

Retrospective Study

Is two-stage reimplantation effective for virulent pathogenic infection in a periprosthetic hip? A retrospective analysis

Yong-Cheol Yoon, Devendra Lakhota, Jong-Keon Oh, Jun Gyu Moon, Kumar Prashant, Won Yong Shon

Yong-Cheol Yoon, Orthopedic Trauma Division, Gachon University Gil Hospital, Incheon 405-760, South Korea

Devendra Lakhota, Jong-Keon Oh, Jun Gyu Moon, Kumar Prashant, Won Yong Shon, Department of Orthopedic Surgery, Korea University College of Medicine, Guro Hospital, Seoul 152-703, South Korea

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Correspondence to: Won Yong Shon, MD, PhD, Professor, Department of Orthopedic Surgery, Korea University College of Medicine, Guro Hospital, 97 Gurodong-gil, Guro-gu, Seoul 152-703, South Korea. shonwy@hotmail.com
Telephone: +82-2-26261163

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Abstract

AIM: To investigate the effectiveness of two-stage reimplantation using antibiotic-loaded bone cement (ALBC) and the risk factors associated with failure to control periprosthetic joint infection (PJI).

METHODS: We retrospectively reviewed 38 consecutive hips managed using two-stage reimplantation with ALBC. The mean follow-up period was 5.4 years (range: 2.5-9 years).

RESULTS: The causative pathogens were isolated from 29 patients (76%), 26 of whom were infected with highly virulent organisms. Sixteen patients (42%) underwent at least two first-stage debridements. An increased debridement frequency correlated significantly with high comorbidity ($P < 0.001$), a lower preoperative Harris hip score (HHS; $P < 0.001$), antimicrobial resistance, and gram-negative and polymicrobial infection ($P = 0.002$). Of the 35 patients who underwent two-stage reimplantation, 34 showed no signs of recurrence of infection. The mean HHS improved from 46 ± 12.64 to 78 ± 10.55 points, with 7 (20%), 12 (34%), 11 (32%)

and 5 (14%) patients receiving excellent, good, fair and poor ratings, respectively.

CONCLUSION: The current study demonstrated that two-stage reimplantation could successfully treat PJI after hip arthroplasty. However, the ability of ALBC to eradicate infection was limited because frequent debridement was required in high-risk patients (*i.e.*, patients who are either in poor general health due to associated comorbidities or harbor infections due to highly virulent, difficult-to-treat organisms). Level of evidence: Level IV.

Key words: Two-stage reimplantation; Periprosthetic infection; Antibiotic-loaded bone cement; Debridement

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Core tip: Two-stage revision with antibiotic-laden bone cement for periprosthetic infection after total hip arthroplasty is generally recognized as the gold-standard treatment. Two-stage revision usually comprises removal of all components, including cement, and radical debridement of all suspected infectious, necrotic tissues and bone. However, despite the success of two-stage revision for the treatment of infected primary hip arthroplasties, not all causative organisms can be successfully eradicated, especially multidrug-resistant virulent microorganisms; therefore we evaluated the efficacy of two-stage reimplantation with antibiotic-laden bone cement against difficult-to-treat microorganisms as well as the risk factors associated with failure to control infection.

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INTRODUCTION

Infection following total hip arthroplasty (THA) is a serious obstacle that incurs high costs and considerably affects the physical and mental health of the patient, and causes stress for the treating surgeon. The general incidence of periprosthetic joint infection (PJI) is 1%-2% in most centers, despite the use of new antimicrobial agents and sterilization appliances in the operating room^[1].

Two-stage reimplantation with antibiotic loaded bone cement (ALBC) is the most widely performed THA procedure and has a high success rate^[2,3]. This procedure has several advantages, including a reduced infective burden, exposure of residual bacteria under the biofilm, and antibiotic elution at a high concentration to assist

with infection control. Moreover, articulating cement spacers help to preserve the limb length and normal tensile forces of the soft-tissues, thereby providing partial joint mobility^[4]. Despite the success of this technique, however, not all infections are successfully eradicated^[5]. A significant number of patients still experience difficult-to-treat complex infections, despite being treated after two-stage reconstruction^[6]. The reported success rates are lower among patients harboring gram-negative organisms, polymicrobial infections, *Enterococci*, methicillin-resistant *Staphylococci*, or any organism that elaborates a glycocalyx, which are considered highly virulent^[7,8]. Some authors recommend against the use of spacers in patients with highly virulent, difficult to treat microorganisms^[9].

