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ORIGINAL STUDY

Periprosthetic infection : Are current treatment strategies adequate ?

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Two-staged resection arthroplasty with delayed reimplantation is currently the method of choice for treatment of an infected total hip arthroplasty. There is paucity of data regarding the risk factors for reinfection after reimplantation. The objective of this study was to determine the efficacy of two-stage resection arthroplasty for infected THA and to identify risk factors for reinfection. The outcome of this procedure was evaluated in 54 consecutive patients at our institution from January 1999 to August 2005. The mean follow-up time for patients who were successfully treated was 32 months (range : 24 to 76 months). Infection with methicillin-resistant organisms occurred in 33 patients (61%). Recurrent infection was diagnosed in 14 patients (26%) after the second stage reimplantation procedure at an average of 10.6 months. An elevated ASA, which is an indicator of advanced comorbid health status, and infection with methicillin-resistant organisms were risk factors for treatment failure. An additional 8% of the cohort developed early mechanical failure at a mean of 13.8 months. The increase in the number of resistant organisms and the rise in the number of patients with comorbid conditions have compromised the efficacy of two-stage exchange arthroplasty. Hence novel techniques for the treatment of periprosthetic infection are desperately needed.

Keywords : total hip replacement ; infection ; revision ; recurrence.

INTRODUCTION

Periprosthetic joint infection (PJI) is a serious complication that can develop after total hip arthroplasty (THA) and affect the quality of life of the patient. The number of joint arthroplasties is expected to increase dramatically in the near future, and a concomitant rise in the incidence of PJI is very likely (*14*). Greater expenditure on the treatment of infected joint arthroplasties will undoubtedly lead to added strain on the health care system (*27*). The indications for THA are continuously expanding to include patients with greater comorbid conditions that predispose them to PJI. The liberal use of antibiotics during the past decade has raised concern regarding the emergence of resistant organisms and their detrimental effect on joint arthroplasty (*5,12*). Therefore, the current treatment strategies for eradicating infection must be thoroughly investigated and reviewed.

Two-staged resection arthroplasty with delayed reimplantation is the preferred method for treatment

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of infected hip prostheses in North America (*7,13*). Successful eradication of PJI has been reported using this technique, with infection-free rates of greater than 90% at latest follow-up (*3,10,17*). However, there are numerous variables that influence the success of this procedure including patient characteristics, the complexity of surgery, the severity of infection, and the virulence of the infecting organism. There is paucity in the literature regarding the risk factors for reinfection after reimplantation of infected THA. Furthermore, the impact of virulent organisms especially methicillin-resistance on the survivorship of reimplanted hip prostheses remains controversial with varying success rates reported (*6,16,18,26,29*). The small sample size and heterogeneous mix with total knee arthroplasty of previous studies are possible reasons for this variation (*1,25,31*).

The purpose of our study was two-fold. First this study sought to determine the efficacy of two-stage resection arthroplasty followed by delayed reimplantation for infected THA in a relatively large number of patients treated at our center during recent years. Second objective of the study was to evaluate the impact of various factors, in particular methicillin-resistance, on the outcome on two-stage exchange arthroplasty with the intention of identifying risk factors for failure.

MATERIALS AND METHODS

We performed a review of our joint arthroplasty database to identify patients who underwent two-stage resection arthroplasty as treatment of their infected THA. A total of 77 patients with an infected THA were managed at our institution from January 1999 to August 2005 with removal of their components. Only 54 (70%) patients underwent delayed reimplantation with cementless components, while the remaining 23 cases were not reimplanted for various reasons. Four patients died postoperatively consequent to septic shock, hepatorenal syndrome, myocardial infarction, and *Clostridium difficile* toxic colitis. The comorbid state and advanced age of the other 19 patients precluded reimplantation since the risks outweighed the benefits.

