Two-stage revision for periprosthetic joint infection of the hip: Culture-negative versus culture-positive infection

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ABSTRACT

Introduction: Negative culture findings are common in periprosthetic joint infection (PJI) of the hip.

Methods: Retrospective study was performed to total 84 patients which divided into two groups: culture-negative (n: 27) and culture-positive (n: 57).

Results: The reimplantation rate was 96.3% and 91.2% in the culture-negative and culture-positive groups, respectively. The overall infection control rate was 92.6% and 82.4% in the culture-negative and culture-positive groups, respectively.

Conclusion: Two-stage revision resulted a comparable outcome for the treatment of culture-negative periprosthetic joint infection of the hip compared to the culture-positive group

1. Introduction

Periprosthetic joint infection (PJI) is one of the most serious and difficult complications following hip arthroplasty.¹ Several procedures are available for the management of PJI of the hip, including debridement, one-stage revision, two-stage revision, and resection arthroplasty.² Of these, two-stage revision is considered the gold-standard and is the most popular procedure.³ Both the diagnosis and treatment of PJI of the hip can create significant difficulties for the managing surgeon.⁴ Accurate identification of the causal pathogen is very important for successful treatment, but unfortunately, pathogen identification in PJI of the hip is often difficult, and negative culture results are common,^{4,5} making the treatment of PJI of the hip more challenging. The negative culture findings often result in an uncertain diagnosis, and it is difficult to choose the appropriate antibiotics. Here we compared the treatment outcomes of two-stage revision arthroplasties for culture-negative versus culture-positive PJI of the hip.

2. Material and methods

Between January 2010 and May 2015, there were 94 hips (94 patients) diagnosed with PJI which were treated with the two-stage revision technique. Ten patients were lost to follow-up and were excluded

from the study. The remaining 84 cases were divided into 2 groups: culture-negative (n: 27) and culture positive (n: 57). Among the ten excluded patients, two had negative and 8 had positive culture results. The mean age of participating patients was 67.4 years (range, 40–85 years) in the culture-negative and 67.3 years (range, 36–84 years) in the culture-positive group. The diagnosis of PJI was made based on the criteria from the workgroup of the Musculoskeletal Infection Society,⁶ wherein patients have to meet one major or more than three minor criteria. The major criteria include: the presence of a sinus tract communicating with the prosthesis and growth of the microorganism from at least two separate tissue or joint fluid specimens from the affected prosthetic joint. The minor criteria include: elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), elevated synovial white blood cell count (WBC), elevated synovial neutrophil percentage, presence of purulence in the affected joint, isolation of a microorganism in one culture of tissue or fluid, and more than 5 neutrophils per high-power field on histopathologic examination. Cultures were obtained from both preoperative aspiration and intraoperative periprosthetic tissue with at least 2 weeks period of free antibiotic state for patients who received previous antibiotic treatment. Three or more intraoperative specimens were obtained from areas representative of inflammation during each surgical procedure. Every specimen was sent for aerobic, anaerobic, fungal, and acid-fast bacilli cultures. Culture

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Fig. 1. (A) Radiograph of a 68-year-old female (culture-negative group) who experienced right periprosthetic joint infection after receiving a bipolar hip hemiarthroplasty 5 years prior; (B) An extended trochanteric osteotomy was required to remove the femoral component in the first stage surgery, then an articulating antibiotic cement-spacer was inserted; (C) The second stage surgery was performed approximately 4 months after the first stage surgery; (D) Anteroposterior pelvic radiograph at her 2-year follow-up visit.

period was 7 days for aerobic and anaerobic bacteria, and 1 month for fungal and acid-fast bacilli. Culture results were presumed to be negative when none of the obtained specimens yielded a positive finding.

