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Original Article

A Strategic Protocol to Improve the Process and Outcomes of Two-stage Revision Total Hip Arthroplasty

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Two-stage revision total hip arthroplasty (THA) is the most commonly used treatment approach for deep prosthetic infection. However, in this approach the interval between the first and second stage tends to be prolonged. We devised a strategic protocol for improving the infection eradication rate and shortening the interval between the stages in two-stage revision THA. This study analyzed a series of 14 patients (14 hips) from 2008 to 2012, who were treated using an antibiotic-loaded acrylic cement (ALAC) spacer at the first stage and re-implantation at the second stage. The ALAC included vancomycin and amikacin for most of the cases. Patients with MRSA infection were additionally administered intravenous vancomycin in combination with either oral rifampicin or trimethoprim-sulfamethoxazole. The average interval between the stages was 54.2 days overall, and 58.7 days for cases with MRSA infection. Our infection eradication rate was 100%, with no reported recurrence of infection. The presence of MRSA tended to be associated with a longer interval between the two stages. Our protocol for two-stage revision THA was associated with a high eradication rate of infection and a shortened interval between the stages.

Key words: two-stage revision, infection, total hip arthroplasty, antibiotic-loaded acrylic cement, methicillin-resistant *Staphylococcus aureus* (MRSA)

The number of patients treated with total hip arthroplasty (THA) has increased year by year. THA provides pain relief and improves the activities of daily living and the quality of life of affected patients. However, deep prosthetic infection is a serious complication following THA, and is reported to occur in about 0.3 to 3% of primary THA, and 4 to 6% of revision procedures [1,2]. Although several strategies have been described for managing deep prosthetic infection following THA [3-6], to date there is no consensus on the best strategy. Two-stage revision is the most commonly used treatment for deep prosthetic infection, with reported infection eradication rates of 90% or higher [7-9]. It is the recommended technique for antibiotic-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), gram-negative bacilli, and fungi, and for patients with immunodeficiency (e.g., diabetes mellitus (DM), malignant tumors, use of steroids) or widespread chronic infected fistulae [3,5,7,10-13]. However, two-stage THA revision is poorly tolerated by patients, owing to the restriction of weight-bearing and mobility during the interval between the first and second stages. Patients are known to be severely distressed during this interval, both physically and mentally [15].

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The recent introduction of antibiotic-loaded acrylic cement (ALAC) as an effective local delivery system of antibiotics has contributed to effective control of deep prosthetic infection [7,8,15]. The antibiotic concentration in resected joint spaces following the use of ALAC exceeds systemic levels [15].

Cement-less femoral fixation is generally used for second-stage re-implantation, and is reported to have good results [13,16,17]. One benefit of this choice is avoiding the difficulty of removing the implant and cement in the event of recurrence of infection. This is especially relevant in cases wherein removal of the femoral stem may result in femoral fracture and bone stock loss. However, the interval between the stages in cement-less revision tends to be longer because surgeons must wait until the markers of infection are completely negative.

Several studies have reported good eradication rates of infection with one-stage ALAC fixation in selected patients [6,18,19]. Although the treatment duration of one-stage revision is shorter than that of the other available treatments [20], its application is limited. In the event of infection recurrence in these cases, the course of treatment becomes difficult. In view of these concerns, we have been treating infected THAs with a short-term ALAC spacer followed by ALAC implant fixation as a part of the two-stage revision of THAs since 2008. This method has the advantage of a prolonged period of local antibiotics at a high concentration owing to the use of ALAC both as a spacer and for implant fixation. In this study, we examined the success rate of two-stage revision using ALAC in these dual roles. In addition, we analyzed the factors that contributed to prolongation of the interval between the first and second stage of THA revision.

