Complications - Infection

Time to Reimplantation: Waiting Longer Confers No Added Benefit

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A B S T R A C T

Background: While the preferred surgical treatment for chronic periprosthetic joint infection (PJI) in North America is a 2-stage exchange arthroplasty, the optimal time between first-stage and reimplantation surgery remains unknown. This study was conceived to examine the association between time to reimplantation and treatment failure.

Methods: Using an institutional database, we identified PJI cases treated with 2-stage exchange arthroplasty between 2000 and 2016. Musculoskeletal Infection Society criteria were used to define PJI, and treatment failure was defined using Delphi criteria. The interstage interval between first-stage and reimplantation surgery for each case was collected, alongside demographics, patient-related and organism-specific data. Multivariate logistic regression analyses were used to examine association with treatment failure.

Results: Our final analysis consisted of 282 patients with an average time to reimplantation of 100.2 days (range, 20-648). Sixty-three patients (22.3%) failed at 1 year based on Delphi criteria. Time to reimplantation was not significantly associated with failure in both univariate (P = .598) and multivariate (P = .397) models. However, patients reimplanted at >26 weeks were twice as likely to fail in comparison to those reimplanted within <26 weeks (43.8% vs 21.1%), and this finding reached marginal significance (P = .057). Patients who failed had significantly more comorbidities (P = .008). Charlson comorbidity index was the only variable significantly associated with treatment failure in regression analysis (odds ratio, 1.40; 95% confidence interval, 1.06-1.86; P = .019).

Conclusion: The length of the interstage interval was not a statistically significant predictor of failure in patients undergoing 2-stage exchange arthroplasty for PJI.

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The management of periprosthetic joint infection (PJI) of the hip and the knee remains imperfect and clinicians are constantly striving to improve treatment outcomes by modifying surgical protocols and host risk factors based on evidence-based literature. In recent years, the preferred surgical treatment for chronic PJI of the hip and knee in North America has trended toward 2-stage exchange arthroplasty [1–6]. The 2-stage protocol generally consists of an initial stage, during which the infected prosthesis is explanted and a temporary antibiotic-laden cement spacer is placed into the joint, and a second stage consisting of reimplantation of revision prosthesis. One question often asked by surgeons in this setting is when patients should be reimplanted within the context of a 2-stage exchange arthroplasty, and whether delaying reimplantation confers a higher rate of treatment success.

Prior attempts at answering this question within the literature have been largely inconclusive due to the heterogeneity of cohorts examined with respect to PJI definition, host factors, organism profile, and surgical treatments employed. A study by Kubista et al [7] found that a longer time period between spacer insertion and reimplantation was associated with PJI recurrence, whereas other authors suggest improved outcomes with a prolonged interim interval [8]. The optimal duration for the interstage interval has not been established within the literature and varies between institution and surgeon from a few weeks to several months or years [9,10].

The aim of our study is to determine whether the timing between the first and second stages of a 2-stage exchange arthroplasty for PJI influences the rate of failure, defined using

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Delphi consensus criteria [11]. We hypothesize that prolonging the interstage interval gives no additional advantage with respect to treatment outcome. In addition, we report other independent predictors of failure for 2-stage exchange arthroplasty in the treatment of chronic PJI, such as host factors and microbial characteristics. To our knowledge, this work represents the largest single institutional cohort of reimplanted PJIs using the standardized Musculoskeletal Infection Society (MSIS) definition for PJI, as well as the Delphi consensus definition for treatment failure.

Materials and Methods

We retrospectively reviewed the clinical characteristics of 580 patients with late chronic PJI of the hip and the knee, treated with 2-stage exchange arthroplasty at a tertiary arthroplasty institution. Electronic databases were used to identify patients undergoing 2-stage exchange arthroplasty for the treatment of PJI at our institution between January 2000 and June 2016. Patient demographics were collected including age, gender, ethnicity, body mass index, and Charlson Comorbidity Index (CCI) (Table 1). Details of the 2-stage exchange were also collected including definition relative to the MSIS criteria [12], affected joint, length of stay (LOS), number of days between stages, details of the infecting organism, type of spacer used (static vs articulating), the need for a spacer exchange before final reimplantation, and subsequent treatment failure, as defined by the Delphi consensus method [11].

A total of 680 cases of chronic PJI were identified who underwent surgical procedures for the treatment of infection. Of these, 580 patients underwent 2-stage exchange arthroplasty. Among the 580 patients undergoing 2-stage exchange, 481 went surgical procedures for the treatment of infection. Of these, 28 underwent reoperation for infection with a different organism; 28 underwent reoperation for infection with a different organism; and 23 died as a complication of the infection. Patient characteristics and surgical details stratified by the failure/success of treatment are presented in Table 2.