2.1. Surgical procedure

The first stage surgery consisted of drainage, sinus excision, removal

of the prosthesis, and thorough debridement of all infected tissues. If needed, the femoral component was removed by an extended trochanteric osteotomy (ETO) and fixed with wire and/or cable. This procedure was followed by the implantation of a spacer containing antibiotic-loaded cement. Smaller, presterilized prostheses retrieved from previous patients were used to provide an endoskeleton for the spacers. The femoral prostheses were implanted with a collar of

antibiotic-loaded cement (1 pack, 41 g). Acetabular components were made by inserting a bolus of cement (1 pack, 41 g) into the acetabular cavity and molding it into the shape of the cup. One or two screws were applied to fix the acetabular cement spacer to the bone if needed (Fig. 1). The choice of antibiotic depended on the results of the preoperative bacterial culture if it was positive. Two grams of Vancomycin (Hanomycin®, Samjim pharmaceutical, Seoul, Korea) and 1 g of a Piperacilin-Tazobactam mixed antibiotic (Tazocin®, Wyeth Pharm, Seoul, Korea) were used on each acetabular and femoral cement spacer if preoperative culture were negative. Antibiotic Simplex cement (Stryker, Allendale, NJ) impregnated with erythromycin was used for both the femoral components and the acetabular cavities. A negative suction drain was used after wound closure and was retained until the drainage was clear and less than 20 mL per day. Postoperative intravenous and oral antibiotics were administered, depending on the degree of wound healing and the CRP level. Postoperative antibiotics were selected in consultation with the Department of Infectious Disease at our institution. For the culture-negative group, broad spectrum cephalosporin antibiotics were used in 23 out of 27 (85%) patients, vancomycin in 8 patients, and ciprofloxacin in 2 patients. Postoperatively, patients were allowed to ambulate with partial weight bearing depending on their pain tolerance and muscle strength. Total WBC counts, ESR, and CRP levels were measured at weekly intervals for the first month and then at 4-week intervals. The criteria for conversion to THA were: (1) healing of wound and sinus (if any), (2) return of CRP and ESR levels to normal, and/or (3) medical fitness for surgery.⁷

During the second stage surgery, our protocol was to use a cementless prosthesis on both the femoral and acetabular components. Cemented fixation, however, was also done for acetabular or femoral reconstruction whenever it was not possible to perform cementless fixation. First generation cephalosporin antibiotics were administered for 3–5 days postoperatively. Two patients in culture-positive group still on antibiotic treatment during reimplantation, while none of the patient in culture-negative group received antibiotic treatment during reimplantation. Patients were allowed to walk with a walker or crutches as soon as their conditions permitted. Patients were followed at 1, 3, 6, and 12 months postoperatively and annually thereafter. Radiographs were obtained, and measurements for total WBC, ESR, and CRP levels were repeated at each follow-up visit. Clinical results were analyzed by calculating the Harris hip scores.⁸

The Chi-square test was used to compare all of the categorical data and the Student's *t*-test was used to compare numerical data between the culture-negative and culture-positive groups. All data were analyzed using the SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined by *p* values less than 0.05.

3. Results

The overall rate of negative culture results, including the patients who were lost to follow-up, was 30.8% (29/94). The mean follow-up period was 29.5 months (range, 12–78) in the culture-negative group and 30.9 months (range, 12–71) in the culture-positive group (*p* = 0.74). The reimplantation rate was 96.3% and 91.2% in culture-negative and culture-positive groups, respectively (*p* = 0.39). Five out of 52 patients (9.6%) who received reimplantation in the culture-positive group needed an additional procedure after the first stage operation prior to undergoing reimplantation total hip arthroplasty (Table 2). The mean interval between the first and second stage operations was 140.4 days (range, 62–534) in the culture-negative group and 147.8 days (range, 28–584) in the culture-positive group (*p* = 0.78). Five patients in the culture-positive group did not receive reimplantation until the final follow-up: four had spacer retention and one received a girdlestone operation. Among the patients who experienced spacer retention, one had ipsilateral lower leg cellulitis at the final follow-up visit, one refused the second surgery despite infection control, and two were in poor general condition due to chronic kidney

disease. One patient who did not undergo reimplantation in the culture-negative group was also in poor general condition due to stomach cancer. The infection was controlled in all of the patients who were in poor general condition by the final follow-up visit. The overall infection control rate was 92.6% (25/27) in the culture-negative group and 82.4% (47/57) in the culture-positive group (*p* = 0.21).

