EVALUATION OF TWO PROCEDURES FOR TREATMENT OF KNEE PROSTHETIC JOINT INFECTION (PJI)

A Thesis in
Public Health Sciences
by
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Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Science

May 2017
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ABSTRACT

Background PJI remains a tremendous burden for individuals and the global health care industry because it can bring severe adverse outcomes. There are typically two surgical methods to treat PJI, however, whether one procedure is superior to the other remains controversial.

Purpose The purpose of this study was to evaluate and compare the health outcomes of two types of surgical procedures for the treatment of knee prosthetic joint replacement (PJI) using a large health insurance claims database.

Methods The MarketScan Commercial Claims and Encounters database for the years 2013 to 2014 was used to identify a cohort of 7,540 patients treated for PJI. Cure rates associated with one-stage versus two-stage procedures were compared, as were demographic characteristics, use of antibiotic treatment after discharge, and health care costs.

Results In the cohort of 7,540 PJI cases, 6,218 (82.5%) patients received a one-stage procedure and 1,322 patients received a two-stage procedure. A chi-square test showed that the proportion of patients receiving antibiotic medication after discharge was not significantly different between the two procedure groups (p=0.34). However, length of antibiotic treatment after discharge varied between the groups. Patients who underwent a two-stage procedure had longer period of antibiotic use (39.8 days vs 25.5 days, p<0.0001). Geographical factors (rural vs urban, region of residence), health care costs, and individual characteristics (age, gender, and etc) were significantly associated with the use of surgical procedures (p<0.05).

Conclusions Although the two-stage procedure is the gold standard for treatment of PJI, the one-stage procedure was more prevalent in this sample of privately-insured patients. Post-procedure
use of antibiotic medication suggested that the cure rate of PJI did not differ significantly across the two surgical procedures. However, the length of antibiotic treatment was significantly different between two procedure groups. Choice of surgical procedure for treatment of PJI was associated with health care costs, geographical factors and characteristics of patients.
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CHAPTER 1. Introduction

Prosthetic Join Infection (PJI)
PJI is a life threatening complication that significantly decreases quality of life of patients after joint replacement surgery.\(^1\) While the majority of joint arthroplasties provide pain-free function to patients with damaged joints, some patients will suffer from PJI after the original surgery due to aseptic failure.\(^1\) There are many reasons for aseptic failure, such as loosening of the inserted device, fracture of the prosthetic material itself, wear, implant malposition, dislocation-instability, or material fatigue.\(^1\) Various studies have shown the incidence of prosthetic joint infection to be within the range of 0.3% to 5.9%.\(^2\)\(^-\)\(^8\)

Main Treatment Procedures for PJI
Among available surgical methods, there are typically two procedures to treat patients with PJI after the original surgery – one-stage and two-stage revision procedures. During a two-stage exchange arthroplasty, the implants are removed, infected tissues are debrided and a temporary antibiotic-impregnated spacer is placed (stage one). Afterwards, the patient undergoes many weeks of intravenous antibiotics, followed by re-implantation at a later date (stage two).\(^3\) During the time between the first and second stage of the revision, patients are often immobile, suffer severe pain due to the lack of the functioning joint, and may experience systemic toxicity associated with the administration of antibiotics. In a one-stage exchange revision procedure, the infected prosthesis is removed, infected tissues are debrided, and a new prosthesis is re-implanted during the same procedure.\(^3\) The selection of revision procedure depends on multiple factors such as the severity of infection, microbiology of the pathogen, acceptability of patients, and even physicians’ preference.\(^2\)

Limitations of Previous Research
Whether or not a two stage revision operation is superior to a single stage procedure remains one of the most important controversies in the treatment of PJI. The two-stage revision procedure is considered by infectious disease professionals to be the ‘gold standard’ of treating prosthetic joint infection,\(^18\) with an overall efficacy reported to be 65-100%.\(^9\)\(^-\)\(^16\) However, many patients still receive the one-stage procedure.\(^17\) A systematic review comparing the two procedures was published in 2013 and questioned the advantage of a two-stage procedure over a one-stage
procedure. The study included 63 original studies and showed that the single stage procedure had a lower reinfection rate after revision (rates ranged from 0% to 41% in two-stage studies, and 0% to 11% in single stage studies). This review also showed that two-stage procedures were used more often than one-stage procedures, and that the low quality of evidence of both procedures calls for direct comparison between these procedures.