Our final cohort consisted of 29 females and 25 males with an average age of 65 years (range : 39-86 years) at reimplantation. The primary diagnosis leading to initial THA was degenerative osteoarthritis in 38 patients, avascular necrosis in 6 patients, posttraumatic osteoarthritis in 6 patients, rheumatoid arthritis in three, and congenital dysplasia of the hip in one. Periprosthetic infection occurred after primary arthroplasty in 27 patients while the other 27 cases were previously revised for non-infection reasons. For 24 patients, the initial arthroplasty was performed at our institution, while the remaining 30 patients had their index surgery performed at a referring hospital. Although 19 patients underwent previous irrigation and debridement with retention of components for infection prior to admission, all patients underwent their first resection arthroplasty for PJI at our institution.

Patients were diagnosed with PJI according to the following criteria : positive preoperative aspiration cultures on solid media, positive intraoperative cultures, and/or the presence of an abscess or sinus tract communicating with the joint space. An organism could not be isolated in seven cases, three of whom were on chronic antibiotic treatment. Nonetheless, resection arthroplasty was performed in these patients due to high clinical suspicion and elevated erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values. The organisms cultured from the aspirate fluid or intraoperative specimens are listed in table I. The average ESR and CRP were 81 mm/hr (range : 14 to 120 mm/hr) and 9.3 mg/dl (range : 0.5 to 33.2 mg/dl) respectively.

The interval from index surgery to the diagnosis of infection averaged 36 months (range : 1 to 204 months). The periprosthetic infection was classified as acute, acute haematogenous, or chronic according to clinical presentation (*28*). There were 23 patients who presented acutely, 6 of whom had haematogenous seeding, while the remaining 31 patients presented with chronic infection. The initial clinical symptoms of infection included pain in 39 patients, an abscess or draining sinus tract in four patients, and systemic symptoms including fever and rigors in 13 patients.

All patients underwent resection arthroplasty with removal of implants and cement in cemented arthroplasties with thorough debridement of devitalized tissues and insertion of an antibiotic laden cement spacer block. Four grams of vancomycin and 3.6 grams of tobramycin were added to 40 grams of cement in each patient. The patients were then treated with 6 weeks of intravenous antibiotics based on the results of the sensitivities of the organism cultured. The most commonly used antibiotics were vancomycin, cefazolin, rifampin, and ciprofloxacin. Revision of the cement spacer block was performed in seven patients due to persistent purulent drainage or systemic symptoms of fever and rigors which delayed

Table I. — Organisms cultured from infected total hip arthroplasty

Organism Type	Number	Percentage
Staphylococcus aureus (MRSA)	15	27.7
Staphylococcus epidermidis (MRSE)	10	18.4
Staphylococcus aureus (MSSA)	8	14.8
Streptococcus species	4	7.4
Staphylococcus epidermidis	2	3.7
Enterococcus faecalis Group D	2	3.7
Pseudomonas aeruginosa	1	1.9
Proteus mirabilis	1	1.9
Corynebacterium striatum	1	1.9
Klebsiella pneumoniae	1	1.9
Candida albicans	1	1.9
No growth	8	14.8

reimplantation. Six of the seven patients were originally infected with methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE). One patient became septic postoperatively but was resuscitated. One patient developed a myocardial infarction (MI), while another suffered a common peroneal nerve injury. Four patients were diagnosed with symptomatic deep vein thrombosis and/or pulmonary embolism.

The second-stage procedure consisted of delayed reimplantation with primarily cementless revision components at an average of 139 days (range : 58 to 609 days). Seven patients required an anti-protrusio cage with a cemented all polyethylene cup for acetabular reconstruction due to severe bone loss. All revision stems implanted were press-fit and either monoblock or modular in nature. Morselized bone allograft was used in 11 cases for structural support and bone defect filling. Multiple intraoperative cultures were obtained at time of reimplantation. Cultures were positive in three patients who were treated with appropriate intravenous antibiotics for six weeks. Postoperatively, two patients suffered acute blood loss that necessitated intubation and resuscitative measures. Another patient developed a myocardial infarction, while two additional patients were diagnosed with deep vein thrombosis and/or pulmonary embolism.

We collected patient specific information including demographics, BMI, smoking habits, preoperative wound classification, and nutritional status. Intraoperative factors such as estimated blood loss, operative time, the administration of prophylactic antibiotics, and the use of allogenic transfusion were included in our analysis. Bone loss was determined using the Paprosky classification scheme for the acetabulum and femur (*21*). Comorbid risk factors for reinfection including diabetes, vascular disease, chronic obstructive pulmonary disease, and heart disease were assessed. The prevalence of inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis along with the use of steroids or other immunosuppressant medications were retrieved.

