Arch Orthop Trauma Surg (2010) 130:1221–1226
DOI 10.1007/s00402-009-0991-9

ORTHOPAEDIC SURGERY

Two-stage revision surgery for hip prosthesis infection using antibiotic-loaded porous hydroxyapatite blocks

Iori Takigami · Yoshiki Ito · Daichi Ishimaru · Hiroyasu Ogawa · Nobuyuki Mori · Takashi Shimizu · Nobuo Terabayashi · Katsuji Shimizu

Received: 24 May 2009 / Published online: 30 October 2009

Abstract
Background Infection of a hip prosthesis is one of the most severe complications encountered in orthopedic practice. Two-stage reconstruction using an antibiotic-impregnated cement spacer has become a popular procedure for the treatment of this condition. However, there are some disadvantages with the use of antibiotic-loaded cement, including low biocompatibility, a very low release ratio, and the possibility of thermal damage to the antibiotic. We have developed an effective drug delivery system for osteomyelitis in which porous hydroxyapatite (HA) blocks are loaded with an antibiotic by the vacuum method. We report here a modification of this delivery system applied for the first stage of two-stage reconstruction surgery against infected hip prosthesis.
Patients and methods Eight consecutive patients who developed hip prosthesis infection underwent two-stage revision total hip arthroplasty (THA) using antibiotic-loaded porous HA blocks prepared by the vacuum method. Thorough debridement and insertion of antibiotic-loaded HA blocks was performed in the first stage, followed by conversion to THA after eradication of infection in the second stage.
Results The mean interval between the stages was 16.8 weeks. There were no complications related to the use of the antibiotic-loaded HA blocks. The patients were followed up for an average of 49 months with no evidence of recurrent infection. The mean Japanese Orthopedic Association hip score improved from 45.1 before surgery to 79.6 at the latest follow-up.
Interpretation This simple approach utilizing antibiotic-impregnated HA blocks prepared by the vacuum method is considered to be effective for treatment of hip prosthesis infection.

Keywords Total hip arthroplasty · Infection · Two-stage revision · Hydroxyapatite · Drug delivery system

I. Takigami (✉) · Y. Ito · D. Ishimaru · H. Ogawa · N. Mori · T. Shimizu · N. Terabayashi · K. Shimizu
Department of Orthopaedic Surgery,
Gifu University Graduate School of Medicine,
1-1 Yanagido, Gifu 501-1194, Japan
e-mail: ioritigers@yahoo.co.jp

Introduction

Infection after total hip arthroplasty (THA) is a devastating complication with a reported incidence of 1–2% [1, 2]. Girdlestone resection arthroplasty, arthrodesis, or even amputation may be required when such infection cannot be controlled. Acute infection of THA is often treated initially by debridement with component retention. It appears that the longer the infection has been present in the hip, the more difficult it is to eradicate without removal of the prosthesis. Despite expeditious management, this approach frequently leads to recurrent infection [3–5]. It is well accepted that chronic infections are best managed by removal of the implants. Basically, there are two types of treatment for this condition: one-stage revision THA and two-stage revision THA. The current standard treatment is considered to be two-stage reconstruction using an antibiotic-impregnated cement spacer [6–15]. However, the use of antibiotic-loaded cement has several disadvantages, such as low biocompatibility, a very low release ratio, and the possibility of thermal damage to the antibiotic [16, 17].

Porous hydroxyapatite (HA) ceramic, which has excellent biocompatibility with bone, can be used to administer antibiotics or anticancer drugs because its porous structure

allows the slow release of pharmacologic agents [18–21]. We have successfully treated osteomyelitis and pyogenic arthritis using antibiotic-impregnated porous HA blocks [18, 22, 23]. Here we report eight cases of hip prosthesis infection that were treated by two-stage revision THA using antibiotic-loaded HA blocks prepared by the vacuum method.

Patients and methods

Between 1999 and 2006, we performed two-stage revision THAs using antibiotic-loaded HA blocks for eight consecutive patients with hip prosthesis infection (Table 1). There were 6 men and 2 women with a mean age at the first stage of 65 (49–79) years. The diagnoses for the initial operations were osteoarthritis (4 cases), avascular necrosis (2 cases) and femoral neck fracture (2 cases). The diagnosis of infection was based on clinical, radiological, and histological evidence, together with cultures obtained at the time of preoperative joint aspiration or surgery. The infected implants had been in place for an average of 18.6 (1–56) months and between one to four previous operations had been performed. Clinical evaluation were based on the Japanese Orthopaedic Association hip score system (JOA hip score), in which the maximum score of 100 points is divided into a "pain" score (40 points), "walking ability" score (20 points), "range of motion" score (20 points), and "activity of daily living" score (20 points) [24]. Higher score indicates better condition.