In addition to lack of direct comparison between the two surgical methods and strong evidence supporting either of the procedures, almost all the studies were oriented from a clinical perspective and ignored social-economic factors such as cost of procedures and types of health insurance. Furthermore, most published studies focused only on hip PJI and involved small sample sizes (usually <400 patients), making it difficult to conduct multivariable analyses and to generalize the results to a broader population. Therefore, further work is needed to compare the two surgical methods.

**Study Purpose**

Using a national health insurance claims database, we are able to obtain a large sample of patients with PJI and evaluate multiple risk factors and multiple health outcomes. The purpose of this study was to assess and compare the health outcomes of the two-stage procedure versus the one-stage procedure for treating knee PJI and to answer the following questions: 1. Does the two-stage procedure improve clinical outcomes in a large, commercially insured population? 2. How does length of antibiotic treatment vary by medical procedure and socioeconomic factors? 3. Do socioeconomic factors affect choice of revision procedure?
CHAPTER 2. Materials and Methods

Data Source Data for this study came from the MarketScan Commercial Claims and Encounters (CCE) database for the years 2013-2014, which contains real-world data for healthcare research and analytics.\(^1\) The MarketScan CCE database consists of reimbursed health care claims for employees, retirees, and their dependents of over 250 medium and large employers nationwide. Individuals included in the database are covered under commercial (private) insurance plans (Medicaid or Medicare data are not included).\(^1\) The database includes individual-level claims information from more than 130 payers, and records the health care service use and expenditures for more than million covered individuals each year.\(^1\) The databases consist of several core data sets, including the Inpatient Service data set, Outpatient Pharmaceutical claims and RedBook pharmacy reference data. The information contained in each data set can be combined and linked within an individual using a unique identifier (Enroll ID).

Study Population PJI cases with at least one revision operation were identified originally in the MarketScan Inpatient Service data set based on Current Procedural Terminology 4th Edition [CPT-4] codes (27486 and 27487 indicated one-stage revisions and codes 27488, 27319-58 and 27447-58 indicated two-stage revisions). In this cohort, 7,540 PJI cases were targeted based on CPT-4 codes in the Inpatient claims and then outpatient claims were linked to each case through their Enroll ID. Therefore the new data set contains both inpatient and outpatient pharmaceutical information of the study sample.

Study Outcomes The outcomes are related to antibiotic treatment after discharge from the hospital. If the infection is cured, then the patients would not need antibiotics after being discharged. Otherwise, if reinfection occurs, the patients would be on post-discharge antibiotic treatment. Two outcome variables related to post-discharge antibiotics course were assessed in this research: 1. Treatment Failure, which is a binary variable indicated by whether or not the patients were on antibiotic treatment after discharge. 2. Length of antibiotic treatment, which measures the number of days of antibiotic treatment. To access the information about antibiotic treatment, first, all pharmaceutical claims for each individual were linked with RedBook data based on National Drug Code. Then, claims for antibiotics were identified based on the RedBook Therapeutic Class (classes 4-12 indicate antibiotics). Length of antibiotic treatment was
calculated by summing up Days Supplied of all the antibiotic claims for each Enroll ID. If the length of antibiotic treatment was greater than zero, then the patient was assumed to have failed treatment.

Co-variables (predictors) The main predictor is Treatment Procedure, which indicates if the individual went through a one-stage revision or two-stage revision, identified based on the procedure codes described above. If the patients had multiple claims and received both procedures, we considered them as two-stage patients. We also obtained information on individual’s age, sex, geographic location, type of health insurance plan, cost of procedures, and cost of antibiotics. The cost of procedures was measured from the perspective of the patient and included all co-insurance, deductible and copayments for each inpatient claim. The cost of antibiotic medications was calculated by adding up co-insurance, deductible and copayment for all the antibiotic pharmaceutical claims.