All patients were followed-up in clinic on regular basis with radiographs. An SF-36 health questionnaire was administered preoperatively and postoperatively at date of last follow-up. Reoperation for infection was defined as failure of treatment. The mean follow-up time for patients who were successfully treated was 32 months (range : 24 to 76 months). One patient died two months after reimplantation due to causes not related to the surgery ; the patient was asymptomatic at first postoperative visit. Therefore, we were left with a total of 53 patients that were reimplanted and had at least a two year follow-up. Institutional review board approval was obtained to conduct our study.

Statistical Analysis

All statistical analyses were performed using SAS version 9.1 software. A univariate analysis with means and standard deviations for continuous variables and proportions for categorical variables were performed. The means of a continuous outcome were compared using T-test (parametric) and Wilcoxon (non parametric) test. Proportions of a categorical outcome were compared using Chi square (parametric) and Fisher Test (non- parametric). A p-value less than 0.05 was considered to be significant. Unadjusted analysis was performed to assess the differences in demographics, comorbidities, intraoperative variables, and complications between patients who failed treatment and those who had a successful outcome. Multiple regressions analysis was performed after adjusting for the above potential confounders to determine the risk factors for reinfection.

RESULTS

Recurrent infection was diagnosed in 14 patients (26%) after the second stage reimplantation procedure at an average of 10.6 months (range : 1 to 17 months). Four patients presented with systemic symptoms of fever and rigors, while the remaining 10 patients had recurrent purulent drainage and persistent hip pain. Seven cases required repetitive

irrigation and debridement procedures to control their infection with retention of components. An organism was isolated on solid media in all 7 patients. However, the organism(s) isolated from the site of recurrent infection was the same as that cultured from time of resection in only two cases, while a different organism(s) manifested in the remaining five cases. An additional seven patients required resection arthroplasty for treatment for their relapsing PJI. The same organism was isolated in three patients as that of the index resection. Only three of the seven patients underwent secondary reimplantation with cementless components ; the advanced age and comorbid condition of the remaining four cases precluded reimplantation. All patients with recurrent infections were treated with effective intravenous antibiotics determined according to the antibiogram for a six week period after revision surgery.

A total of five patients in our cohort were revised for aseptic failure at a mean of 13.8 months (range : 1 to 24 months) after reimplantation. One patient had two prior irrigation and debridement procedures performed to control recurring infection, while the remaining four cases were infection free prior to mechanical failure. Multiple intraoperative specimens were obtained during revision surgery ; all were negative after five days of incubation. Three of the five patients presented with recurrent dislocation, two of whom were found to have dissociation of a constrained liner. The remaining two patients presented with persistent groin and thigh pain and were found to have a loose acetabular and femoral component respectively. Revision surgery was successfully performed using revision components without complications, and all five patients were asymptomatic at latest follow-up.

Therefore, the reinfection rate in our study group was 26%, while the combined revision rate for both reinfection and mechanical failure (18/53) after reimplantation reached 34% at the latest follow-up. The mean preoperative SF-36 scores for the physical and mental health dimensions prior to resection were 43 and 56 respectively. The postoperative scores after reimplantation in patients who had a functional prosthesis at latest follow-up were 48 for physical function and 60 for mental health. There was a significant improvement in physical function ($\Delta = 8$; $p = 0.02$) and preservation of mental health ($\Delta = 4$; $p = 0.21$) compared to baseline status.