Treatment protocol

First stage

The first stage consisted of abscess drainage, sinus excision, and total removal of the prosthesis, foreign material and any potentially infected tissues. The wounds were thoroughly irrigated with a pulse lavage system, followed by implantation of antibiotic-loaded HA blocks.

In this series we used commercially available APACERAM porous HA blocks (Hoya, Tokyo, Japan; composition $Ca_{10}(PO_4)_6(OH)_2$; porosity 50–55%; pore size 0.5–500 μm). The HA blocks were immersed in antibiotic solution and decompressed at 250 mmHg for 15 min in a cement-mixing device (Mixevac III, Stryker, Allendale, NJ, USA). The choice of antibiotic depended on the results of bacterial cultures obtained from the draining sinuses or preoperative joint aspirations. We used broad-spectrum antibiotics when no growth was evident upon preoperative culture.

Interval between first and second stages

Active and passive exercise and muscle training were started 2 days after the operation. Patients were permitted to ambulate using crutches without weight-bearing, depending on pain tolerance. Total leukocyte count and C-reactive protein (CRP) level were examined at weekly intervals for the first month, and at 2- to 3-week intervals thereafter. Systemic intravenous antibiotics were given until the CRP level had become normalized for 2 weeks or more. Antibiotic selection was determined according to the microbiological assessment before surgery. If no preoperative culture was positive, we used broad-spectrum antibiotics.

Second stage

The timing of the second stage surgery was dependent on the control of infection and clinical symptoms. The criteria for conversion to THA were (1) healing of the wound, (2) return of CRP to a normal level, persisting for at least 4 weeks with no antibiotic coverage, and (3) negative findings upon culture of a joint aspiration sample. After the HA blocks had been removed, tissue samples were obtained for culture and biopsy. Eradication of infection was reconfirmed by intraoperative frozen section analysis according to the criteria of Athanasou et al. [25]. The final decision about the implant to be used was based on the quality of the residual bone stock.

Table 1 Patient data (preoperative)

Case	Age	Sex	Previous diagnosis	No. of previous Ops	Type of implant	Time since last OP (months)
1	66	M	Osteoarthritis	1	THA	42
2	70	M	Avascular necrosis	1	THA	19
3	66	M	Femoral neck fracture	1	THA	2
4	76	M	Osteoarthritis	4	Revision THA	4
5	79	F	Osteoarthritis	2	THA	21
6	63	F	Femoral neck fracture	1	Hemiarthroplasty	4
7	49	M	Avascular necrosis	2	Revision THA	1
8	51	M	Osteoarthritis	4	Revision THA	56

Postoperative care

The patients were allowed to walk with crutches as soon as their general condition permitted. Antibiotics were administered for at least two weeks postoperatively. The patients were examined at 1, 3, 6 and 12 months, and every half year thereafter. Radiographs were obtained at each follow-up. Clinical findings including pain at rest and elevation of the serum CRP level were used as indicators of recurrent infection.

Results

The mean interval between the first and second stages was 16.8 (12–27) weeks. Preoperative joint aspiration yielded cultures with positive findings in six of eight patients. Two patients with negative cultures were diagnosed as having infection on the basis of elevated levels of inflammation markers in the blood (total leukocyte count, erythrocyte sedimentation rate, and CRP), the presence of periprosthetic purulence, and histopathologic findings of acute inflammation of periprosthetic tissue samples that were consistent with infection. Details of the infecting organisms and the antibiotics used to impregnate the HA blocks in each patient are given in Table 2. All the patients who suffered deep infection were treated successfully by revision THA after the infection had been controlled using antibiotic-loaded HA blocks. In the second-stage procedure, there were no difficulties with removal of the HA blocks. No complications related to their use were observed. One patient (Case 2) required curettage and repeat insertion of antibiotic-loaded HA blocks because cultures obtained from joint aspiration before the planned second stage operation were positive. This patient underwent revision THA at 27 weeks after the first stage and 14 weeks after the second insertion of HA blocks. At the last follow-up, the patient had no sign of infection, and the CRP level was normal.