Statistical Analysis After construction of the cohort and selection of variables of interest, the statistical analysis could begin. Statistical analysis of the results was performed with SAS 9.4. The following statistical methods were employed in the analysis (Table 1): 1. A chi-square test was used to test if there was an association between treatment procedures and cure rate (indicated by antibiotic treatment). 2. A logistic regression model was used to assess the effects of multiple predictors on whether patients were cured. All the variables of interest were included at the beginning. Then, backward-selection was done to include only significant factors in the model. 3. The simple linear regression was used to examine predictors’ influence on the length of antibiotic course.

**Table 1 Statistical Plan**

<table>
<thead>
<tr>
<th>Question</th>
<th>Study Outcomes</th>
<th>Predictors</th>
<th>Statistical Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question 1</td>
<td>Treatment Failure</td>
<td>Treatment Procedure, Age, Gender, Region</td>
<td>Chi-square Logistic Regression</td>
</tr>
<tr>
<td>Question 2</td>
<td>Length of Treatment</td>
<td>Treatment Procedure, Cost of claims, Age, Gender, Region</td>
<td>T-test Linear Regression</td>
</tr>
<tr>
<td>Question 3</td>
<td>Treatment Procedure</td>
<td>Cost of claims,</td>
<td>Logistic Regression</td>
</tr>
</tbody>
</table>

4
| Insurance type, Age, Gender, Region |  |
CHAPTER 3. Results

A total of 7,540 commercially insured PJI cases with at least one revision operation in 2013-2014 were included in this study (Table 2). The average age of the cohort was 56.5 years and there was no difference in age between the two procedure groups. The sample included slightly more women (56.4%) than men (43.6%), a difference that was highly significant. Without considering other factors simultaneously, the p-value associated with sex was highly significant, indicating choice of the revision procedure was different by sex. Revision procedures also differed significantly by geographic location. The majority of cases were from the north central and south regions, with fewer cases identified in the northeast and west regions. The out-of-pocket cost was significantly higher for two-stage procedures, which averaged $129 compared to $75 for one-stage procedures. The cost of antibiotics was also higher after two-stage procedures; the average was 6 dollars for one-stage procedures and 10 dollars for two-stage procedures.

Table 2 Basic Statistics by Revision Procedures

<table>
<thead>
<tr>
<th></th>
<th>Overall, N=7,540</th>
<th>One-Stage, N=6,218</th>
<th>Two-stage, N=1,322</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, Mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, Mean ± SD</td>
<td>56.5 ± 6.9</td>
<td>56.5 ± 6.7</td>
<td>56.1 ± 7.8</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Male</td>
<td>3,286</td>
<td>43.6</td>
<td>2,557</td>
<td>41.1</td>
</tr>
<tr>
<td>Female</td>
<td>4,254</td>
<td>56.4</td>
<td>3,661</td>
<td>58.9</td>
</tr>
<tr>
<td><strong>Urban/Rural</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.0510</td>
</tr>
<tr>
<td>Urban</td>
<td>6,217</td>
<td>82.4</td>
<td>5,152</td>
<td>82.9</td>
</tr>
<tr>
<td>Rural</td>
<td>1,312</td>
<td>17.6</td>
<td>1,066</td>
<td>17.1</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.0016</td>
</tr>
<tr>
<td>Northeast</td>
<td>1,379</td>
<td>18.3</td>
<td>1,128</td>
<td>18.1</td>
</tr>
<tr>
<td>North Central</td>
<td>1,976</td>
<td>26.2</td>
<td>1,610</td>
<td>25.9</td>
</tr>
<tr>
<td>South</td>
<td>2,656</td>
<td>35.2</td>
<td>2,164</td>
<td>34.8</td>
</tr>
<tr>
<td>West</td>
<td>1,308</td>
<td>17.4</td>
<td>1,124</td>
<td>18.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>221</td>
<td>2.9</td>
<td>192</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>Cost of procedure (dollars), Mean ± SD</strong></td>
<td>119.7 ± 307.2</td>
<td>75.1 ± 211.5</td>
<td>129.2 ± 323.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Cost of antibiotic treatment (dollars), Mean ± SD</strong></td>
<td>6.6 ± 29.5</td>
<td>5.9 ± 27.7</td>
<td>9.7 ± 36.4</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
The majority (82.5%) of the PJI patients received a one-stage procedure, and only 17.5% of them received a two-stage procedure (Fig 1). The patterns of post-discharge antibiotic course are similar in two procedure groups (chi-square test: p=0.34). For treatment failure, 36.7% of patients experienced treatment failure after one-stage procedures, while 38.1% of patients had treatment failure after two-stage procedures. Overall, 37% of patients had treatment failure.

