ORIGINAL ARTICLE

Duration of Prophylactic Antibiotic and Prosthetic Joint Infection in a Developing Country: A Retrospective Cohort Study

Keerati Chareancholvanich, MD[1], Chaturong Pornrattanamaneewong, MD[1], Pakpoom Ruangsomboon, MD[1], Waiwit Sanguanwongwan, MD[1], Piyanuch Musikachart, MD[1], Rapeepat Narkbunnam, MD[1]

[1] Division of Adult Reconstructive Surgery, Department of Orthopedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Perioperative antibiotic prophylaxis is one of the standard measures for preventing periprosthetic joint infection (PJI). In developing countries, poor surgical environment and patient hygiene are often cited as reasons for prolonged antibiotic duration without any evidence to support its effectiveness.

Objective: To investigate the infection rate after total knee arthroplasty (TKA) compared between the standard course, which is 24 hours or less and the extended course, which is more than 24 hours of perioperative antibiotic prophylaxis in a developing country.

Materials and Methods: The present was a retrospective study that included patients who underwent unicompartmental knee arthroplasty or TKA between January 2013 and December 2018. Three thousand three hundred and sixteen patients were included. Of those, 1,284 and 2,032 patients received standard and extended course of antibiotic prophylaxis, respectively. The incidence of PJI was compared between the groups. The factors significantly associated with PJI were also analyzed.

Results: PJI developed in 0.5% (6/1,284 patients) of the standard course group, and in 1.2% (24/2,032 patients) of the extended course group. The difference and 95% confidence interval for the difference between groups were –0.71% (–1.34 to –0.04), which confirmed the non-inferiority status of the standard course group compared to the extended course group. Longer hospital length of stay significantly associated with higher infection rate ($p<0.001$). Postoperative wound infection was not found to be associated with age, body mass index, American Society of Anesthesiologists classification, blood transfusion, or surgery type.

Conclusion: Twenty-four hours of perioperative antibiotic prophylaxis was found to be adequate for PJI prevention in a developing country setting.

Keywords: Infection rate; Total knee arthroplasty; Standard course; Extended course; Perioperative antibiotic prophylaxis

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Total knee arthroplasty (TKA) is the most frequently performed operative procedure among older adults. Periprosthetic joint infection (PJI) is one of the most feared complications after TKA with an estimated risk ranging from 0.39% to 2% worldwide[1-3]. Multi-study analysis reported that sepsis (odds ratio [OR] 8.73) and death (OR 3.25) were significantly higher in patients undergoing revision for PJI compared to those without infection[3]. Factors found to influence PJI included patient factors, such as diabetes mellitus (DM), obesity, anemia, American Society of Anesthesiologists (ASA) class 3 or higher, malnutrition, and procedural factors, such as prolonged surgery and antibiotic prophylaxis[2-6].

Perioperative antibiotic prophylaxis is accepted as the standard protocol for reducing the rate of superficial wound infection and PJI after TKA. The microorganisms that most commonly cause postoperative infection are Gram-positive bacteria, including *Staphylococcus aureus*, coagulase-negative *Staphylococcus* (*S. epidermidis*), and group B *Streptococcus*. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important causative pathogen necessitating reoperation of primary TKA after debridement with polyethylene liner exchange due to infection[7]. In 2021, the American Association of Hip and Knee Surgeons (AAHKS) Annual Meeting recommended 24 hours of antibiotic prophylaxis for

Correspondence to:

Narkbunnam R.

Division of Adult Reconstructive Surgery, Department of Orthopedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanlang Road, Bangkoknoi, Bangkok 10700, Thailand.

Phone: +66-2-4197968, **Fax**: +66-2-4128172

Email: mai_parma@hotmail.com

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infection prevention after primary TKA[8].

Even though the recommended duration of postoperative prophylactic antibiotics is 24 hours, the majority of cases in developing countries are prescribed a prolonged course for reasons that include poor hygiene, low socioeconomic status, low patient education level, and limited availability of healthcare workers and medical supplies. The purpose of the present study was to perform a retrospective review in a public hospital that provides care to patients from all socio-economic backgrounds. Two groups of patients receiving the standard course (24 hours or less) and extended course (more than 24 hours) of antibiotics following TKA were compared. The specific aim of the present study was to determine whether prolonged duration of antibiotics can reduce the infection rate after TKA compared with the standard 24-hour course of perioperative antibiotic prophylaxis.