Patients who failed had significantly more comorbidities (P = .008) and a longer length of hospital stay (P = .024), compared to those who did not fail. While not reaching statistical significance, cultures from PJI patients who failed were nearly twice more likely to grow resistant organisms (19.0% vs 10.0%; P = .076) and almost half as likely to be negative (15.9% vs 27.9%; P = .069). After adjusting for age, gender, CCI, LOS, resistant organisms, culture-negative PJI, type of spacer, and time to reimplantation (interstage interval) within a multivariate regression model (Table 3), the CCI was the only variable significantly associated with treatment failure (odds ratio [OR], 1.40; 95% confidence interval [CI], 1.06-1.86; P = .019). It was also the only variable significantly associated with a shorter time to failure (hazard ratio, 1.27; 95% CI, 1.02-1.58; P = .036).

Time to reimplantation was not significantly associated with failure in univariate (P = .598) and multivariate (P = .397) analyses. Average time to reimplantation was 109.0 (SD ± 79.3) days in the group of patients who failed at 1-year follow-up compared to 95.6 (SD ± 64.5) days in the group of patients who did not fail. The receiver operating characteristic curve did not point out a specific threshold time to reimplantation above which patients are at significantly higher risk of failure (area under the curve = .52; Fig. 1). While time to reimplantation was not associated with failure as a continuous variable, stratifying patients based on weeks to reimplantation showed a trend toward higher failure rates in those with longer time to reimplantation (Fig. 2). The highest failure rates were seen in patients who were reimplanted after more than 26 weeks. These patients were almost twice as likely to fail compared to those who were reimplanted within less than 26 weeks (43.8% vs 21.1% failure) and this nearly reached significance (P = .057).

Discussion

Two-stage exchange arthroplasty is the preferred treatment for chronic PJI in North America that has a variable success rate [13]. One of the issues regarding 2-stage exchange arthroplasty relates to the optimal timing of reimplantation. There are no metrics that can guide surgeons in determining the optimal interstage interval between initial resection and second-stage reimplantation. Timing

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Charlson Comorbidity Index Parameters.</th>
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<tbody>
<tr>
<td>Clinical Conditions</td>
<td>Weights</td>
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<tr>
<td>Myocardial infarct</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>2</td>
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<tr>
<td>Dementia</td>
<td>3</td>
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<tr>
<td>Cerebrovascular disease</td>
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<td>Chronic lung disease</td>
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<td>Connective tissue disease</td>
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<td>Ulcer</td>
<td>3</td>
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<td>Chronic liver disease</td>
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<tr>
<td>Diabetes</td>
<td>3</td>
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<tr>
<td>Hemiplegia</td>
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<tr>
<td>Moderate or severe kidney disease</td>
<td>3</td>
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<tr>
<td>Diabetes with end-organ damage</td>
<td>3</td>
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<tr>
<td>Tumor</td>
<td>6</td>
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<tr>
<td>Leukemia</td>
<td>6</td>
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<td>Lymphoma</td>
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<tr>
<td>Moderate or severe liver disease</td>
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<td>Malignant tumor</td>
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<td>Metastasis</td>
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<td>AIDS</td>
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to reimplantation still varies considerably between different institutions and individual surgeons from a few weeks to several months [9,10]. One commonly held notion is that delaying reimplantation confers a higher rate of treatment success. However, this practice is based on limited evidence and may subject patients to a considerable duration of interstage morbidity. Furthermore, the reported failure rates for 2-stage revision surgery remain between 9% and 33%, warranting further investigation into the operative and patient-specific factors that may increase the likelihood of a successful outcome [14].

In the present study, we assessed the rates of treatment failure in patients who underwent a 2-stage exchange for chronic PJI and examined whether the time period before reimplantation was associated with treatment success, defined using Delphi consensus criteria [11]. We also assessed for any association of host-specific and organism-related factors on treatment failure following reimplantation. The main finding of our study was that delaying the time to reimplantation did not significantly improve treatment success of 2-stage exchange arthroplasty (OR, 1.00; 95% CI, 0.997-1.007; P = .397). That said, our data demonstrated a general trend toward higher failure rates in those with longer time to reimplantation. Patients reimplanted at ≥26 weeks were almost twice as likely to fail compared with those reimplanted in <26 weeks (Fig. 2; P = .057; 43.8% vs 21.1% failure).

There is no consensus in the literature about the optimal timing between stages. Prior studies have suggested various timings for reimplantation. Fitzgerald [15] recommended a minimum interstage interval of 3 months for PJI caused by less virulent organisms and 1 year for highly virulent organisms. McDonald et al [10] reported higher rates of reinfection in a small cohort of patients who were reimplanted within 1 year (n = 26), in comparison to patients with a prolonged interstage interval over 1 year (n = 56). In contrast, Lieberman et al reported no increase in failure rates for patients who underwent reimplantation based on a 6-week interstage protocol vs those who were reimplanted after 1 year [16]. Haddad et al [17] also reported no increase in rates of reinfection by reducing the interval period to 3 weeks in most cases.