**Figure 1** Treatment Procedures by Treatment Failure

For the individuals who experienced treatment failure, the length of antibiotic treatment varied in the two procedure groups (t-test: p<0.0001). In the one-stage group, the average length of treatment was 23.5 days while in two-stage group, the average days of antibiotic treatment was 39.8 days.

Table 3 shows the factors associated with patients’ use of treatment procedure. Age, gender, employment status, region, cost, region, insurance type, and metropolitan area were included in the original model. Then, metropolitan area, insurance type and employment status were excluded because those factors were not significantly contributing to the model. Age was left in the model because it was marginally significant. The final model was highly significant (p<0.001)
and indicated that age, gender, region and cost of procedures were closely associated with the choice of procedure. After adjusting for co-variables (Table 4), women are nearly 2 times more likely to choose single stage procedures than men. Although age was a marginally significant factor, the odds ratio was very close to 1, indicating the age effect is small in scale. Region as a co-variable was always significantly associated with choice of procedure in all the models used, indicating that the preference of revision procedure was not the same in different geographic regions.

Table 3 Factors Associated With Choice of Treatment Procedure (Logistic Regression)

<table>
<thead>
<tr>
<th>Factors</th>
<th>DF</th>
<th>Chi-Square Statistics</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
<td>6.3826</td>
<td>0.0892</td>
</tr>
<tr>
<td>Gender</td>
<td>1</td>
<td>82.2456</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Region</td>
<td>4</td>
<td>18.5877</td>
<td>0.0009</td>
</tr>
<tr>
<td>Rural/Urban</td>
<td>1</td>
<td>2.8896</td>
<td>0.0115</td>
</tr>
<tr>
<td>Cost of Procedure</td>
<td>1</td>
<td>22.1867</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Table 4 Odds Ratio and 95% Confidence Interval

<table>
<thead>
<tr>
<th>Factors</th>
<th>Odd Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.009</td>
<td>0.995 1.023</td>
</tr>
<tr>
<td>Female vs Male</td>
<td>1.841</td>
<td>1.513 2.239</td>
</tr>
<tr>
<td>North Central vs Northeast</td>
<td>0.948</td>
<td>0.709 1.269</td>
</tr>
<tr>
<td>South vs Northeast</td>
<td>0.963</td>
<td>0.729 1.273</td>
</tr>
<tr>
<td>West vs Northeast</td>
<td>1.423</td>
<td>0.988 2.050</td>
</tr>
<tr>
<td>Unknown vs Northeast</td>
<td>1.735</td>
<td>0.828 3.633</td>
</tr>
<tr>
<td>Cost of Procedure</td>
<td>1.001</td>
<td>1.000 1.001</td>
</tr>
</tbody>
</table>
CHAPTER 4. Conclusion and Discussion

Major Findings

This study compared the health outcomes and social-economic factors associated with two revision procedures for the treatment of knee PJI. First, we found that the single stage procedure was more commonly used than the two-stage procedure in real-world settings (87.5% to 17.5%). In previous research, the two-stage procedure was more commonly studied than the one-stage procedure because it is recommended by health care professionals and there were more records of two-stage procedures. Factors associated with the choice of revision procedure to treat knee PJI include sex and cost: females are less likely to receive the recommended two-stage procedures compared to males, and the higher cost also seems to affect the choice of revision procedure. Because limited clinical information is available in the claims data, we are unable to assess why there is a sex disparity in choice of PJI procedure. It is possible that female patients may have fewer risk factors (e.g., smoking or comorbidities) that prevent them from getting the two-stage procedure.