Materials and Methods

Patients and study design

The present study was a retrospective study conducted at a tertiary university hospital, single center. After receiving Institutional Review Board approval (COA No. 847/2559(EC3)), the medical records of the patients diagnosed with osteoarthritis of the knee who underwent unicompartmental knee arthroplasty (UKA) or TKA between January 2013 and December 2018 were reviewed. Unilateral and bilateral surgical patients were both eligible for the study. The inclusion criterion was the knee arthroplasty performed for primary osteoarthritis or secondary osteoarthritis. Patients were excluded if they received revision knee arthroplasty, were administered systemic antibiotics more than 60 minutes before or after skin incision, had a follow-up time less than three months, or had incomplete medical information.

The national recommendation for prevention of surgical site infection (SSI) was applied. Patients with a body weight less than 80 kg received a single dose of cefazolin 1 gram intravenously within 60 minutes before skin incision, and three additional doses during the first 24 hours after the operation. A single dose of cefazolin 2 grams was considered optimal for patients weighing more than 80 kg. Vancomycin or clindamycin was alternatively prescribed if patients had a history of cephalosporin allergy. Other antimicrobial prophylaxis was given according to surgeon's preference and intraoperative findings. The surgical limb was painted with either povidone-iodine or chlorhexidine with alcohol, and the surgical site was covered with a 3M Ioban 2 Antimicrobial Incise Drape (3M Company, St. Paul, MN, USA). A pneumatic tourniquet was inflated during the procedure and deflated after wound closure or when the duration of tourniquet exceeded 120 minutes. All surgeons routinely used double gloves.

Demographic and clinical patient characteristics, such as gender, age, body mass index (BMI), comorbidities, and ASA score were recorded. Operative data, such as surgery type, type of antibiotic prophylaxis, duration of antibiotic prophylaxis, blood transfusion, and hospital length of stay (LOS) were reviewed from medical records during the primary surgical period. Patients were divided according to the amount of time they received antibiotic prophylaxis. The standard course group included patients who received antibiotics for less than or equal to 24 hours after surgery, and the extended course group consisted of patients who received antibiotics for longer than 24 hours after surgery.

The primary outcome in the present study was the incidence of PJI after knee arthroplasty according to the diagnosis criteria by the Musculoskeletal Infection Society (MSIS) 2011[9] and modified to the international consensus review (International Consensus on Musculoskeletal Infection [ICM]) in 2013[10]. The diagnosis of PJI was made by the attending physician during admission period for treatment of PJI.

Sample size calculation and statistical analysis

For non-inferiority test calculation and assuming an infection rate between groups of 1% (δ=0.01), an inferiority margin of 0.01, and type-1 (α) and type-2 errors (β) of 0.05 and 0.2, respectively, at the ratio of 1 to 1 of population between group 1 (24 hours or less of postoperative prophylactic antibiotics) and group 2 (more than 24 hours of postoperative prophylactic antibiotics). The calculated sample size required 1,225 patients per group. In the present study, the total sample size was 3,316 with 1,284 in group 1 and 2,032 in group 2.

Student's t-test was used to compare continuous variables, and the chi-square test or Fisher's exact test was used to compare dichotomous variables. Continuous data were presented as mean ± standard deviation, and categorical data were given as number and percentage. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA).

Table 1. Demographic and clinical characteristics of patients compared between the standard course and extended antibiotic course groups (n=3,316)

Characteristics	ATB ≤24 hours (n=1,284)	ATB >24 hours (n=2,032)	p-value
Age (years); mean±SD	69.5±8.5	68.6±8.4	0.006
Antibiotic; n (%)			<0.001
Cefazolin	1,178 (91.7)	782 (38.5)	
Clindamycin	52 (4.1)	60 (3.0)	
Fosfomycin	20 (1.6)	972 (47.8)	
Cefuroxime	31 (2.4)	212 (10.4)	
Others	3 (0.2)	6 (0.3)	
Blood transfusion; n (%)			0.178
Yes	1,102 (85.8)	1,777 (87.5)	
No	182 (14.2)	255 (12.5)	
Hospital length of stay (days); mean±SD	5.9±2.5	5.3±1.8	<0.001
Body mass index (kg/m^2); mean±SD	27.1±4.4	27.3±4.2	0.275
ASA classification; n (%)			0.035
1	84 (6.5)	121 (6.0)	
2	884 (68.9)	1,476 (72.6)	
3	316 (24.6)	431 (21.2)	
4	0 (0.0)	4 (0.2)	
Follow-up (months); n (%)			0.555
3 to 6	105 (8.2)	175 (8.6)	
6 to 12	871 (67.8)	1,367 (67.3)	
12 to 24	221 (17.2)	359 (17.7)	
24 to 36	75 (5.9)	122 (6.0)	
Procedure; n (%)			<0.001
TKA	1,203 (93.7)	1,736 (85.4)	
UKA	81 (6.3)	296 (14.6)	

