiotic-impregnated cement spacer is put in place to prepare for the second stage of the revision arthroplasty after the infection has subsided. Although infection can be controlled by two-stage reimplantation revision arthroplasty better than by one-stage revision arthroplasty,[5,6] two-stage reimplantation revision arthroplasty is associated with various problems: it is a more invasive treatment for the patient, it can cause muscle weakness of the lower extremities and diminished range of motion in the knee joint, and it requires long-term hospitalization.

An alternative approach, involving treatment of the infection while retaining the components, has also been reported. In a retrospective examination of 60 cases of infected TKA and analyses of the 7 knees that showed subsidence of the infection among the 39 knees for which retention of the implant was attempted, Burger et al.[7] reported the following as potential factors favoring

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Correspondence to: Jun Aikawa and Ken Urabe, Department of Orthopaedic Surgery, Kitasato University School of Medicine
1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan
E-mail: jun-aikawa@jcom.home.ne.jp, kenurabe@med.kitasato-u.ac.jp

retention: (1) treatment within 2 weeks after the first signs of infection; (2) infection by gram-positive bacteria sensitive to antibiotics; (3) no infection involving the surgical wound, absence of prolonged postoperative drainage, or the development of a sinus tract; and (4) no prosthetic loosening or signs of infection on radiography.[7]

To explore the potential for retention of the metal components, we treated infected TKA cases, including those with long-term infection and signs of chronic infection shown on radiography, by arthrotomy, anterior capsulectomy,[8] curettage of the infected osseous lesion, and filling the osseous defect with antibiotic-impregnated calcium phosphate cement (CPC).

Materials and Methods

Of the infected TKA cases diagnosed from 2003 onwards at our hospital, 5 knees in 5 patients that were followed up for 3 years or longer after final surgery were examined. All 5 patients underwent surgery to eradicate infection performed by one senior surgeon. During this period, the surgeon operated on 11 cases of infected TKA. Two patients underwent debridement and continuous irrigation, and 3 patients underwent two-stage reimplantation revision surgery because treatment of infected TKA with retention of metal components was not launched at their surgeries. Two-stage revision surgery was selected for 1 case instead of treatment of infected TKA with retention of metal components because multiple operations were performed in the previous hospital. The average age at surgery was 71 years (range 50-83 years), and the average post-operative follow-up period was 45 months (range 36-59 months). Two patients had rheumatoid arthritis (RA) and 3 had osteoarthritis, and the causal bacteria were methicillin-sensitive *Staphylococcus aureus* (MSSA) in 1 case, *Staphylococcus sp.* in 1, *Streptococcus agalactiae* in 1, and *Staphylococcus epidermidis* in 2 cases. Details of the cases are shown in Table 1. The period from the onset of symptoms to the operation was 1 month or more in 4 cases. Only Case 3 was treated relatively soon during the acute phase. The study was approved by the Institutional Review Board of the Kitasato University Hospital (Approval number: C rin 08-486).

With regard to the patients' co-morbidity, 2 patients had diabetes. One patient with RA had received an oral corticosteroid, and 1 patient was treated with etanercept injected subcutaneously. One patient had had malignant melanomas on the ipsilateral sole and had undergone tumor resection and popliteal lymphadenectomy.

Infected TKA was diagnosed based on local findings, white blood cell counts and fractions, C-reactive protein (CRP) values, erythrocyte sedimentation rate, and isolation of bacteria from synovial fluid collected by puncture and aspiration. The color and glucose content of the synovial fluid (blood sugar levels at half or below

Table 1. The patients' characteristics

Case No.	Age (years)	Disease	Period from first operation to signs of infection	Period from onset of symptoms to operation	Causal bacteria	Complications	Period of antibiotic treatment (antibiotics)	Postoperative period	Pretreatment JOA score	Posttreatment JOA score
1	75	OA	10 mo	7 mo	*Staphylococcus epidermidis*	Diabetes	3 d (CEZ)	4 y 11 mo	80	80
2	74	RA	2 y 8 mo	4 mo	*Staphylococcus sp.*	Steroid	12 d (CEZ)	3 y 5 mo	45	50
3	50	RA	2 mo	1 wk	MSSA	Etanercept	25 d (MINO), 1 wk oral intake (CFPN-PI)	3 y	80	85
4	73	OA	4 y 9 mo, knee swelling 7 mo after surgery for malignant melanoma	1 mo	*Streptococcus agalactiae*	Malignant melanomas on the sole, diabetes	6 mo (MINO)	4 y 3 mo	70	40
5	83	OA	2 y 3 mo	3 mo	*Staphylococcus epidermidis*	Diabetes	3 d (MINO)	3 y 2 mo	65	65