Second, we found that the overall risk of treatment failure (indicated by post-discharge antibiotic use) was 40%, and the risk was not significantly different in the two procedure groups. In previous studies, some researchers reported that the two-stage procedure had a lower failure rate, while others showed one-stage procedures gave a lower failure rate. The failure rate of two-stage revision procedures was comparable with the rates observed in the previous studies, but for the one-stage procedure, the failure rate in our study was much higher than the rates found in the systematic review (38% vs 11%). This can be explained by the inclusion of more one-stage procedure users in the MarketScan data. This finding is contrary to previous studies.
showing a better health outcome from the two-stage procedure. Because our study population is relatively younger (the majority of them are under 60 years) compared to the overall patient population with degenerative joint diseases, it is possible that patients in our study are in better health generally and thus are less likely to experience treatment failure, even though they received different surgical procedures.

Third, the length of post-discharge antibiotic treatment depended on surgical procedure. People receiving one-stage procedures had a shorter course of antibiotic treatment after hospital discharge. Length of antibiotic treatment is related to the microbiology and severity of the infection, so it is possible that people receiving one-stage procedures had less severe infection and therefore shorter course of antibiotics.

**Clinical and policy implications**

According to our study results, it seems that the choice of knee PJI procedure is not simply based on the clinical recommendation. Social-economic factors were not mentioned in previous studies. In our study, we showed that cost of procedure, geographic location of the claims and sex also affected which procedure was used. Therefore, even though the two-stage procedure is preferred by physicians in terms of treating the infection, one-stage revision procedures are more common, perhaps due to patient preferences or insurance policies. Interestingly, we do not find that the two-stage procedure is superior over the one-stage procedure with respect to the treatment failure rate, raising a concern that insurance companies may further deny the two-stage procedure for patients with PJI. This question cannot be answered by any observational studies without fully
controlling patients’ risk factors. Carefully-designed randomized trials with large sample sizes would be ideal to evaluate health outcomes following knee PJI surgery.

Limitations
Several major limitations need to be discussed when interpreting our study findings. First, MarketScan data are not representative of the US general population. The sample population was relative young individuals with private health insurance, so the conclusions are not necessarily applicable to the U.S. population. Moreover, MarketScan data lack information on microbiology of infections and other detailed clinical data. Without the data on pathogens, severity of the infection and patients’ health conditions, the association suggested above could be attenuated. The second limitation came from the definition of treatment failure. In other studies, failure was diagnosed clinically by health care professionals by specific statistics. In this study, post-discharge use of antibiotic treatment was used as an indication of treatment failure of PJI. Thus, the indirect definition of study outcome may cause some bias.

Another limitation is the follow-up time that was used. The reinfection can occur within 3 months or more than 24 months after the surgery. Therefore, by using data from 2013-2014, we only captured early reinfections (within 3 months) and some delayed reinfections (3-24 months after surgery), but failed to capture the late reinfections, which can occur after 24 months of operation. Hence, the failure rates reported in this study do not represent overall treatment failures.

Conclusions
Despite these limitations, this study shows that in real-world practice, two-stage surgery was not commonly conducted for patients with knee PJI. In addition to clinical factors, socioeconomic factors also play an important role in determining which procedure patients receive. Interestingly, there was no difference in the treatment failure rates between the two procedures. Randomized clinical trials are needed to better evaluate health outcomes following different surgical procedures for the treatment of knee PJI.
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