Original Article

Prevalence and Risk Factors of Reinfection after Two-Stage Exchange Procedure for Treating Periprosthetic Knee Infection

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Background: Two-stage exchange procedure has been considered as the gold standard treatment of chronic periprosthetic joint infection (PJI) after total knee arthroplasty. However, reinfection still occurs.

Objective: The present study aimed to identify prevalence and risk factor of reinfection after two-stage exchange procedure.

Materials and Methods: Thirty-one patients, who diagnosed chronic PJI and underwent two-stage exchange procedure in our institute, were retrospectively reviewed with a minimum follow-up of 2 years. Reinfection was recorded and defined as a case. Risk factors were compared between case and control groups.

Results: Reinfection was found in 4 cases (12.9%). Age, gender, body mass index, history smoking, presence of sinus tract before the first stage procedure, time between the first and second stage procedure, pre-operative hemoglobin level, operative time, blood transfusion and types of organism were similar between groups. In univariate analysis, American Society of Anesthesiology classification in reinfection cases was higher than control group. However, in multivariate analysis, there were no any significant risk factors in our study.

Conclusion: The present study demonstrates that two-stage exchange procedure has a high success rate with 2-year reinfection rate of 12.9%.

Keywords: Knee, Infection, Two-stage exchange procedure, Prevalence, Arthroplasty, Risk factors

J Med Assoc Thai 2019;102(Suppl.9): 15-9
Website: http://www.jmatonline.com

Periprosthetic joint infection (PJI) is the most common cause of failure after total knee arthroplasty (TKA)[1]. From the Medicare data, incidence of PJI occurs in approximately 1.1% after primary TKA[2]. This complication is associated with substantial patient morbidity and high socioeconomic burden[3]. The principle of management in this condition is eradication of infection and maintaining knee functionality.

According to Tsukayama classification[4], PJI can be divided into 4 types; positive intraoperative culture, early postoperative infection, acute hematogenous infection and chronic infection. For chronic PJI, two-stage exchange procedure that originally described by Insall et al[5] has been widely considered as the gold standard of treatment. This procedure consists of previous implant removal, extensive debridement of infected tissue, and antibiotic impregnated cement spacer insertion. Following antibiotic administration and eventual revision surgery[5-8].

Although two-stage exchange procedure is reported to have a high success rate[2,8,9], reinfection can still occur and carries significant additional morbidity and cost. Risk factors for failure after two-stage exchange procedure usually can be categorized into patient, surgical and pathogen factors. However, the information about this issue is limited.

Therefore, the purpose of the present study is aimed to determine the prevalence and identify the risk factors of reinfection after two-stage exchange procedure for treating PJI after TKA.

Materials and Methods

The authors conducted a retrospective analytic study of the PJI patients who were diagnosed and treated at our hospital between January 2003 and December 2013. The present study was approved by our institutional review board. The inclusion criteria were patients who were diagnosed PJI after primary total knee arthroplasty and treat either first or second stage exchange procedures at our institute. PJI was defined using the criteria of International consensus meeting in 2013[10]. The authors excluded the patients who

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How to cite this article: Sukontahong S, Ruangsomboon P, Narkbunnam R, Chareancholvanich K, Pornrattanamaneewong C. Prevalence and Risk Factors of Reinfection after Two-Stage Exchange Procedure for Treating Periprosthetic Knee Infection. J Med Assoc Thai 2019;102(Suppl.9): 15-9.

had incomplete data, follow-up time less than 2 years after second stage exchange procedure, and PJI due to fungal or zoonotic organisms.

After diagnosing PJI, all patients were undergoing the first stage procedure. This stage consisted of open arthrotomy, prosthetic removal, extensive debridement of infected tissue and antibiotic impregnated cement spacer insertion. Postoperatively, an infectious disease specialist was consulted to consider the proper type and duration of antibiotic administration. Clinical symptoms and signs, level of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were monitored during the follow-up period. After the antibiotic-free period, the second stage exchange procedure, including cement spacer removal and revision arthroplasty would be performed when infection was subsided. The criteria for second stage exchange procedure was determined as follows: 1) no clinically suspected infection, 2) CRP and ESR return to normal level, 3) either surgeon or an infectious disease specialist had the consistent opinion to go on revision surgery, and 4) intra-operative frozen section had less than 5 polymorphonuclear cell per high power field. All procedures were performed by experienced arthroplasty surgeons in our hospital.

Demographic data including age, gender, body mass index (BMI) and history of smoking were collected. Comorbidity status was recorded and categorized using American Society of Anesthesiology classification (ASA)[11]. Presence of sinus tract before the first stage procedure, time between the first and second stage exchange procedure, pre-operative hemoglobin level, operative time and blood transfusion at the second stage exchange procedure, and types of organism were also recorded. Reinfection within 2 years after the second stage procedure was also diagnosed using the same criteria and recorded as the primary outcome.

