Poor Implant Retention Rate in Patients Treated with Beta-Lactam Antibiotics for Initial Intravenous Empirical Therapy in Acute Periprosthetic Knee Joint Infection

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Abstract

Background: Beta-lactam antibiotics are frequently selected as initial intravenous empirical therapy in acute periprosthetic joint infection (PJI), but show poor drug migration to the knee joint.

Methods: We retrospectively assessed 23 patients undergoing irrigation and debridement surgery for acute PJI after primary TKA. First, we compared the success rate of implant retention between patients receiving beta-lactam antibiotics as initial intravenous empirical therapy and those receiving antibiotics other than beta-lactams. Second, multivariate logistic regression analysis was used to control for confounding factors and to distinguish independent risk factors for the failure of implant retention.

Results: Twelve patients received beta-lactam antibiotics as initial intravenous therapy (67% received cefazolin) and 11 patients received antibiotics other than beta-lactams (82% received linezolid). Patients receiving beta-lactam antibiotics had significantly lower implant retention rate than those receiving other antibiotics (5 of 12 patients [42%] versus 10 of 11 patients [91%], respectively, p = 0.027). Logistic regression analysis showed that use of beta-lactam antibiotics as initial intravenous empirical therapy was a significant independent risk factor predicting implant failure.

Conclusion: The rate of implant retention was lower in patients administered beta-lactam antibiotics as initial intravenous empirical treatment.

Introduction

Periprosthetic joint infection (PJI) is a devastating complication following total knee arthroplasty (TKA) [1]. PJI is associated with increased morbidity, long periods of hospitalization, and high costs [1].

Debridement, antibiotics, irrigation, and retention (DAIR) is one treatment option for PJI [2]. Appropriate antibiotic selection is essential for resolution of acute PJI without implant removal [3]. In the perioperative period of irrigation and debridement surgery, broad-spectrum antibiotics are used as initial intravenous empirical therapy before confirmation of the causative organism [3]. Although excellent drug migration to the knee joint is a crucial factor in selection of empirical antibiotics, bone penetration of antibiotics has been given less priority. For example, cefazolin, a cephalosporin antibiotic, is selected as initial intravenous empirical therapy in acute PJI due to its strong antimicrobial activity against methicillin-sensitive *Staphylococcus aureus* (MSSA) [4]. However, cefazolin shows poor migration to the knee joint [5, 6]. When 2 g of cefazolin was intravenously given before the skin incision in TKA, the concentration of cefazolin in the resected proximal tibia and distal femur was less than one tenth of the serum concentration and also less than the minimum inhibitory concentration for MSSA [5]. Most beta-lactam antibiotics including cephalosporins, cephamycins, penicillins, and carbapenems show poor bone penetration as well as cefazolin [6].

Acute PJI becomes difficult to eradicate in the chronic phase as the causative organisms can form mature biofilms and some organisms may parasitize osteoblasts [7, 8]. Thus, eradication of the causative

organisms in the acute phase with optimal initial intravenous empirical therapy would increase implant retention rate because the absolute number of causative organisms is at a minimum when the irrigation and debridement surgery is performed. The present study was performed to investigate the differences in implant retention rates among the drugs used as initial intravenous empirical therapy. We hypothesized that the implant retention rate would be poorer in patients treated with beta-lactam antibiotics with poor bone penetration properties than in those treated with antibiotics other than beta-lactams.

Patients And Methods

This retrospective study was performed after receiving approval from the institutional review board. The inclusion criterion was patients undergoing irrigation and debridement surgery for acute PJI after primary TKA between 2012 and 2019 in the two institutions. Four attending surgeons (ST, MW, MM, MN) performed approximately 3800 primary TKAs during the study period. All PJIs with acute onset were initially treated with irrigation and debridement surgery. All surgical site infections were validated according to the 2018 International Consensus Meeting on Musculoskeletal Infection [9]. The clinical presentation of PJI was classified as early postoperative infection, acute hematogenous infection, or chronic infection according to Segawa et al. [10]. The exclusion criteria were patients with chronic PJI and patients who experienced PJI after revision TKA.