Materials and Methods

The medical records of 14 patients treated for infected THA between April 2008 and September 2012 were reviewed in this retrospective study. All patients underwent two-stage revision THA on 1 hip each per our protocol. There were 8 men and 6 women with a mean age of 69.4 years (SD, 11.6 years; range, 58-83 years). The average body mass index was 22.5 ± 3.3 kg/m^2. The average follow-up period was 4.9 ± 1.5 years. The diagnosis of infection in all patients was based on clinical history, physical examination (e.g., fever, pain on movement, night pain, flare, swelling), diagnostic imaging (plain radiographs, magnetic resonance imaging, and three-layer bone scintigraphy with Tc99m), laboratory evaluation (leukocyte cell total and differential count, C-reactive protein [CRP], erythrocyte sedimentation rate, and aspirated hip synovial fluid analysis (differential white blood cell count, glucose concentration, and bacterial culture) [3,5,7,21]. The diagnosis of infection was based on a comprehensive assessment of these parameters in the absence of clear bacterial identification. After establishing the diagnosis of infection, patients were managed according to our strategic protocol for shortening the treatment duration of the two-stage revision (Fig. 1). Our protocol mainly consisted of customized antibiotics in ALAC, addition of intravenous and oral antibiotics for MRSA, timing of cultures after antibiotics, and specific criteria for determining the time required to perform re-implantation. In the first stage, we removed the implant and set an ALAC spacer after thorough debridement of the implant site. The relevant antibiotic powder was added at a ratio of 5 g to 40 g of cement spacer. Vancomycin (Shionogi, Osaka, Japan) and amikacin (Nichiiko, Toyama, Japan) were used for most patients, and also in the absence of sensitivity data. One patient received teicoplanin (TARGOCID®; Sanofi, Paris, France) in ALAC as he was allergic to vancomycin. We used a 2-mm k-wire (Mizhuho, Tokyo, Japan) as the core for the cement rod in the femoral bone marrow cavity, and beads in the acetabular space. All patients with non-MRSA infection received intravenous first-generation cefazolin sodium (NIPRO, Osaka, Japan) at 4 g/day for three days, to prevent surgical site infections following the first-stage procedure. Patients with MRSA infection received vancomycin injection through a central venous access. In addition, these patients received a rifampicin capsule (Sandoz, Tokyo, Japan) at 450 mg/12 h or trimethoprim-sulfamethoxazole (TMP-SMX) (Bactor®; Shionogi, Osaka, Japan) at 1 tablet/8 h through the oral route. The maximum duration of antibiotic therapy was 4 weeks for MRSA. During treatment, patients were monitored for side effects by laboratory evaluations repeated once or twice a week. The antibiotic regimen was shortened to less than 4 weeks if the infection marker showed improvement (CRP < 1.0 mg/dL) in the postoperative period. Two weeks following the cessation of antibiotic therapy, the synovial fluid was cultured for bacteria and analyzed for differential white

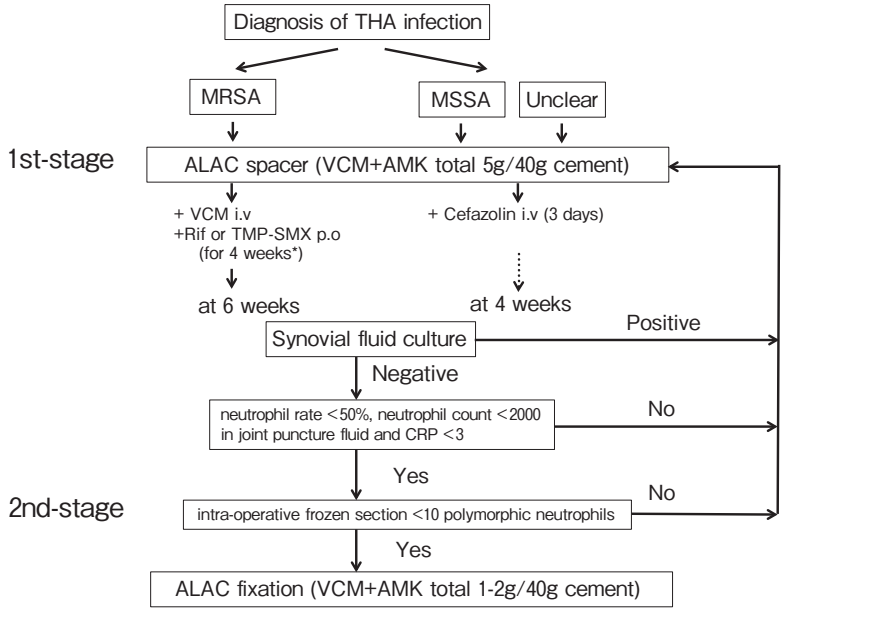

Fig. 1 Treatment protocol for two-stage revision THA in our hospital. ALAC, antibiotic-loaded acrylic cement; MRSA, methicillin-resistant *Staphylococcus* aureus; MSSA, methicillin-sensitive Staphylococcus aureus; VCM, vancomycin; AMK, amikacin; Rif, rifampicin; TMP-SMX, trimethoprim-sulfamethoxazole.