RA, rheumatoid arthritis; OA, osteoarthritis; MSSA, methicillin-sensitive Staphylococcus aureus; MINO, minocycline hydrochloride; CEZ, cefazolin sodium; CEPN-PI, cefcapene pivixil hydrochloride

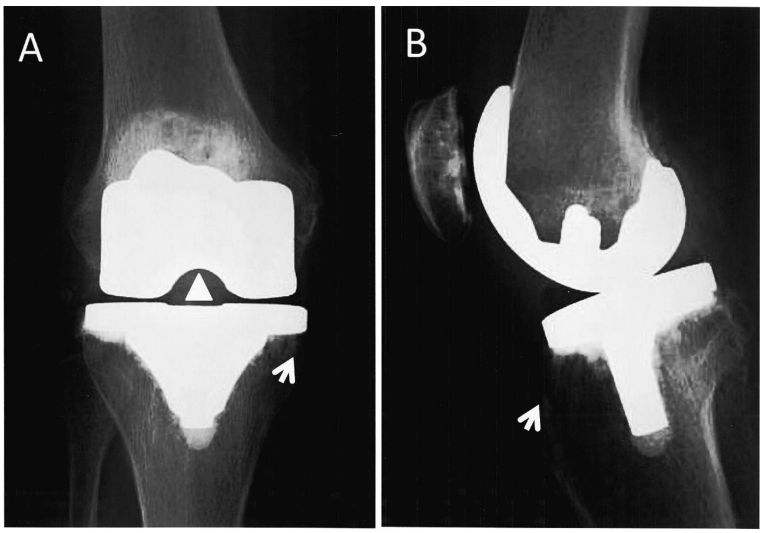

Figure 1. Preoperative radiographs

(**A**) anterior-posterior view of the knee joint, (**B**) lateral view of the knee joint. Radiolucent bone lesions can be observed at the lower medial side of the tibial components (white arrow ↑) and the femoral intercondylar fossa (white arrowhead △).

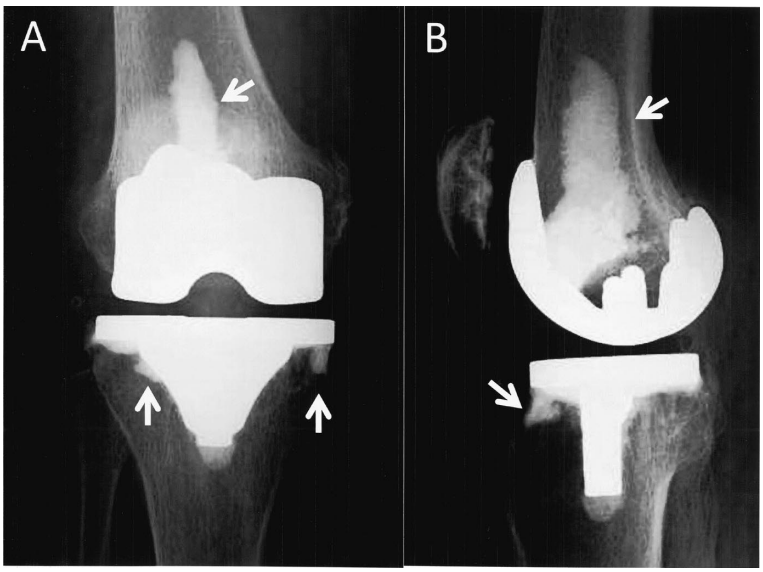

Figure 2. Postoperative radiograph

(**A**) anterior-posterior view of the knee joint, (**B**) lateral view of the knee joint. The femoral intercondylar fossa and the bone marrow were filled with antibiotic-impregnated calcium phosphate cement (white arrows).

normal values) were referenced. Before surgery, radiolucent bone images around the components were evaluated by knee joint radiographs taken from 4 directions (anterior-posterior, lateral, and bilateral oblique views) (Figure 1) and by computed tomography (CT).

All 5 patients underwent arthrotomy with debridement. Synovectomy, including resection of part of the articular capsule (anterior capsulectomy[8]), and thorough debridement were performed. Infected bone lesions identified on radiographs and CT images before surgery, and any cancellous bone surrounding them, which was found to be fragile during the operation, were thoroughly removed by curettage. The joint was subsequently lavaged with more than 10 L of physiological saline solution. The osseous defect was then filled with 2 mg of vancomycin (VCM)-impregnated CPC (Biopex; HOYA Corporation, Tokyo) (Figure 2). In all 5 cases, only the bearing insert was replaced, and the metal components were retained.