The potential associations of an increased failure rate with the virulence of the infecting organism^[10-12], clinical effectiveness of ALBC^[13,14], and the etiology of treatment failure in patients with PJI^[15] remains controversial. The aim of this study was to assess the efficacy of two-stage reimplantation with ALBC against virulent difficult-to-treat microorganisms and the risk factors associated with failure to control infection.

MATERIALS AND METHODS

Research subjects

This retrospective study involved 43 patients treated between 2003 and 2011. Five patients were excluded because of death unrelated to the relevant surgery. The mean age of the remaining 38 patients (24 men and 14 women) was 63.97 ± 12.66 years (range 41-89 years). The patients had undergone primary arthroplasty (16 THA and 15 bipolar hemiarthroplasty) or revision THA (seven patients). The mean follow-up duration was 5.4 years (range 2.5-9 years). Patient comorbidity data are shown in Table 1.

Diagnostic methods

A PJI was confirmed if at least two of the following criteria were present 3 mo after arthroplasty: (1) a chronic, discharging sinus in communication with the prosthesis; (2) clinical symptoms and signs of unexplainable pain, persistent local erythema, swelling, and a high erythrocyte sedimentation rate ($ESR \geq 30$ mm/h) and C-reactive protein level ($CRP \geq 10$ mg/L); (3) isolation of a microorganism in one culture; and (4) the presence of purulence in the affected joint or > 5 neutrophils per high-powered field upon histopathological examination of at least two different sites^[16,17].

Surgical procedure

The first stage consisted of sinus excision and abscess drainage, if present, prosthesis removal, and extensive debridement, followed by insertion of ALBC (Figure 1). The type of antibiotics loaded in the cement was based on the result of presurgical bacterial cultures. In cases with gram-positive and negative bacterial cultures, 3 g of vancomycin was used; in cases with gram-negative



Figure 1 Pelvic radiograph of a 54-year-old man after first-stage reimplantation. This patient had a periprosthetic infection with methicillin-resistant *Staphylococcus aureus* after total hip arthroplasty. The hip prosthesis was removed, and a vancomycin-impregnated cement spacer (right hip) was inserted after debridement.

or mixed bacterial infections a combination of 2-3 g of vancomycin and 2 g of fortimicin was mixed with 40 g of bone cement (Surgical Simplex-P; Stryker, Allendale, NJ, United States). For one patient infected with tubercle bacillus and *Pseudomonas aeruginosa*, a combination of 2 g each of vancomycin, fortimicin, and streptomycin was used.

Intravenous antibiotics were given for 4-8 wk depending on the bacterial cultures. In patients with increased inflammatory markers associated with clinical findings despite a 6-8 wk antibiotic course, repeated debridement was performed. Secondary reimplantation was scheduled when the ESR and CRP levels remained within normal limits with no evidence of persistent infection for two consecutive reviews.

Clinical and radiological evaluation

All patients were examined at 1, 2, 3 and 6 mo, and then yearly. Clinical evaluations including Harris hip score (HHS) and hematological evaluations, were performed at every follow-up. Acetabular loosening was defined as a shift of the acetabulum > 4 mm, change in the inclination angle of > 5°, and a radiolucent line demarcation of > 1 mm in all three zones^[18]. The Harris criteria were used to determine loosening of the cemented femoral stem^[19]. Subsidence or radiolucency was evaluated for the cementless femoral component^[20].

Statistical analysis

A data analysis was conducted using SPSS software, version 20.0 (SPSS, Inc., Chicago, IL, United States); a modified Kruskal-Wallis test was used, as a non-parametric method to analyze factors influencing the frequency of debridement and cure rate of treatment with ALBC. The statistical significance was set at $P < 0.05$.

RESULTS

Microorganisms were identified in 29 patients (76%), including four cases with methicillin-sensitive bacteria,

Table 1 Comorbidities and frequencies

Comorbidities	No. of cases
Heart diseases, including hypertension	15
Uncontrolled diabetes mellitus	11
Liver cirrhosis	6
Repeated urinary tract infection	6
Brain lesions including stroke	4
Chronic gout	3
Psoriasis	2
Systemic lupus erythematosus	1
Chronic renal failure	2
Autoimmune hepatitis	1
Cushing's syndrome	1
Asthma	1
Chronic obstructive pulmonary disease	1

nine cases with methicillin-resistant bacteria, three cases with vancomycin-resistant *Enterococcus* (VRE), nine with multiple bacterial organisms (including methicillin-resistant and tubercular bacillus), and four cases with gram-negative bacteria such as *Pseudomonas* and *Salmonella* (Table 2).