blood cell count and glucose concentration. A 2-week interval was used to account for any residual effect of the antibiotics. Our criteria for presuming an absence of infection were a CRP value < 3 mg/dL in addition to synovial fluid demonstrating the following: absence of bacterial isolates; neutrophil rate < 50%; and neutrophil count < 2,000 cells/mL. At the second stage, the final decision for re-implantation was taken intra-operatively, provided that there were no signs of persistent infection and that the intra-operative frozen section demonstrated less than 10 polymorphic neutrophils (PMN; at 400× magnification). In the presence of more than 10 PMN, re-implantation was deferred and the cement spacer was replaced. The ALAC used during revision surgery consisted of only 1-2 g of antibiotic powder for 40 g of cement to avoid weakening the cement. If the acetabular bone defect was large, we used a Kerboull-type acetabular reinforcement device (K-MAX KT plate S®; Kyocera Medical, Kyoto, Japan).

The following study parameters were analyzed to assess their role in prolonging the waiting period between the first- and second-stage procedures: 1) presence of fistula; 2) comorbidity; 3) classification of infection (referring to Tsukayama's report [22], we defined the following types: type 1, positive intraoperative cultures; type 2, early postoperative infection (< 4 weeks); type 3, acute hematogenous infection; and type 4, late chronic infection (> 4 weeks)); and 4) presence of MRSA.

Statistical analyses. All numerical data are expressed as the means ± standard deviations. The unpaired T test (Welch's t test) or Fisher's exact test were used to identify statistically significant differences between continuous variables or discrete variables, respectively. All analyses were performed using statistical software JMP pro 12 (SAS Institute, Cary, NC, USA). *P* values < 0.05 were considered statistically significant.

Ethics statement. This study met the guidelines of the responsible government agency and complied with the principles of the Declaration of Helsinki. The study design was approved by the Ethics Committee at Wakayama Medical University. The patients or their families were informed that the data from the cases would be submitted for publication, and their consent was obtained.

Results

All 14 patients managed according to our protocol eventually recovered from prosthetic infection. The overall average ALAC spacer period between the first- and the second-stage was 54.2 ± 17.1 days. A single use of ALAC spacer was adequate in 11 patients (mean

Table 1 Patient characteristics

Patient	Age sex	Identified bacteria	Antibiotics in ALAC	Total days between stages	Times of ALAC	Infection type	Fistula	Comorbility
1	63y M	MSSA	VCM, AMK	45	1	4	−	
2	70y M	MRSA	VCM, AMK	63	2	3	−	
3	63y M	MRSA	VCM, AMK	55	1	3	+	RA, Nephrosis
4	83y F	MSSA	VCM, AMK	42	1	3	+	Cardiac insufficiency
5	71y F	unclear	VCM, AMK	45	1	4	−	DM
6	58y M	unclear	VCM, AMK	35	1	4	−	RA, Myasthenia gravis
7	73y M	MSSA	VCM, AMK	102	2	1	−	Coronary aneurysm
8	76y F	MSSA	VCM, AMK	33	1	3	−	
9	80y M	unclear	VCM, AMK	57	1	3	+	Cardiac insufficiency
10	72y M	MSSA	VCM, AMK	49	1	3	−	
11	38y M	MSSA	TEIC, AMK	49	1	2	−	Congenital insensitivity to pain
12	82y F	unclear	VCM, AMK	54	1	3	−	Mammakrebs
13	74y F	MRSA	VCM, AMK	62	2	2	+	DM
14	68y F	MRSA	VCM, AMK	68	1	4	−	DM, Hepatic cirrhosis

MSSA, Methicillin-sensitive Staphylococcus aureus; MRSA, Methicillin-resistant Staphylococcus aureus; VCM, vancomycin; AMK, amikacin; ALAC, antibiotic-loaded acrylic cement; RA, rheumatoid arthritis; DM, diabetes mellitus.

waiting period, 48.3 ± 10.1 days). Three patients required a second use of ALAC (40.0 ± 15.1 days before ALAC replacement; 75.7 ± 22.8 days of total ALAC spacer period). There was no recurrence of infection at the final follow-up in any of the cases. Thus, our infection eradication rate was 100%, which represents a good result.