The infection recurred in 2 out of 26 (7.7%) patients in the culture-negative group and 8 out of 52 (15.4%) patients in the culture-positive group (*p* = 0.33). Six out of eight (75%) cases of recurrence in the culture-positive group were due to methicillin-resistant pathogens (3 *Methicillin-resistant Staphylococcus aureus* and 3 *Methicillin-resistant Staphylococcus epidermidis*). Two patients with recurrent infection in the culture-negative group received only irrigation and debridement surgery. Five out of eight (62.5%) patients with recurrent infection in the culture-positive group received a two-stage revision similar to the previous procedure. *Enterobacter cloacae* was isolated in one of the recurrent cases in the culture-negative group, while the other remained negative. In the culture-positive group, the isolated pathogen in the recurrent cases was: a similar pathogen in 3 cases, a different pathogen in 3 cases, and no isolated pathogen in 2 cases. The infection in all of the recurrent cases was controlled by the final follow-up. We obtained higher postoperative Harris hip scores in the culture-negative group at the final follow-up (*p* = 0.04), however, there was no significant difference in the time to normal CRP, time to recurrence, or complication rates between the two groups. Methicillin-resistant bacteria were the predominant cause of infection in the culture-positive group (27 of 57; 47.4%). Details on the isolated pathogens in the culture-positive group are shown in Table 3.

There was no significant difference in the general characteristics of the participating patients between the two groups, including age, gender, body mass index, preoperative C-reactive protein, preoperative erythrocyte sedimentation rate, preoperative white blood cell count, type of hip arthroplasty, previous history of irrigation and debridement, and preoperative Harris hip score. However, the culture-negative group had a significantly higher history of preoperative antibiotic use (*p* = 0.003) (Table 1).

4. Discussion

Previous studies have reported the rate of negative culture in periprosthetic joint infection of the hip from 0 to 25%.^{1,5,9,10} There have been only few previous studies comparing the treatment outcomes of culture-negative versus culture-positive PJI. Choi HR et al.⁵ reported the culture-negative PJI group showed significantly higher success rates compared to culture-positive group (85% vs 61%) with a mean follow-up period of 52 months and 60 months, respectively. However another study by Huang R et al.¹¹ reported no difference in infection control rates between culture-negative and culture-positive groups (70% vs 78%, respectively) with a minimum follow-up period of 12 months. Those two previous studies included both PJI of the hip and knee with various modalities of treatment (including the one-stage revision procedure) in their study. The present study, however, included only PJI of the hip treated with the two-stage revision procedure. This could possibly explain why a relatively higher infection control rate was seen in our study. Furthermore, our rate of recurrent infection was also relatively lower compared to the studies reported by Choi HR et al.⁵ which was 15% vs 39% and by Huang R et al.¹¹ which was 29% vs 21%; both in culture-negative group versus the culture-positive group. Recently, Li H et al.¹² compared the treatment outcomes of two stage-revision in PJI of the knee between culture-negative and culture positive groups. They found recurrence rates of 11% and 6.9% in culture-negative and culture positive groups, respectively.¹²

Antibiotic selection is challenging in culture-negative infections, and vancomycin is the most commonly used antibiotic in these cases. Choi HR, et al.⁵ and Huang R, et al.¹¹ both used vancomycin in 70% and 81% of their culture-negative PJI patients, respectively. Li H, et al.¹²

Table 1
Baseline data of culture-negative versus culture-positive patients.