Statistical analysis

Data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL). Shapiro-wilk test was done for checking the normal distribution of data. Continuous data were presented as mean (SD) or median (min-max) that depended on the normality of data. Categorical data were presented as percentage. According to reinfection, the patients were categorized into reinfection or case group and control group. Univariated analysis using unpaired t-test, Mann-Whitney U test, Chi-squared or Fisher-exact test was performed to compare the parameters between case and control groups. Logistic regression analysis was performed to identify the risk factor. Model fitting for logistic regression was done with all factors. The survivorship after two-stage exchange procedure was analyzed using Kaplan-Meier curve. The starting point was the time of the second stage procedure and the end point was the time of reinfection. Statistical significance was set as a p-value <0.05.

Results

A total of 40 patients was included in the present study. Nine patients were excluded due to follow-up time less than 2 years (4 cases), incomplete data (3 cases) and fungal infection (2 cases). Finally, the remaining 31 patients were analyzed. Four cases had reinfection at 5, 14, 15 and 20 months after the second stage procedure, respectively. Thus reinfection rate in the present study was 12.9%.

There were no significant differences in patient characteristics and surgical parameters between control and case group except ASA (Table 1). In post-hoc analysis for ASA, the patients were divided into two groups; healthy (ASA 1) and non-healthy (ASA 2 to 3) group. The authors found that there was no significant difference of healthy patients between control and case group ($p = 0.999$).

In logistic regression analysis, there was no significant risk factor in our study. In survival analysis, the mean survival time was 127.2 ± 7.9 weeks (95% CI; 111.7 to 142.6). Kaplan-Meier curve of two-stage exchange procedure was shown in Figure 1. The median survival time could not be calculated due to a small number of reinfection.

Discussion

PJI is one of the most challenging problem encountered in TKA. In chronic PJI, two-stage exchange procedure is commonly performed as the gold standard for treatment[5,13]. It seems to have the highest success rate to eradicate infection[2]. However reinfection is still occurred with a wide range from 9% to 27%[6-8,13-15]. In accordance with above mentioned studies, our study revealed that the prevalence of reinfection after two-stage procedure was 12.9%. Unlike previous studies[14,16] that recruited the patients with inflammatory arthritis and post traumatic osteoarthritis, the authors focused on index diagnosis of primary osteoarthritis. Inflammatory arthritis and post traumatic osteoarthritis were associated with increasing risk of PJI[16,17]. Thus It might lead to the lower reinfection rate in the present study. Reinfection rate from recent studies was shown in Table 2.

The important limitation of our study was small sample size. It makes us unable to find the risk factors. Our institute is a tertiary care center. Many PJI patients were referred to our institute after undergoing the first stage procedure. The important information for PJI diagnosis was often loss. The authors therefore collected the patients who underwent the first and second stage procedure in our institute. That is a reason why our study had limited sample size. Another limitation was retrospective design. It might introduce selection bias and information bias. Lack of nutritional status data and variety of type and dose of antibiotics were problematic. In our study, demographic data including age, gender, BMI, history of smoking and operative time, there were not significant risk factors. These results were similar to previous literatures[8,14-16]. Although Watt et al[18] found that morbid obesity (BMI $\geq$40 kg/m^2) was a significant reinfection after two-stage exchange procedure, there was no morbid obesity patient in the present study. For comorbidity status, ASA were significant risk factors in univariate analysis. But the results did not reach statistical significance in multivariate analysis. These outcomes were

Table 1. Patient characteristics

Characteristics	Total (n = 31)	Control (n = 27)	Case (n = 4)	*p*-value
Age (yrs), mean (SD)	66.7 (13.0)	65.7 (13.6)	72.8 (3.8)	0.321
Gender, female	18 (58.1%)	16 (59.3%)	2 (50%)	0.999
BMI, mean (SD)	25.9 (3.9)	26.2 (4.0)	23.9 (1.6)	0.286
Smoking	5 (16.1%)	4 (14.8%)	1 (25%)	0.525
ASA				
1	4 (12.9%)	4 (14.8%)	0 (0%)	0.048*
2	18 (58.1%)	17 (63%)	1 (25%)	
3	9 (29%)	6 (22.2%)	3 (75%)	
Presence of sinus tract	11 (35.5%)	10 (37.0%)	1 (25.0%)	0.553
Time between first and second stage procedure (wks), median (min-max)	26 (6 to 126)	26 (8 to 126)	27 (6 to 70)	0.859
Preoperative Hb level (g/dL), mean (SD)	12.3 (1.7)	12.1 (1.3)	13.4 (3.5)	0.532
Operative time (min), median (min-max)	165.0 (105.0 to 250.0)	160.0 (105.0 to 250.0)	172.5 (155.0 to 225.0)	0.461
Blood transfusion	14 (45.2%)	12 (44.4%)	2 (50%)	0.622
Type of organism				
MRSA	6	5	1	0.598
CNS	7	6	1	0.662
Streptococcus agalactiae	2	2	0	0.755
Streptococcus pyogenes	1	0	1	0.129
Pseudomonas aeroginosa	3	3	0	0.651
Eschericia coli	1	1	0	0.871
ESBL positive *Eschericia coli*	1	0	1	0.129
Enterococcus faecalis	3	3	0	0.651
Mycobacterium fortuitum	2	2	0	0.755
Negative culture	5	5	0	1.000