In the patients overall, the CRP level normalized at an average of 4 (2–7) weeks, and the mean duration of systemic intravenous antibiotics treatment was 4.2 (2–8) weeks after the first-stage operation. At the second stage, there was no evidence of infection in the intraoperative frozen section analyses and the cultures obtained were all negative. The JOA hip score was 45.1 (40–58) before the first stage and 46.8 (37–52) between stages, and this had improved to 79.6 (70–97) by the final follow-up. The limb length inequality evaluated from an anteroposterior radiograph [26] averaged 35.4 (15–50) mm during the interim period and 4.1 (0–13) mm after second-stage surgery. None of the patients had to use shoe lifts for equalization of limb length or complained of limb length inequality. No recurrence of infection was observed in any patient at a mean follow-up interval of 49 (24–81) months. The radiographs at the final evaluation showed no loosening of the components in any of the patients.

Figure 1 shows the radiological findings in a representative case after two-stage revision of an infected THA using antibiotic-loaded HA blocks.

Discussion

Deep infection after THA is a challenging clinical problem. The treatment goals are eradication of the infection and preservation of joint function. A major problem in treating an infected hip prosthesis is obtaining effective bactericidal concentrations of antibiotics at the focus of infection. For infection control, it is reasonable to combine systemic intravenous with local antibiotic administration. Antibiotic-impregnated cement beads and spacers are commonly used as a local antibiotic carrier system. In the past few years, a two-stage protocol with implantation of an antibiotic-impregnated spacer in addition to systemic administration has become a popular procedure for treatment of infected prosthetic hip joints [6–15]. However, there are several reports of complications that are specific to the use of

Table 2 Patient data (bacteriological and postoperative)

Case	Organism	Loaded antibiotics	Interval between stages (weeks)	Interval to normal CRP level (weeks)	Duration of follow-up (months)
1	Nondetected	ABK 400 mg	16	4	81
2	*Enterococcus faecalis*[a]	ABK 500 mg	27	4	79
3	*E. faecalis*	IPM 1 g, PIPC1 g	19	7	39
4	MRSA	ABK 600 mg	15	3	51
5	Nondetected	AMK 800 mg	13	3	27
6	*E. faecalis*	ABK 500 mg	12	2	24
7	*Staphylococcus epidermidis*	ABK 600 mg	18	4	32
8	*S. epidermidis*	ISP 1,600 mg	15	5	59

MRSA methicillin-resistant *Staphylococcus aureus*, *ABK* arbekacin sulfate, *IPM* imipenem, *PIPC* piperacillin sodium, *AMK* amikacin sulfate, *ISP* isepamicin sulfate, *CRP* C-reactive protein