Repeated debridement was performed in 16 patients (Table 3). Ten, one, four, and 1 patient required a second, third, fourth and seventh debridement, respectively. Ten of the 16 patients were infected with resistant bacteria (methicillin-resistant *Staphylococcus epidermidis*, VRE, and methicillin-resistant *Staphylococcus aureus*). Six patients with nine polymicrobial infections harbored resistant bacteria (Table 3) and underwent multiple debridements (two or more). The remaining four patient harboring resistant bacteria had monobacterial infections and underwent multiple debridements. A 66-year-old woman with methicillin-resistant organisms, VRE, and *Pseudomonas aeruginosa* required seven debridements, with methicillin-resistant organisms isolated during the second, third, and fourth debridements and *Pseudomonas* during the seventh debridement.

The average period of parenteral antibiotic administration was 5.6 wk (range: 4-8 wk) in 22 patients who underwent one debridement. Patients who underwent more than two debridements were subjected to antibiotic therapy for variable durations. The mean duration between primary and secondary surgeries was 5.4 mo (range: 1.2-24 mo). Secondary reimplantation could not be performed in three patients. One of these patients had a poor general condition and the other patients refused to undergo the procedure despite successful control of the infection.

Thirty-four (97.1%) of 35 patients did not show any sign of recurrence after secondary reimplantation. In one case, *Escherichia coli* infection recurred after 4 years. In that case an initial THA was performed to treat a pelvic-acetabular fracture, along with diversion colostomy.

Factors influencing the success of debridement

The rate of repeated debridement was higher in

Table 2 Analysis of factors affecting debridement and treatment of infected hip arthroplasty

Variable	No. of debridements (38 hips)			P value
	1 (n = 22)	2 (n = 10)	> 3 (n = 6)	
Mean age (yr)	61.09	68.50	68.33	0.168
Infesting organism (n)				0.002
Methicillin sensitive	2	2		
Resistant <i>Staphylococcus</i>	6	2	1	
Vancomycin-resistant <i>Enterococcus</i>	2	1		
<i>Pseudomonas</i>	1	2		
<i>Salmonella</i>	1			
Polymicrobial	1	3	5	
Negative culture	9			
Comorbidities (n)				< 0.001
0	10	1		
1	8	2	1	
2	2	5	2	
3	2	2	1	
4			1	
5			1	
Preoperative HHS				< 0.001
20-29			1	
30-39		1	3	
40-49	1	6	2	
50-59	7	1		
60-69	8	2		
70-80	6			

HHS: Harris hip score.

Table 3 Microbiological findings from 16 patients with periprosthetic hip infection who underwent multiple debridements (two or more)

Patient	Microorganism	No. of debridements
1	MRSA	2
2	<i>Streptococcus parasanguis</i>	2
3	<i>Staphylococcus haemolyticus</i>	2
4	<i>Enterococcus faecalis</i> (VRE)	2
5	MRSE	2
6	<i>Pseudomonas aeruginosa</i>	2
7	<i>Pseudomonas stutzeri</i>	2
8	MRSA, <i>Acinetobacter baumannii</i>	2
9	<i>Enterococcus faecium</i> (VRE), MRSA	2
10	<i>Serratia marcescens</i> , <i>Acinetobacter baumannii</i>	2
11	MRSE, <i>Escherichia coli</i> , <i>Staphylococcus haemolyticus</i>	3
12	MRSA	4
13	<i>Salmonella</i> , MRSE, MRSA	4
14	<i>Acinetobacter baumannii</i> , <i>Proteus penneri</i> , MRSA, <i>Enterococcus faecium</i> (VRE)	4
15	<i>Pseudomonas aeruginosa</i> , <i>Acinetobacter baumannii</i>	4
16	MRSA, MRSE, <i>Pseudomonas aeruginosa</i> , <i>Enterococcus faecium</i> (VRE)	7

MRSA: Methicillin resistant *Staphylococcus aureus*; MRSE: Methicillin-resistant *Staphylococcus epidermidis*; VRE: Vancomycin-resistant *Enterococcus*.

patients with associated comorbidities ($P < 0.001$), a low preoperative HHS ($P < 0.001$), and infection with resistant, gram-negative, and polymicrobial organisms ($P = 0.002$). We did not find any statistically significant disparity in the frequency of debridement with respect to patient age ($P = 0.168$).