During irrigation and debridement surgery, the modular polyethylene insert was routinely exchanged. We removed hematoma, fibrous membrane, devitalized soft tissue, and scrubbed the surface of the implant. The selection of antibiotics was left to the discretion of the attending surgeons.

This study focused on the implant retention rate after acute PJI. We reviewed all medical records of patients undergoing irrigation and debridement surgery for acute PJI and investigated retention of all knee prostheses other than tibial inserts without the use of suppressive antibiotics at the final follow-up. We also identified the antibiotics used as initial intravenous therapy, causative organism, age, sex, height, body weight, body mass index, Charlson comorbidity index, and the time interval from symptom onset of infection to irrigation and debridement surgery.

Statistical analysis

First, eligible patients were divided into those receiving beta-lactam antibiotics as initial intravenous empirical therapy (beta-lactam group) and those receiving antibiotics other than beta-lactams (non-beta-lactam group). We compared the success rate of implant retention after acute PJI between the two groups. In addition, other parameters were compared between the groups. Tests were two-sided, and the level of significance was set at $p < 0.05$.

Second, multivariate logistic regression analysis was used to control for confounding factors and to distinguish independent risk factors for the failure of implant retention after irrigation and debridement surgery. The beta-lactam antibiotic as initial intravenous empirical therapy was included as a risk factor in the model. In addition, we employed the following factors that were shown in previous studies to affect

the success rate of implant retention: (1) whether the causative organism was resistant to antibiotics or not [11], (2) the Charlson comorbidity index [12], and (3) the time interval from onset of infection to irrigation and debridement surgery [13]. Adjusted odds ratios and 95% confidence intervals are presented.

All analyses were performed using the R statistical package (version 3.4.1; R Foundation for Statistical Computing).

Results

A total of 23 patients underwent irrigation and debridement surgery for acute PJI. Of 23 patients, 12 patients received beta-lactam antibiotics as initial intravenous therapy (8 patients received cefazolin and 4 received imipenem-cilastatin) and 11 patients received antibiotics other than beta-lactams (9 patients received linezolid and 2 received teicoplanin).

Table 1 summarizes the demographic characteristics of the patients in the two groups. The beta-lactam group had a significantly lower implant retention rate than the non-beta-lactam group (5 of 12 patients [42%] versus 10 of 11 patients [91%], respectively, p = 0.027).

Table 1
Patient demographic and baseline clinical characteristics

	β-lactam group (n = 12)	Non-β-lactam group (n = 11)	*p*-value
Follow-up after irrigation and debridement surgery, years	2.5 ± 1.7	2.3 ± 1.3	0.65*
Age, years	79 ± 5	78 ± 9	0.85*
Sex (female/male)	7/5	7/4	> 0.99†
Height, cm	153 ± 6	151 ± 7	0.42*
Weight, kg	57.6 ± 8.5	62.2 ± 13.6	0.34*
Body mass index, kg/m^2	24.6 ± 2.5	27.4 ± 5.6	0.12*
Clinical presentation of infection (early postoperative infection/acute hematogenous infection)	10/2	9/2	> 0.99†
Charlson comorbidity index (0/1/2/>3)	5/4/1/2	6/2/2/1	0.82†
Time interval from symptom onset of infection to irrigation and debridement surgery (days)	7 ± 6	7 ± 6	0.93†
Organism	5	6	0.94†
Methicillin-sensitive *Staphylococcus aureus*	1	1	
Methicillin- resistant *Staphylococcus aureus*	2	0	
Coagulase-negative *Staphylococcus*	1	1	
Methicillin-resistant coagulase-negative *Staphylococcus*	1	2	
Streptococcus species	0	0	
Gram-negative	1	1	
Culture-negative	1¶	0	
Polymicrobial			
The results are expressed as means ± standard deviation, unless otherwise indicated.			
* *p*-values were determined with Student's *t* test.			
† *p*-values were determined with Chi-square test.			
¶ Methicillin-sensitive *Staphylococcus aureus* and *Enterococcus faecalis*.			