ATB=antibiotic; ASA=American Society of Anesthesiologists; TKA=total knee arthroplasty; UKA=unicompartmental knee arthroplasty; SD=standard deviation

A p<0.05 indicates statistical significance

Results

Of the 3,374 patients with osteoarthritis of the knee who underwent UKA or TKA at the authors' center during the study period, 58 patients were excluded. Of those, revision arthroplasty was performed in 15 cases, three cases were lost to follow-up, and 40 cases had incomplete medical information. The remaining 3,316 patients were included, and those patients were categorized into the standard course group (24 hours or less) or the extended course group (more than 24 hours). There were 1,284 (38.7%) of the patients in the standard course group, and 2,032 (61.2%) of the patients in the extended course group (Figure 1). The mean age at the time of operation was 69.5±8.5 years and 68.6±8.4 years in the standard course and the extended course groups, respectively. The difference in age between the standard and extended groups was statistically significant for 69.5±8.5 versus 68.6±8.4, respectively (p=0.006). Concerning the choice of antibiotic, fosfomycin and cefuroxime (Zinacef) were prescribed significantly more often among patients being prescribed antibiotic prophylaxis for 48 hours. Demographic and clinical characteristics of patients compared between the standard course and the extended course groups are shown in Table 1.

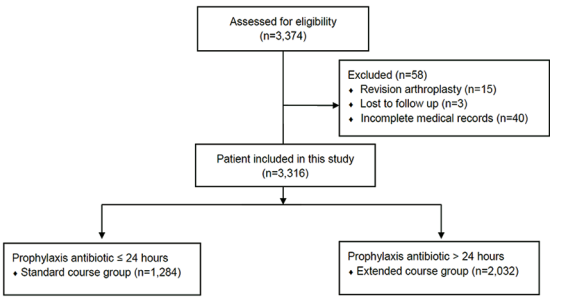

Figure 1. Patients flow chart.

Table 2. Analysis for factors significantly associated with prosthetic joint infection

Factors	No infection (n=3,286)	Infection (n=30)	p-value
Hospital length of stay (days); mean±SD	5.7±2.2	8.2±6.9	<0.001
Age (years); mean±SD	69.5±8.5	68.6±8.4	0.546
Body mass index (kg/m^2); mean±SD	27.2±4.3	28.1±5.0	0.242
ASA classification; n (%)			0.728
1	203 (6.2)	2 (6.7)	
2	2,338 (71.1)	22 (73.3)	
3	741 (22.6)	6 (20.0)	
4	4 (0.1)	0 (0.0)	
Blood transfusion; n (%)			0.104
No	2,856 (86.9)	23 (76.7)	
Yes	430 (13.1)	7 (23.3)	
Procedure; n (%)			0.486
TKA	2,911 (88.6)	28 (93.3)	
UKA	375 (11.4)	2 (6.7)	

ASA=American Society of Anesthesiologists; TKA=total knee arthroplasty; UKA=unicompartmental knee arthroplasty; SD=standard deviation

A p<0.05 indicates statistical significance

The primary outcome was the difference in the rate of infection between patients who received 24 hours or less and more than 24 hours of antibiotic prophylaxis. PJI developed in 0.5% (66/1,284) of the standard course group, and in 1.2% (24/2,032) of the extended course group. The difference and 95% confidence interval for the difference between groups were –0.71% (–1.34 to –0.04), which confirmed the non-inferiority status of the standard course group compared to the extended course group. Analysis for factors significantly associated with PJI is shown in Table 2. Longer hospital LOS was found to be significantly associated with PJI (p<0.001). Postoperative wound infection was not found to be associated with age, BMI, ASA classification, blood transfusion, or surgical type.

Discussion

No significant difference in the incidence of PJI was observed between the standard course and the extended course of perioperative antibiotic prophylaxis group in the present study. Longer hospital LOS was the only factor found to be significantly associated with PJI. Despite the study setting being in a developing country with lower hygiene standards, the present study results are consistent with prior evidence that an extended course of antibiotic prophylaxis does not reduce PJI.

PJI remains a paramount concern after TKA[11]. Feng et al. reported the highest percentage of revision operations to be among patients that had SSI diagnosed during follow-up visits[12]. In addition to increased rates of morbidity and mortality, revision knee replacement is expensive. Antimicrobial prophylaxis has been proven to reduce the SSI rate in many types of surgery. The adverse effects of antibiotic overuse in arthroplasty surgery included worsened MRSA outbreak, increased incidence of *Clostridioides difficile* infection, and acute kidney injury[13]. A 24-hour course of antibiotic prophylaxis is considered enough to prevent SSI by reducing transient bloodstream infection[14,15]. Thus, the International Consensus on Periprosthetic Joint Infection recommended a 24-hour course for the prevention of SSI.