Radioclinical results

The mean HHS improved from 46 ± 12.64 (range: 27-67 points) to 78 ± 10.35 points (range: 60-98

points), with 7 (20%), 12 (34%), 11 (32%), and five (14%) patients categorized as excellent, good, fair, and poor, respectively. During follow-up, a demarcation line was observed on the acetabular side in zones 1 and 2 in one patient and in zones 2 and 3 in another patient. Both of these patients presented with mild pain but required no further treatment.

Complications

Posterior hip dislocation in three patients was succe-

Table 4 Literature review: Two-stage treatment of infected hip arthroplasty

Ref.	Local cement device	Follow up (mo)	Infection control after first debridement	Infection control after reimplantation	Hips with resistant organisms	Successful control of infection
Hofmann <i>et al</i> ^[3]	Spacer	76	26/42 (62%)	26/27 (96%)	NA	NA
Salgado <i>et al</i> ^[11]	Spacer	6	28/45 (62%)	18/25 (72%)	12 (MRSA-12)	6/12 (50%)
Lim <i>et al</i> ^[35]	Spacer	54	38/45 (84%)	35/42 (83%)	24 (MRSA-14 MRCNS-10)	16/24 (67%)
Fink <i>et al</i> ^[2]	Spacer	35	40/40 (100%)	40/40 (100%)	3 (MRSA-3)	3/3 (100%)
Toulson <i>et al</i> ^[36]	Spacer	64.8	80/84 (95%)	80/84 (95%)	21 (MRSA-7, MRSE-12, VRE-2)	21/21 (100%)
Parvizi <i>et al</i> ^[25]	Spacer	12	61/127 (57%)	49/72 (67%)	66 (MRSA-34, MRSE-32)	48/66 (75%)
Romano <i>et al</i> ^[22]	Spacer	48	98/102 (96%)	98/102 (96%)	NA	NA
Leung <i>et al</i> ^[5]	Spacer	58	30/38 (79%)	30/38 (79%)	38 (MRSA-10, MRSE-26, Both-2)	30/38 (79%)
Uchiyama <i>et al</i> ^[12]	Spacer	48	33/36 (92%)	21/31 (67%)	15 (MRSA-10, MRCNS-4)	10/14 (71%)
Volin <i>et al</i> ^[10]	No spacer	48	43/46 (93%)	43/46 (93%)	9 (MRSA-2, MRCNS-7)	8/9 (89%)
Cordero-Ampuero <i>et al</i> ^[37]	No spacer	53	30/36 (83%)	20/20 (100%)	19 (MRSA-19)	17/19 (89%)
Van Diemen <i>et al</i> ^[26]	No spacer	96	118/136 (87%)	118/138 (87%)	7 (MRSA-7)	5/7 (71%)
Current study 2015	Spacer	64	37/38 (97%)	34/35 (97%)	26 (MRSA-4, MRSE-5, VRE-3, ¹ Poly-9)	25/26 (96%)

¹6 of 9 patients harbored resistant bacteria. MRSA: Methicillin resistant *Staphylococcus aureus*; MRSE: Methicillin-resistant *Staphylococcus epidermidis*; MRCNS: Methicillin-resistant coagulase-negative *Staphylococcus*; VRE: Vancomycin-resistant *Enterococcus*; NA: Not applicable; Poly: Polymicrobial infections.

successfully treated *via* closed reduction. Three patients experienced periprosthetic femoral fractures (Vancouver type C in one and B1 in two) that were successfully managed *via* open reduction and internal fixation. Limb length discrepancies of > 2 cm were observed in two patients.

DISCUSSION

Two-stage reimplantation with ALBC is a well-established procedure with a success rate exceeding 95% in recent studies^[21,22]. However, other studies have reported methicillin-resistant *Staphylococcus* infection control rates of 50%-80% with this procedure^[5,11,17]. In the present study, we achieved equivalent or better results, although first-stage debridement had to be repeated at least twice in 16 patients (42%), thus raising doubts about the effectiveness of two-stage revision with ALBC, especially for the control of virulent pathogens.

First-stage debridement was declared a failure after 6-8 wk for the following reasons: (1) a 6-8 wk course of an appropriate systemic antibiotic is sufficient for the eradication of pathogens^[23]; (2) ALBC becomes surrounded by reactive fibrous tissue, which reduces its therapeutic efficacy^[24]; and (3) repeated debridement represents the only possibility of eradicating local infection.