Bacterial cultures isolated MSSA in 3 patients and MRSA in 4 patients. Bacterial cultures were inconclusive in 6 patients. Comorbidity related to underlying medical conditions such as rheumatoid arthritis, DM, cardiac failure and intractable foot ulcer secondary to congenital insensitivity to pain were seen in 10 patients. Four patients had fistulae. On classifying the infection, 4 patients were of type 4 (Table 1). Almost all patients received vancomycin and amikacin as the antibiotic components of ALAC, except one patient who was allergic to vancomycin.

In these case series, there was none of the included cases; a value of CRP > 3 mg/dL (the average value in all cases was 0.68 ± 0.27 mg/dL); neutrophil rate > 50%, and neutrophil count > 2,000 cells/mL (the average value in all cases was 2,272 ± 729 cells/mL) before undergoing the second-stage procedure. The average CRP value just before the second-stage procedure was 0.62 ± 1.02 mg/dL for patients managed by a single setting of ALAC spacer (group A), and 0.43 ± 0.18 mg/dL for patients requiring ALAC spacer replacement (three-stage procedure) (group B). The difference between the CRP values of the two groups was not significant (Table 2a).

The presence of MRSA infection was associated with prolonged interval between the first- and the second-stage procedures. The interval between the stages was significantly longer in the MRSA group compared to the non-MRSA group (62.0 ± 5.4 days vs. 51.1 ± 19.4 days, $p = 0.0335$) The presence of fistulae, comorbidity, and classification of infection (type 1-3 vs. 4) was not found to be associated with prolonged interval between the stages (Table 2b). Moreover, the Fisher's exact test showed no significant difference in risk factors between groups A and B (Table 2c). Group B has a higher trend of the presence of MRSA than group A, although the difference was not significant ($p = 0.1768$)

Discussion

The use of our protocol was associated with an average interval of 54.2 ± 17.1 days between the two stages of revision THA in our series. In patients with MRSA infection, this duration was significantly longer (average period, 58.7 days). The intervals recorded in the present series were shorter than the waiting periods reported in systematic reviews or meta-analysis reports [8, 9, 16, 23, 24]. In addition, our final infection eradication rate was 100% with no reported infection recurrence. These results are indicative of a favorable outcome with the adoption of our protocol, and likely contributed to patient satisfaction.

We used vancomycin and amikacin as components of ALAC in most of the cases we managed. This is

Table 2 Factors contributing to prolonged interval between the 2 stages

a

	Two-stage group	Three-stage group	*p* value
CRP	0.62 ± 1.02	0.43 ± 0.18	$p = 0.2475$

b

	total periods betwwen stages		*p* value
non-MRSA/MRSA	51.1 ± 9.4	62.0 ± 5.4	$p = 0.0335$
fistula −/+	54.3 ± 20.0	54.0 ± 8.5	$p = 0.6707$
infection type 1–3/4	56.6 ± 18.3	48.3 ± 14.0	$p = 0.3951$
comorbility −/+	47.5 ± 8.6	56.9 ± 5.4	$p = 0.8128$

c

	Two-stage group	Three-stage group	*p* value
non-MRSA/MRSA	9/2	1/2	$p = 0.1758$
fistula −/+	8/3	2/1	$p = 0.6703$
infection type 1–3/4	7/4	3/0	$p = 1.0000$
comorbility −/+	3/8	1/2	$p = 0.8242$

because aminoglycosides are known to have a synergistic effect on the bactericidal activity of vancomycin [25]. The duration of antibiotic therapy remains controversial. Most centers prescribe intravenous antibiotic therapy for 6 weeks followed by a further course of oral antibiotics. Re-implantation is usually conducted at 6 to 12 weeks in many centers [8, 24]. Vielgut reported that their average waiting period between the two stages was 12.6 weeks [26]. In their study, the eradication rates of cases having 4- to 11-week intervals were better than those under 4 weeks, or over 11 weeks. Although our most important goal was the eradication of infection, the duration of intravenous antibiotic therapy was limited to 4 weeks to reduce the interval between the two stages. According to our protocol, the main approach to the treatment of infection was the use of ALAC, with intravenous antibiotic therapy playing a secondary role. It has been reported that the inhibitory concentration of ALAC is maintained for 4-6 weeks with the antibiotic combination of vancomycin and aminoglycosides [15, 27]. However, Chang reported sustained 3 to 4 weeks' delivery of vancomycin from ALAC, above the minimum inhibitory concentration, when 4 g of antibiotic powder was used per 40 g of cement [28]. Stockley reported that ALAC alone was adequate for treatment of implant site infections, without the need for additional oral or intravenous antibiotics [29]. Therefore, we considered the continuation of intravenous antibiotic therapy beyond 4 weeks as unnecessary.