Prophylactic antibiotics were infused intravenously for 3 days including the operative day. Oral antibiotics were not administrated except in Case 4, where oral medication was continued because of recurrent infection. Evidence that infection had resolved was based on negative CRP (CRP levels before infection in RA patients) and disappearance of signs of infection, e.g., redness, swelling, and pain at the affected knee joint.

Knee function and range of motion were evaluated before the onset of infection and at the final observation. Knee joint function was evaluated using the Japanese Orthopaedic Association (JOA) score.

Results

Infection subsided in 4 of the 5 cases. However the TKA infection did not subside following our treatment regimen in the patient with a history of resection of malignant melanoma on the ipsilateral sole. In this case lymphatic edema of the lower extremity was severe due to popliteal lymphadenectomy, and the wound left from lymphadenectomy became open to the joint, which resulted in reinfection. Postoperative chemotherapy was scheduled and performance of two-stage reimplantation revision arthrotomy was difficult. Because continuation of oral antibiotics failed to resolve the infection, curettage and debridement with retention of the metal components and filling with vancomycin-impregnated CPC were performed again 6 months after the first operation. This patient has now been followed up for 4 years and 3 months postoperatively. Antibiotic treatment was continued for 6 months after reoperation; and, to date, the infection is under control without medication.

Figure 3 shows changes in the JOA score before and after treatment of the infection. Knee joint function did not deteriorate in the 4 cases in which the infection subsided. Due to ipsilateral lymphedema in Case 4, the range of motion and walking capacity decreased, and the JOA score decreased from 70 points before infection to 40 points after treatment.

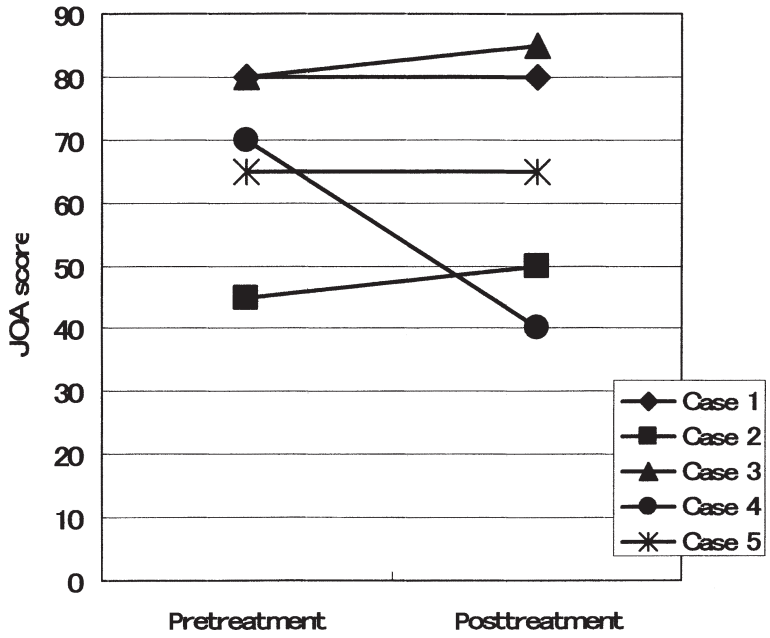

Figure 3. Changes in the Japanese Orthopaedic Association (JOA) scores before and after treatment of infection

Discussion

There is one report suggesting the possibility that components can be retained in infected TKA, if the infection is treated at an early stage of postoperative infection or during the acute phase of hematogenous infection.[9] Borden et al.[9] were able to bring inflammation under control and preserve the components in 5 of 6 cases which were treated during the acute phase, whereas relapses occurred in all of 5 cases of chronic infection. They assumed from these results that debridement combined with an antibacterial agent could probably cure infected TKA if treatment was initiated during the acute phase within 2 weeks after the operation or within 2 weeks of the appearance of signs or symptoms of infection. They suggested that a surgical-site infection could be controlled under retention of the metal components prior to subsequent development of osteomyelitis. In the majority of TKA cases, infection, if it occurs, takes a chronic course since infection occurs insidiously or its diagnosis takes a long time. Schoifet et al.[10] reported that component preservation was difficult in patients that had presented with signs or symptoms of infection 4 weeks or more before treatment. Therefore, chronic infection is generally treated either with 1-stage reimplantation or with 2-stage reimplantation revision knee arthroplasty.[2,11] This is also the case in our hospital where reimplantation revision arthroplasty has been performed following removal of metal components and subsequent infection control by means of placing a cement spacer containing an antibacterial agent. However, there are problems with such 2-stage reimplantation revision arthroplasty as follows. The procedure is highly invasive for the patient. The patient experiences reduced muscle power of the affected limb and reduced range of motion of the affected knee joint. A longer period of hospitalization is mandatory. And operative procedures are not easy. We, therefore, thought that we should develop a therapeutic method that could preserve the metal components, even in cases of chronic indolent or insidious periprosthetic infection.