Studies have demonstrated persistent infection in 6%-28% of patients after first-stage debridement, thus requiring repeated debridements^[5,14,25,26]. Biofilm formation is a well-known and important step in the pathogenesis of polymer-associated infections^[27], necessitating a 1000-fold higher dose of antibiotics than that needed to eradicate a planktonic population^[28]. Although some studies demonstrated that the antibiotic levels remain well above the minimum inhibitory concentration for common microbes even several weeks after implantation^[29], in reality, the hydrophobic nature of bone cement permits effective elution of only 10%

of the antibiotic^[30]. Furthermore, ALBC has a favorable surface for bacterial growth, and long-term antibiotic use at a sub-inhibitory concentration facilitates the development of mutational resistance^[31,32].

Many studies have emphasized the emergence of bacterial strains with altered resistance profiles following adherence to ALBC in both *in vivo* and *in vitro* models^[32,33]. Therefore, the development of resistant organisms on cement spacers that lack suitable antibiotics is a matter of concern, and Giulieri^[34] suggested that, in patients with infections due to difficult-to-treat organisms such as *Enterococcus* or other multidrug-resistant organisms, two-stage reimplantation without the use of ALBC is preferred.

The most recently published success rates for a two-stage exchange without the use of ALBC were between 80% and 90%, comparable to the results of the current standard procedures that include ALBC (Table 4). The reasons for the high failure rate in our series during the first-stage remain unclear, although the overall treatment success rate was 97% despite that 26 (68%) patients were infected with virulent organisms. We found that the virulence of the causative microorganisms, including resistant microorganisms, gram-negative microorganisms (*Pseudomonas*, *salmonella*), and polymicrobial microorganisms, was associated with the persistence of infection and need for repeated debridement. Other important prognostic factors in our study were the presence of comorbidities and a low preoperative HHS. Medical conditions that impair host immunity, such as uncontrolled diabetes mellitus and liver cirrhosis, also increase the risk of persistent infection. We believe that a low HHS might predict the severity and duration of PJI.

Our study has several limitations. First, this was a retrospective study and most patients were referred; accordingly, there may have been variations in the data collection methods as well as referral bias. Second, the sample size was small, making it difficult to draw definitive conclusions. Third, we could not determine

the respective contributions of ALBC and systemic antimicrobial therapy to infection control. However, our analysis yielded some significant results. We believe that our findings are remarkable because we included an adequate number of patients for achieving statistically significant results, and the same surgeon performed all operations by using a standardized protocol.

Based on the results of this study, two-stage reimplantation can successfully treat PJI after hip arthroplasty, but the ability of ALBC to eradicate infection is limited because frequent debridements are required in some patients who are either in poor general health due to associated comorbidities or harbor infections with highly virulent, difficult-to-treat organisms.

COMMENTS

Background

Two-stage reimplantation is the preferred treatment protocol for chronic periprosthetic infection. However, the effectiveness of antibiotic-loaded cement spacers for chronic periprosthetic infection with difficult-to-treat microorganisms remains controversial. This study aimed to investigate the clinical effectiveness of two-stage reimplantation with antibiotic cement spacers for chronic periprosthetic hip infection and the risk factors associated with failure to control infection.

Research frontiers

Effectiveness of two-stage reimplantation with antibiotic-loaded bone cement and risk factors associated with failure to control periprosthetic joint infection.

Innovations and breakthroughs

Infection was controlled in 37 patients (97.3%) after the first stage. Second-stage reimplantation was possible in 35 patients (92%), and there was no evidence of infection recurrence in 34 (97.1%). Two or more first-stage debridements were performed in 16 patients (42%). A mean of 1.8 (range: 1-7) debridements were required to control infection. An increase frequency of debridement correlated significantly with increase comorbidity ($P < 0.001$), a low preoperative Harris hip score ($P < 0.001$), antibiotic resistance, and polymicrobial culture results ($P < 0.001$).

Applications

More repeated debridements were required in patients with chronic periprosthetic infections caused by resistant organisms, as well as in the patients with medical comorbidities at the time of two-stage reimplantation with antibiotic-loaded cement spacers.

Terminology

Although a few studies have demonstrated the maintenance of antibiotic levels above the minimum inhibitory concentration for common pathogens at several months after implantation, the relative hydrophobicity of bone cement allows the effective elution of only 10% of the antibiotic. Furthermore, the antibiotic-loaded cement spacer has an optimum surface for colonization, and prolonged exposure to antibiotics at sub-inhibitory levels facilitates mutational resistance.

Peer-review

This is an well-written paper.

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