Our analysis demonstrated that the presence of MRSA infection could be a factor associated with a prolonged interval between the first and second stage. Neither the presence of fistulae or comorbidity, nor infection classification was a risk factor for a prolonged interval in our analysis. Our protocol included additional treatment using intravenous vancomycin with oral administration of rifampicin or TMP-SMX for patients with MRSA infection. The choice of additional antibiotic therapy was based on pharmacokinetics/pharmacodynamics theory [30]. It has been reported that the addition of rifampicin is effective in breaching the bio-film of *Staphylococcus aureus* often associated with deep prosthetic infection [3, 31, 32]. Similarly, the combination of TMP-SMX is known to be effective against MRSA [3, 33, 34]. Although it is difficult to control MRSA infection following THA, and the published eradication rates are lower than in non-MRSA infections [23, 35], our final eradication rate was 100%.

In our study, there was no significant difference in CRP levels before re-implantation between the two-stage revision and the three-stage revision groups. Hoell reported that serum CRP levels (cut-off-value: 2.3 mg/dL) before re-implantation had a sensitivity of 42.1% and specificity of 84.2% for persistent infection.

Moreover, he reported a sensitivity and specificity of 5% and 99% for synovial fluid cultures, and 31.3% and 39.1% for synovial fluid leukocyte count (cut-off-value: 970) before re-implantation [36]. The sensitivity data of all these markers are very low, and although they contributed to the decision to perform a re-implantation in our series, the final decision was made only intra-operatively. We relied on an intra-operative frozen section demonstrating less than 10 PMN (at ×400 magnification). This approach has a sensitivity and specificity of 84% and 99%, respectively [37], and appears to be a reliable indicator for decisions regarding re-implantation. Hoell reported that the sensitivity and specificity for synovial fluid leukocyte count before re-implantation was low [36], while Trampuz reported that a synovial fluid leukocyte differential of > 65% neutrophils or a leukocyte count of > 1,700 cells/mL is a sensitive (97%) and specific (98%) test for the diagnosis of prosthetic infection [38]. Another report showed that a synovial fluid leukocyte count of < 2,000 cells/mL and a differential with < 50% polymorphonuclear leukocyte cells had a 98% negative predictive value for the absence of prosthetic infection [39]. In a recent study, a leukocyte count of 4,200 cells/mL had a sensitivity of 84% and a specificity of 93% at detecting prosthetic hip infection [40]. Based on these pieces of evidence, one of our criteria for deciding the absence of infection was a neutrophil rate < 50% and a neutrophil count < 2,000 cells/mL in the synovial fluid.

Recent reports have demonstrated good clinical results with one-stage revision THA [6, 18, 19]. However, the choice of a one-stage revision requires careful judgement because it is difficult to remove the implant and the cement in the event of recurrence of infection. Two-stage revision is the gold standard for revision THA. However, two-stage revision contributes to physical and mental distress for patients owing to the prolonged interval between the stages [14]. Our protocol may clarify the principles of treatment in these cases. Our results showed a high infection eradication rate and a shortened interval between the stages in two-stage revision THA. Therefore, we propose our protocol as a reliable approach in the management of deep prosthetic infection following THA.

There are certain limitations of our study. First, the sample size was small and our results need to be validated by a larger study. Second, we did not perform multivariate analysis to identify factors contributing to a prolonged interval. Third, this was only a retrospective study.

In conclusion, we devised a strategic protocol for improving the infection eradication rate and shortening the interval between the stages of two-stage revision THA. Among patients managed by this protocol, the average interval between stages was 54.2 days overall, and 58.7 days for patients with MRSA infection. In addition, our infection eradication rate was 100%, with no reported recurrence of infection. Our protocol for two-stage revision THA could contribute to a high infection eradication rate and a shortened interval between the stages.

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