When treatment is attempted while retaining components, the first problem to be solved is how to kill the bacteria inhabiting the bone marrow. Our solution was to dissect out a portion of the cortex that was detected by preoperative radiography and CT and to thoroughly remove the infected bone marrow. We conceived the idea of administering an antimicrobial agent locally to any bone defects resulting from bone marrow curettage. However, it is known that bacteria form biofilms on implants. These biofilms protect the organisms from the host's immune system and prevent penetration of antibiotics. Nishimura et al.[13] reported that the concentration of an antibacterial agent required to kill biofilm-forming bacteria was 500- to 1,000-fold as high as that required to kill planktonic bacteria. Therefore, we would need to use a drug delivery system capable of slowly releasing an antibacterial agent in a large quantity and more efficiently at a local site to succeed in preserving the implants.

Recently, there have been several reports on the therapeutic use of antibacterial agent-containing CPC paste, which was developed as a filling material for bone defects, in the management of bone or joint infection, and there have also been reports on basic experiments using CPC.[13-15]

Sasaki et al.[14] used Surgical Simplex (Hawmedica International, London, UK) as the polymethylmethacrylate (PMMA) and Biopex as the CPC and directly compared the elution efficiency of VCM. The elution level from the CPC beads was 13.2-fold greater on day 1, 60.8-fold greater on day 3, and 62.6-fold greater on day 7 than that from PMMA beads. In addition, they reported that VCM-containing CPC eradicated infection in the treatment of osteomyelitis and in infected TKA when used in a 2-stage protocol. We performed an elution test on specimens of CPC (Biopex) and PMMA (Cemex RX), both of which were equivalent with respect to the amount of cement as well as the content of VCM, to evaluate the concentration, drug activities, and material in the eluate.[16] More VCM flowed out over a longer time from CPC (Biopex) impregnated with 2.5% VCM compared to PMMA (Cemex RX) impregnated with the same amount of VCM. VCM contained in CPC (Biopex) or in PMMA (Cemex RX) was found not to have been denatured by the production process of polymerization, maintaining unchanged drug activity and concentration as determined by high-performance liquid chromatography (HPLC) after elution. We concluded from the studies mentioned above that it would be possible for locally-administered VCM to kill biofilm-forming bacteria by the following procedure. Scrap off foci of infection within the bone marrow and filling bone defects produced by scraping with VCM-impregnated CPC, in conjunction with release of VCM from the CPC that would be highly concentrated at the local site.

According to a study by Woods et al.,[17] infections that occurred 1 to 6 months after TKA and were treated with debridement and intravascular injection of antimicrobial agents resulted in control of infection with preservation of components in only 3 of 27 knees (11%) treated. On the other hand, Grogan et al.[18] reported that

2 of 6 patients (33%), who underwent component-preserving therapy after having had infected TKA lasting over 1 month, took an uneventful course for more than 2 years following the eradication of infection. In the present study, 4 patients had suffered from chronic infection lasting more than 1 month and their plain radiographic examination revealed radiolucent lesions in the bone. Infection was suppressed in 3 of the cases while preserving the components, suggesting that our treatment method was better than therapy involving debridement combined with intravenous administration of antimicrobial agents. However, according to Schoifet et al.,[10] infection recurred in 19 of 24 patients that had been doing well, longer than 1 year after the original treatment to suppress the infection. We, therefore, will need to carefully follow up our patients for several years to come.

Concerning infection-causing bacteria, it was reported by Schoifet et al.[10] that 14 of 24 cases (58%), in which preservation of components failed, were infected by drug-resistant *Staphylococcus aureus*. They concluded that component retention was difficult if gram-negative bacteria were the causative microorganism, since in all 7 cases infected by these bacteria preservation of the metal components failed. Cases in the present study were only infected by gram-positive cocci and not by gram-negative bacteria or MRSA (methicillin-resistant *Staphylococcus aureus*), which are known to be the causes of intractable infections. Further treatment trials will be necessary to determine whether our treatment method is effective for drug-resistant bacteria.

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