Variable	Culture-negative (n: 27)	Culture-positive (n: 57)	p-value
Age (years)	67.4 (range, 40–85)	67.3 (range, 36–84)	0.94
Gender			0.8
Male	15 (55.5%)	30 (52.6%)	
Female	12 (44.5%)	27 (47.4%)	
Body mass index (kg/m ²)	23.8 (range, 18–32)	23.5 (range, 16–34)	0.59
CRP (mg/l)	7.4 (range, 0.4–14.2)	5.5 (range, 0.4–21.5)	0.14
ESR (mm/h)	70.1 (range, 17–120)	69.5 (range, 9–116)	0.83
WBC ($\times 10^3$ /ml)	14.7 (range, 7.1–25.3)	12.5 (range, 4.3–23.2)	0.05
Follow-up period (months)	29.5 (range, 12–78)	30.9 (range, 12–71)	0.74
Type of infected hip arthroplasty			0.13
Primary THA	14 (51.9%)	21 (36.8%)	
Revision THA	8 (29.6%)	13 (22.8%)	
Bipolar hemiarthroplasty	5 (18.5%)	23 (40.4%)	
Preoperative antibiotic treatment			0.003*
Yes	10 (37.1%)	6 (10.5%)	
No	17 (62.9%)	51 (89.5%)	
History of previous I&D			0.07
Yes	1 (3.7%)	10 (17.5%)	
No	26 (96.3%)	47 (82.5%)	
Preoperative HHS	44.3 (range, 15–76)	47.5 (range, 20–72)	0.40
Comorbidities			–
Hypertension	10 (37%)	23 (40.3%)	
Diabetes mellitus	4 (14.8%)	10 (17.5%)	
Cerebrovascular disease	1 (3.7%)	2 (3.5%)	
Cardiovascular disease	1 (3.7%)	5 (8.7%)	
Renal insufficiency	2 (7.4%)	7 (12.3%)	
COPD	3 (11.1%)	5 (8.7%)	
Liver disease	0	4 (7%)	
Malignancy	1 (3.7%)	3 (5.3%)	

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate; WBC: white blood cell count; THA: total hip arthroplasty; I&D: irrigation and debridement; COPD: chronic obstructive pulmonary disease; HHS: Harris hip score.

used a combination of vancomycin and ceftriaxone in all of their culture-negative PJI of the knee patients. In this study, vancomycin was only used in 29.6% (8 of 27) of culture-negative patients in order to reduce the risk of future bacterial resistance. This decision still resulted in a reasonable treatment outcome in the culture-negative group. An extensive utilization of parenteral vancomycin in culture-negative PJI may, therefore, be unwarranted and further study is needed.

There are several reasons why a pathogen may not be isolated. Beyond the technical issues encountered during the culture process, the use of antibiotics prior to obtaining cultures is known to be the most important factor resulting in negative cultures.¹³ In our study, 10 out of 27 (37.1%) patients in the culture-negative group had a prior history of antibiotic treatment for 1–3 weeks duration before culture samples were obtained. This number was significantly different compared to the culture-positive group, which was 6 out of 57 (10.5%). Choi HR et al.⁵ also found 27 out of 40 (68%) patients with culture-negative PJI had a prior history of antibiotic use, and it was significantly different from the culture-positive group (57 of 135, 42%). In order to increase the pathogen isolation rate, the following general considerations are recommended: refrain from using antibiotics for at least 2 weeks prior to joint aspiration, obtain multiple (3–5) deep tissue samples for culture, avoid preoperative antibiotics if a pathogen has not been isolated preoperatively, and obtain tissue culture samples prior to irrigation.¹³ Although our study showed that failure to identify the causal pathogen of PJI of the hip did not necessarily result in a treatment failure, more

Table 2
Treatment results of two-stage revision of culture-negative versus culture-positive.