In clinical practice, the decision to prescribe antibiotic prophylaxis in TKA or UKA surgery depends on many factors, such as surgeon's preference, drain usage, ambient temperature, degree of leukocytosis, hospital protocols, intraoperative findings, and patient perception. A study conducted in Canada showed that only 42% of orthopedic patients had antibiotics discontinued within 24 hours after surgery, and more than 70% of patients received more than 72 hours of antibiotic after surgery[16]. In developing countries, many surgeons prefer to extend the course of antibiotics beyond 24 hours because of their surgical environment, including operating rooms and surgical draping, or a failure to comply with the principles of surgical asepsis. Concerning patient-related factors, poor hygiene, and history of high incidence of PJI also contributed to the decision regarding how to prescribe perioperative antibiotic prophylaxis[17]. To the authors' knowledge, no study has investigated the

incidence of PJI related to duration of antibiotics in developing countries. The present study compared the surgical outcomes of UKA and TKA patients between those who received antibiotic prophylaxis for 24 hours or less and those who received antibiotic prophylaxis for more than 24 hours. The present study results revealed no significant difference between groups for either superficial or deep SSI. Age at operation, BMI, ASA score, type of surgery, type of antibiotic drug, and hospital LOS were all found not to be significantly associated with infection following TKA. Blood transfusion increased SSI, but without statistical significance. Based on these findings, the authors recommend that antibiotic administration not exceed 24 hours to minimize adverse events associated with antimicrobial drugs, save cost, and reduce the hospital LOS.

Nelson et al. reported no statistically significant difference among patients with total joint arthroplasty (TJA) or hip fracture repair compared between those who received antibiotic for 24 hours or less, and patients who received antibiotic for more than 24 hours after surgery[18]. In a double-blind multicenter study that included 1,354 patients who underwent primary or revision TJA, one day of cefuroxime administration was compared with three days of cefazolin prophylaxis for SSI. The infection rate was lower in patients who received antibiotics for 24 hours postoperatively in both TKA at 0.6% versus 1.4% and total hip arthroplasty (THA) at 0.5% versus 1.2%[19]. A recent study in PJI following aseptic TKA revision demonstrated that first-generation cephalosporin prophylaxis for 24 hours did not result in a significantly different rate of infection compared with an extended course ($p=0.14$)[20]. Moreover, other studies demonstrated that postoperative antibiotic drug continuation with multiple dosing regimen is not more effective than single-dose regimen for preventing SSI or PJI[21-23]. In contrast, recent evidence suggested that prolonged oral antibiotic prophylaxis for up to one week may yield benefit in high-risk patients, especially in those with comorbidities that are associated with increased susceptibility to infection, by reducing the incidence of infection within 90 days following TJA[24].

Blood transfusion was not found to be a significant risk factor for PJI in the present study. The authors found the infection rates of 2.2% and 0.8% in patients with and without blood transfusion, respectively. In contrast, a recently published study investigated the risk factors significantly associated with PJI after TKA and found that red blood cell (RBC) transfusion to be a significant risk factor for postoperative infection (OR 4.60). Other significant risk factors for PJI and TKA found in that study included prolonged operative time (more than 90 minutes), tourniquet time (more than 60 minutes), non-antibiotic-laden cement use, obesity (BMI of more than 30 kg/m^2), diabetes, and ASA grade 3 or higher[25]. In another study, SSI developed in 2.82% of patients who received RBC transfusion, but in only 0.4% of those who did not[26].

The present study has limitations. The first limitation was the present study's retrospective design with many confounding factors that cannot be controlled. The second was that the study groups were not equal in size. The extended course group was approximately two times larger than the standard course group. Third, the baseline characteristics of the study patients were different from those reported in other studies, so comparisons between the present study and the other studies should take this factor into account. Fourth and last, the authors did not perform multivariate analysis to exclude potentially confounding factors. Having acknowledged those limitations, the present study finding that the standard course is not inferior to the extended course of antibiotic prophylaxis against postoperative PJI is consistent with the findings of the previously reported studies.

Conclusion

Twenty-four hours of perioperative antibiotic prophylaxis was found to be adequate for PJI prevention in a developing country setting.

What is already known on this topic?

The recommended duration of postoperative prophylactic antibiotics is 24 hours in developing countries.

What does this study add?

The incidence of PJI was investigated related to duration of antibiotics in developing countries. The duration of antibiotics differs due to the various protocols for prophylactic antibiotics that depend on the surgeon's preference.

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Conflicts of interest

All authors declare no personal or professional conflicts of interest relating to any aspect of this study.

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