Logistic regression analysis showed that use of beta-lactam antibiotics as initial intravenous empirical therapy was a significant independent risk factor for failure of implant retention (Table 2).

Table 2
Multivariate logistic regression analysis of failure of implant retention after irrigation and debridement surgery

Independent risk factor	Adjusted odds ratio (95% CI)	p-value
Beta-lactam antibiotic as initial intravenous empirical therapy	0.051 (0.0038 to 0.69)	0.025*
Methicillin-resistant organism	2.99 (0.12 to 73.2)	0.50
Charlson comorbidity index	0.75 (0.25 to 2.19)	0.60
Time interval from symptom onset of infection to irrigation and debridement surgery (days)	0.91 (0.74 to 1.13)	0.40
* Significant ($p < 0.05$)		

Discussion

The most important finding of this study was that the rate of implant retention failure was higher in patients administered cefazolin or imipenem-cilastatin as initial intravenous empirical treatment than in those administered linezolid or teicoplanin. This tendency was observed not only in univariate analysis but also in multivariate analysis considering the causative organism, comorbidities, and time interval from onset of infection to irrigation and debridement surgery.

The rationale for the poor implant retention rate in the beta-lactam group was related to the poor bone penetration of these drugs. The bone/serum concentration ratios were reported to be 9% for cefazolin and 20% for imipenem [5, 14]. The inappropriate antibiotic concentration can not only fail to eradicate the causative organism, but may also lead to the development of resistant strains [5]. Although many studies have investigated risk factors for failure of DAIR [11−13], the impact of the difference in initial empirical antibiotics has not been well studied. Our study suggested that beta-lactam antibiotics might be inappropriate as initial intravenous treatment for acute PJI.

This study had several limitations. First, the two groups in univariate analysis were divided according to the antibiotics used as initial intravenous empirical therapy. Thus, the comparison focused only on the antibiotics using in initial intravenous therapy, and not on subsequent oral antibiotics. However, the present study was performed to investigate the clinical impact of the antibiotics used in initial intravenous therapy before biofilm maturation. Second, the number of explanatory variables in multivariate analysis was relatively small. However, we strictly chose the variables (resistance of causative organism, number and severity of comorbidities, and time interval from symptom onset to surgery) that were generally accepted to affect the success rate of DAIR [11−13]. We believe that

adjusting for these confounding factors was important to assess the impact of the antibiotics used in initial intravenous therapy on retention rate after acute PJI. Finally, this was a retrospective comparative study without random allocation to the beta-lactam group or non-beta-lactam group. Many factors that influence the range of success of DAIR have been reported [11–13]. The groups in our study underwent similar irrigation and debridement surgery and the patient background characteristics were not significantly different in terms of sex, height, weight, body mass index, Charlson comorbidity index, time interval from symptom onset of infection to irrigation and debridement surgery, and causative organism. However, factors that could not be assessed may have distorted our results because of the lack of randomization.

Conclusion

This retrospective analysis showed that the implant retention rate after irrigation and debridement surgery for acute PJI of primary TKA was significantly poorer in patients treated with beta-lactam antibiotics as initial intravenous empirical therapy.

Abbreviations

DAIR
Debridement, antibiotics, irrigation, and retention
MSSA
methicillin-sensitive *Staphylococcus aureus*
PJI
periprosthetic joint infection
TKA
total knee arthroplasty

Declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Nekoyama Miyao Hospital.

Consent to publish

The consent to publish was approved by the institutional review board of Nekoyama Miyao Hospital.

Availability of data and materials

The datasets used and/or analysed during the current study are not publicly available. Data are however available from the corresponding author on reasonable request.

Competing interests

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