Table II. — Various risk factors and variables were compared between the successfully treated and failed group

Variables	p-value
Patient Specific	
BMI	0.56
ASA	0.03
Smoker	0.86
Heart disease	0.06
Diabetes	0.51
Insulin use	0.02
Lung disease	0.51
Inflammatory disease	0.58
Wound classification	0.44
Surgical Factors	
EBL	0.39
Operative time	0.18
Intraoperative transfusion	0.09
Postoperative transfusion	0.09
Acetabular bone loss	0.95
Femoral bone loss	0.89
Inciting Organism	
Methicillin resistant	0.03

We performed a univariate analysis of the different surgical variables and patient related characteristics that may have played a role in the reinfection of 14 patients in our cohort (table II). The subgroup that was revised for reinfection had significantly higher mean ASA scores compared to the patients that were asymptomatic at latest follow-up ($p = 0.03$). Although diabetes mellitus was not a significant risk factor ($p = 0.51$), insulin use, which is an indicator of advanced diabetes, was more prevalent in patients with reinfection ($p = 0.02$). Methicillin resistant organisms (MRSA or MRSE) were cultured from intraoperative specimens more frequently in cases of reinfection. Patients who were initially resected for MRSA or MRSE were four more times more likely to require reoperation for reinfection after delayed reimplantation (OR = 4 ; $p = 0.03$). Potential risk factors for recurrence of infection that were not statistically significant included inflammatory disease ($p = 0.58$) and

immunosuppressant medication intake (p = 0.1), operative time (p = 0.18) and estimated blood loss (p = 0.39). Pre-existing cardiac disease approached statistical significance (p = 0.06). Morselized bone allograft was used in 11 cases for structural support and augmentation ; all patients were asymptomatic and infection free at latest follow-up. Multivariate analysis that adjusted for the effect of the different confounders revealed that both the ASA score (OR = 9.14 ; p = 0.05) and the presence of methicillin-resistant organisms (OR = 4.57 ; p = 0.03) at time of resection were significant risk factors for reinfection.

DISCUSSION

Despite considerable advancement in surgical techniques and preoperative care, the rate of PJI following THA has remained relatively constant at approximately 1% (*6,8,22*). The current treatment strategies for eradicating infection in THA include one stage reimplantation with cemented components, two stage exchange arthroplasty, or resection arthroplasty (*13,15,17*). The two stage exchange arthroplasty has gained wide support and is the most popular procedure performed in North America for treating PJI (*4,32*). Although highly acclaimed as a successful procedure (*7,31*), the reinfection rate in our cohort (26%) and in some previous studies (18-20%) (*1,8,20*) raises serious concern regarding its efficacy. Therefore, understanding the risk factors for failure may optimize the final outcome, the survivorship of the prosthesis, or even the patient.

Our investigation was designed with the intention of identifying the risk factors for failure for two-stage exchange arthroplasty. However, there are certain limitations that are inherently present in our study. Patients were followed up prospectively, but data collection pertaining to the confounding variables listed above was performed in a retrospective manner. The rate of reimplantation in our study group was 70% of all patients who underwent resection at our institution for PJI. Therefore, our results may be applicable only to patients healthy enough to undergo reimplantation. Although the sample size of our study group is one of the largest to be reported in the literature, the reason for some of the variable not to reach statistical significance may relate to sample size.

The indications for THA are continuously expanding to encompass older patients with greater systemic ailments and morbidities and an increased propensity for developing infection (*23,30*). Patients with an infected THA are faced with a complex course that entails prolonged hospitalization and multiple surgeries to control their disease with possible deleterious consequences. The high postoperative mortality (5%) and major complication rates as reflected in our cohort and in a previous study (10%) conducted by McPherson *et al* (*19*), are testimonies to this concern. Nonetheless, the orthopaedic community has taken immense strides and genuine effort in improving treatment techniques that meet the demand of an ever changing patient population.

Thirty years ago, an infected THA was treated with removal of components and reimplantation with antibiotic impregnated cemented components (*3,25*). The majority of early studies using cemented components reported excellent results in eradicating PJI with reinfection rates ranging from 5% to 13% (*3,6,9,16,18,32*). In a large series of 82 infected THAs treated by resection arthroplasty and reimplantation with a cemented prosthesis, McDonald *et al* documented reinfection in 13% of patients at 2 to 13 years follow-up. On the other hand, Sanzen *et al* (*26*) documented an overall success rate of only 80% using cemented prostheses and attributed the high treatment failure to infections with mixed flora. However, early mechanical failure and loosening of cemented components posed as a deterrent to the long term durability of the implant (*11,24*). Therefore, implanting press fit porous coated components during the second stage reimplantation procedure was an attractive option.