[a] Patient no. 2 was operated on twice for HA blocks insertion

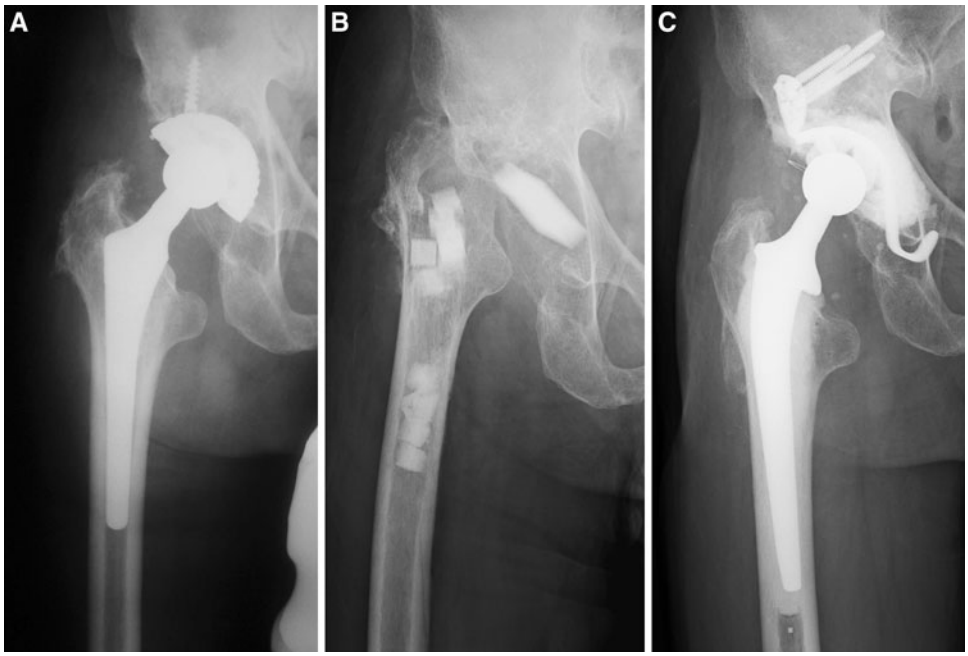

Fig. 1 Radiograph of a 76-year-old man who had infection of a right total hip arthroplasty (Case 4). **A** Preoperative radiograph. **b** After insertion of antibiotic-loaded HA blocks. **c** Four years after second-stage revision THA. Bone defects were filled with antibiotic-loaded HA granules and blocks

a cement spacer, including dislocation and fracture [6, 11–13, 15]. Moreover, there are some disadvantages with the use of antibiotic-loaded cement, including low biocompatibility, a very low release ratio, and the possibility of thermal damage to the antibiotic [16, 17].

HA, which has excellent biocompatibility, is available as a porous ceramic in two forms, granular or block, the latter being able to better resist mechanical forces. It has been employed as a suitable material for filling bone defects [27]. There have been several reports of a delivery system for antibiotics using HA [28, 29]. We have developed porous HA blocks loaded with antibiotics prepared by the vacuum method as a novel drug delivery system, and confirmed that antibiotic solution fully penetrated the HA blocks ($20 \times 20 \times 20$ mm) with decompression below 254 mmHg for 15 min or 127 mmHg for 20 min [21]. Moreover, antibiotics used for impregnating HA blocks were released slowly, and the minimum inhibitory concentrations against the common causative organism of osteomyelitis were maintained for long periods [20, 21]. We have already demonstrated the clinical effectiveness of antibiotic-loaded porous HA blocks for the treatment of osteomyelitis and pyogenic arthritis [18, 22, 23]. This treatment technique was applied for the first stage of two-stage reconstruction surgery against infected hip prosthesis. HA blocks cause no thermal damage enabling broad antibiotic options. Porous HA ceramics have another advantage compared with cement spacers or beads for their excellent biocompatibility with bony tissue. Therefore, removal of the HA blocks is not mandatory should the second-stage reconstruction prove impossible for any reason, or if there are any difficulties in removing the HA blocks during the second stage.

Thorough debridement and irrigation for the treatment of infected hip prostheses may often lead to severe bone defect. Allograft transplantation can be a solution for reconstruction, although re-infection of massive allografts used has been a concern [30] especially in cases with previous infection. Application of HA is another good treatment option [31–33]. We have modified this method with antibiotic-loaded HA even for the second stage of reconstruction surgery after infection (Fig. 1c).

In our series, there were no complications specific to the use of antibiotic-loaded HA blocks. All patients who had deep infections of hip implants were treated successfully by two-stage revision THA using antibiotic-loaded HA blocks prepared by the vacuum method at the first stage. The main drawback of this treatment is that antibiotic-loaded HA blocks are not used for mechanical fixation or support to improve functional outcome during the interval between stages. This method does not help maintain limb length and soft tissue tension during the interim period. Nevertheless, the final limb length discrepancy averaged 4.1 mm and none of the patients expressed dissatisfaction about limb length inequality. Another drawback of our method is that it requires a long interval between the first and second stages, at least in comparison with other reported cases [10, 11, 34]. In the present series, the mean interval was 16.8 weeks. We consider this was attributable to the careful consideration we gave to the second-stage procedure, which was based strictly on our defined criteria that the CRP level had returned to normal for at least 4 weeks, and

that cultures of joint aspiration samples had been negative with no antibiotic coverage before the second-stage operation. Consequently, all the patients were managed successfully using our protocol, and good functional results were evident at the final follow-up. However, there were several limitations to our study, the patients were analyzed retrospectively and the number of patients was small. Therefore, a prospective study with a large number of patients will be required for definitive assessment.

Antibiotic-loaded HA blocks are considered to be an effective treatment for hip prosthesis infection. They can be prepared by a simple vacuum method, and have the potential to eradicate infection.

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