A study by Sabry et al [18] found an increased duration between resection and reimplantation was associated with higher rates of infection recurrence in a cohort of 314 infected TKAs treated with 2-stage exchange. Their median interval between stages for patients who completed both stages of 2-stage revision was 103 days (range, 2-470 days). Differences in findings seen between our investigation and Sabry et al’s may be accounted for by their use of different definitions for PJI and treatment failure, variability in their length of follow-up (59-4202 days), and their inclusion of infected knees only. Our study employed the gold standard MSIS definition for PJI diagnosis, as well as the consensus Delphi criteria for definition of treatment failure, and a minimum of 1-year follow-up.

Prior studies have reported a wide range of failure rates between 0% and 33% following 2-stage exchange arthroplasty [7,9,10,14,17-22]. This variability in proportion of failed cases could be attributed to different PJI treatment failure definitions employed within each study. While some authors defined failure as any further surgical procedure related to the reimplanted joint [14,23], other authors considered procedures with prosthesis retention not to be a mode of failure [18,24,25]. Furthermore, certain studies cite reinfection by the same organism as prerequisite for failure [18], while other studies did not make this organism-specific distinction [7,22]. Differences in sample size and variation in follow-up duration also may have influenced the rates of failure reported. Furthermore, the diagnostic definition of PJI employed can have a considerable effect upon the reported rates of failure; with poorer outcomes likely in patients with established chronic infection in comparison to patients undergoing procedures for indefinite criteria who may not be classified as infected if current MSIS criteria were used [26-28].
The CCI was assessed in this study as an independent risk factor for treatment failure [29]. In both univariate and multivariate analyses, CCI was found to be a significant predictor of future failure following reimplantation (OR, 1.40; 95% CI, 1.06–1.86; \( P = 0.019 \)). It was also the only covariate in our regression model significantly associated with a shorter time to failure (\( P = 0.036 \)).

Multiple published studies also report the preexisting comorbidities as an independent risk factor for failure after 2-stage exchange. This seems logical as a compromised immune status and poor general health may complicate the process of treatment and ability to eradicate infection. Comorbidities, individually or in the context of indices like CCI or American Society of Anesthesiologists, have been associated with a higher risk of reinfection following 2-stage revision. McPherson et al considered the overall medical and immune health of the host as a major factor in determining the natural course of a deep-seated PJI [30]. Earlier studies also showed a higher incidence of reinfection among cases of poor host conditions including malnutrition, immune deficiencies, chronic hypoxia, and diabetes mellitus [31,32]. These reports and our findings may be useful for preoperative risk stratification and to better consent patients of their elevated risk of treatment failure, where applicable.

Previous reports also suggest a higher failure rate in peri-prosthetic infection treatment when methicillin-resistant bacteria are present [14,33,34]. Various methods of antibiotic treatment, different surgical procedures, and small population sizes in majority of studies lead us to uncertainty of importance of resistant microorganism as a risk factor of failure. Also, infection recurrence may be attributed to either infection with new microorganisms resulting in surgical intervention [17,35–39] or reinfection by the same organism despite exchange arthroplasty and antibiotic administration [2,10,34,40]. In the present study, there appeared to be a signal indicating a higher rate of failure in patients infected with resistant organisms. Cultures in patients who failed were 2 times more likely to grow resistant organisms, but with the given number of patients, this did not reach statistical significance.

The main limitation of this study is its retrospective design and reliance upon existing medical records, which may have introduced bias. Furthermore, our institution is a tertiary care referral center and most patients in the study had prior treatment at different institutions. This raises the potential for selection bias in preference of a more complex patient cohort. We were also unable to separately account for certain host variables, such as malnutrition and diabetes mellitus, within our regression due to multicollinearity and model restrictions. Our finding of increased failure in patients reimplanted at >26 weeks could have been biased by a tendency for surgeons to account for subtle clinical factors of concern, such as slow wound healing or persistent effusion, that we were unable to detect in our chart review. The low absolute number of Gram-negative infections (n = 4) within this cohort makes further evaluation of the influence of these infections upon the outcome of a 2-stage revision necessary. We should keep in mind that although the sample size investigated is larger than prior similar studies, it might still be too small to detect certain differences between subsets of patients due to the low event rate of PJI. Therefore, it is possible that additional risk factors for reinfection after 2-stage reimplantation may be found in future studies with larger samples.

Despite the aforementioned limitations, the present study did not detect a clear association between time to reimplantation and treatment failure following 2-stage exchange arthroplasty. Furthermore, we found that delaying the time to reimplantation did not significantly improve treatment success of 2-stage exchange arthroplasty. Patient comorbidity index was significantly associated with treatment outcome, highlighting the importance of host optimization and risk stratification before intervention.

References


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