Treatment Results	Culture-negative (n:27)	Culture-positive (n:57)	p-value
Interval period between stages (days)	140.4 (range, 63–534)	147.8 (range, 28–584)	0.78
Time to normal CRP (days)	72.5 (range, 13–411)	108.9 (range, 11–601)	0.13
Received reimplantation	26 (96.3%)	52 (91.2%)	0.39
Single cement spacer	26	47	
≥ 2 cement spacers	0	3	
Spacer and Girdlestone	0	2	
Never reimplanted	1 (3.7%)	5 (8.8%)	–
Spacer retention	1	4	
Convert to Girdlestone	0	1	
Recurrence of infection (after reimplantation)	2 (7.7%)	8 (15.4%)	0.33
I&D	2	1	
One-stage revision	0	1	
Two-stage revision	0	5	
Girdlestone	0	1	
Overall infection control rate	92.6% (25/27)	82.4% (47/57)	0.21
Time to recurrence of infection (weeks)	38.1 (range, 3–73)	73.9 (range, 4–209)	0.49
HHS at final follow-up visit	86.7 (range, 76–94)	82.9 (range, 47–95)	0.04*
ETO during 1st stage			0.39
Yes	12 (44.4%)	31 (54.4%)	
No	15 (55.6%)	26 (45.6%)	
Adverse events during spacer period			0.85
Spacer dislocation	2 (7.4%)	6 (10.5%)	
Periprosthetic fracture	5 (18.5%)	11 (19.3%)	
Cement dislodgement	0	2 (3.5%)	
Non-union of ETO	1 (3.7%)	0	
Adverse events after reimplantation			0.57
Aseptic loosening	1 (3.8%)	1 (1.9%)	
Dislocation	2 (7.7%)	4 (7.7%)	
Squeaking	1 (3.8%)	0	
Periprosthetic fracture	0	1 (1.9%)	

CRP: C-reactive protein, I&D: irrigation and debridement; HHS: Harris hip score; ETO: extended trochanteric osteotomy.

Table 3
Isolated pathogens in the culture-positive group.

Isolated pathogen	Total Number of cases	Number of cases received reimplantation	Number of cases of recurrent infection
MRSE	16	16	3
MRSA	10	8	3
MRCNS	2	2	–
MSSA	6	6	–
<i>Staphylococcus capitis</i>	3	3	–
<i>Streptococcus haemolyticus</i>	1	1	–
<i>Proteus mirabilis</i>	1	1	–
<i>Pseudomonas aeruginosa</i>	5	4	–
<i>Corinobacterium</i> sp.	1	1	–
<i>Escherichia coli</i>	1	1	–
<i>Streptococcus sanguinis</i>	1	1	1
<i>Acinetobacter baumannii</i>	1	1	–
<i>Klebsiella pneumoniae</i>	1	1	–
<i>Candida albicans</i>	1	–	–
<i>Mycobacterium</i> sp.	1	–	–
Multiorganism	6	6	1

MRSA: Methicillin-resistant *Staphylococcus aureus*; MRSE: Methicillin-resistant *Staphylococcus epidermidis*; MRCNS: Methicillin-resistant coagulase-negative *Staphylococcus*; MSSA: Methicillin-sensitive *Staphylococcus aureus*.

intense pathogen investigation is still recommended in order to prevent unnecessary antibiotic use. Some authors recommend sonication of the retrieved prosthesis¹⁴ or a biomolecular-based test such as polymerase chain reaction (PCR) to increase the probability of isolating a pathogen,¹⁵ although availability of this technology is often a limitation. In our study, those tests were not done, therefore false-negative infections could still be present. The present study has some other limitations as well, including the fact that it was a retrospective evaluation with a relatively short follow-up period. Future studies with a longer follow-up period are needed to confirm our findings.

In conclusion, two-stage revision resulted a comparable outcome for the treatment of culture-negative periprosthetic joint infection of the hip compared to the culture-positive group.

Conflict of interest

None.

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