Numerous investigators reported low reinfection rates using cementless components for delayed reimplantation of infected THA (*4,10,13*). Haddad *et al* (*7*) reported a recurrence rate of 8% in 50 consecutive patients with infected THA who were treated with two-stage exchange arthroplasty using uncemented components. Another series that investigated the functional benefits of articulating

cement spacers concluded that this technique can effectively eradicate infection (22/23) and afford the patient early range of motion during the first stage of treatment for infected THA (*4*). The infecting organism responsible for reinfection has been shown to be different from the one cultured during initial resection in a substantial percentage of cases (*7,18*). It was postulated that treatment did not fail per se in these cases, but that the patient's health status and comorbid state were predisposing factors for reinfection. We noted a similar phenomenon in which a different organism was isolated in 9 out of the 14 relapsing infections.

Contrary to other reports, Nestor *et al* (*20*) reported a rate of infection recurrence approaching 18% in their early experience with cementless revision THA. More disappointingly, the high rate of early loosening and dislocation (14%) prompted caution with regard to the long term durability of cementless fixation. The reinfection rate in our population (26%) and early mechanical failure (7.5%) of successfully treated patients echo the same concerns raised more than a decade ago. A more recent report from the Mayo Clinic reported a similarly high reoperation rate for infection (20%) after cementless reimplantation of septic THA (*8*). Berry *et al* (*1*) noted that 18% of 18 patients treated with reconstruction using cementless components and allograft succumb to reinfection. However, we did not observe any recurring infections among the 11 patients in our cohort who received bone allograft.

Clearly, there is wide variability in the outcome of infected THA using two-stage resection arthroplasty with cementless components. The comorbid profile of patients under study may vary among institutions, in which high volume referral centers are treating cases with more complex problems. We noted that patients with a higher ASA score, which is an indicator of the general comorbid state of the patient, were more prone to reinfection. Another potential risk factor for treatment failure that has been debated is the virulence of the inciting organism. Earlier studies highlighted the detrimental effect of the lipopolysaccharide layer of Gram negative bacteria on the infection free survivorship (*16,18*). Other investigators negated the role of Gram negative organisms and demonstrated no significant difference in success rate with regard to individual bacterial species (*6,26*). Interest in *Staphylococcus epidermidis* and *Staphylococcus aureus* then surfaced, and their recurrent infection rates were compared to other less resistant bacteria (*2,25*). Hope *et al* (*9*) documented a 13% infection recurrence rate in 72 THAs infiltrated with *Staphylococcus epidermidis*. On the contrary, Brandt *et al* (*2*) reviewed 38 total joint arthroplasties infected with *Staphylococcus aureus* (non-methicillin resistant) with a five-year cumulative treatment failure of 2.8% ; the investigators concluded that delayed reimplantation is an efficacious means of eradicating infection.

With the widespread use of antibiotics and growing bacterial resistance, a shift in the organism profile is forthcoming (*5,12*). Hanssen *et al* (*8*) documented a reinfection rate of 22% in 9 THAs treated with two-stage reimplantation for methicillin-resistant Staphylococcus infection. Volin *et al* (*29*) compared the efficacy of delayed reconstruction of infected total joint arthroplasty caused by methicillin-resistant and non-methicillin resistant organisms. Although reinfection occurred similarly in both groups, the failure rate (3/46) was an impediment to reaching any definitive conclusions. In our cohort, methicillin-resistant organisms including MRSA and MRSE were present in 46% of all cultures obtained at time of resection. We found that colonization with MRSA or MRSE was a significant risk factor for reinfection after adjusting for the confounding effect of other pertinent variables. Patients infected with methicillin resistant organisms are 4 times more likely to fail treatment. In fact 6 of the 7 patients that required revision of their cement spacer block due to persistent purulent drainage or systemic symptoms were initially infected with MRSA or MRSE.

Current strategies to treat periprosthetic infection remain imperfect. Two-stage exchange arthroplasty with all its inherent problems and inconveniences imparted a modest success in treatment of PJI at our high volume specialized center. With the rise in number of sick patients undergoing total hip arthroplasty and with the increase in the number of virulent and resistant organisms, novel strategies

for treatment of prosthetic joint infection are desperately needed.

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