BMI = Body mass index, ASA = American Society of Anesthesiology classification, Hb = Hemoglobin, MRSA = Methicillin-resistant *Staphylococcus aureus*, CNS = Coagulase negative Staphylococcus, ESBL = Extended spectrum beta-lactamase
* *p*-value <0.05

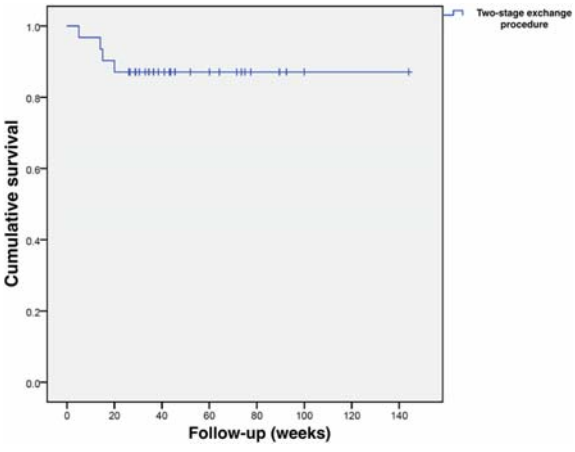

Figure 1. Kaplan-Meier curve of two-stage exchange procedure in the study.

also similar to the previous studies[14,15].

In analysis of organisms, the present study demonstrated the prevalence of culture negative PJI was 16.1%. For culture positive PJI, coagulase negative Staphylococcus and Methicillin-resistant *Staphylococcus aureus* (MRSA) were the most common pathogens in our series. Although MRSA[14,15] and culture negative infection[15] were reported as the significant risk factors of reinfection, these factors were not statistically significant in the present study. Furthermore, Wimmer et al[19] revealed that polymicrobial infection reduced the cure rate in PJI after two-stage exchange procedure. Nevertheless, we had no polymicrobial infection in our series. Risk factors from recent studies are shown in Table 2.

Conclusion

The authors study demonstrates that two-stage exchange procedure has a high success rate with 2-year reinfection rate of 12.9%. This procedure should be considered as gold standard treatment for chronic PJI. These results could help surgeons in counselling patients regarding their prognosis. However, further well-designed studies with larger sample sizes are required for identifying the risk factors.

What is already known on this topic?

Two-stage exchange procedure has a high success rate for treating chronic PJI. It has been considered as the gold standard of treatment. Several studies reported the prevalence and risk factors for reinfection after performing two-stage procedure.

Table 2. Recent studies of reinfection rate and risk factors in periprosthetic knee infection after two-stage exchange procedure

Authors	Year	n	Follow-up time	Reinfection rate	Risk factors	
					Univariate analysis	Multivariate analysis
Kurd et al (9)	2010	96	≥2 yrs	27%	MRSA infection	MRSA infection (OR 3.37, 95% CI 1.31 to 8.72)
Mortazavi et al (2)	2011	117	≥2 yrs	28%	MRSA infection, Purulent or sinus tract in first stage procedure	MRSA infection (OR 2.8, 95% CI 0.8 to 10.3), Culture negative infection (OR 4.5, 95% CI 1.3 to 15.7)
Kubista et al (3)	2012	368	6 to 2,853 days	15.8%	Vancomycin, Re-debridement between stages, Chronic lymphedema, Cefazolin (protective factor)	Chronic lymphedema (HR 2.28, 95% CI 1.16 to 4.54), Cafazolin (HR 0.48, 95% CI 0.25 to 0.90)
Sakellariou et al (4)	2015	110	≥2 yrs	13.6%	Inflammatory arthritis, Chronic Staphylococcal carrier, Postoperative hematoma, Wound dehiscence, Antibiotic administration >6 weeks	Chronic Staphylococcal carrier (OR 11.42, 95% CI 1.38 to 94.73), Wound dehiscence (OR 5.12, 95% CI 1.37 to 19.17)

MRSA = Methicillin-resistant *Staphylococcus aureus*, OR = Odds ratio, HR = Hazard ratio, CI = Confidence interval

What this study adds?

As far as we know, this is the first study conducted in a large tertiary care hospital in Thailand. This study demonstrates the prevalence of reinfection after two-stage exchange procedure for treating chronic PJI.

Acknowledgements

The authors would like to thank Miss Nichakorn Khomawut for her assistance with data collection in the present study.

Potential conflicts of interest

The authors declare no conflicts of interest.

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