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Infection After Total Knee Arthroplasty: Does Timing of Pre-operative Antibiotics Matter?

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Abstract

Introduction: Since the 2003 NIH consensus statement, the use of prophylactic antibiotics in total knee arthroplasty (TKA) has been the standard of care. Some studies recommend antibiotic administration within 1 h of skin incision, but no specific time frame has been delineated. The objective of this study was to determine if timing of pre-operative antibiotics is associated with post-operative infection after TKA.

Materials and Methods: An institutional database from a multi-center health-care system was queried with ICD-10 codes and reviewed for patients undergoing primary TKA between March 2020 and December 2020. The rate of superficial surgical site infection (SSI) and periprosthetic joint infection (PJI) was compared with pre-operative antibiotic timing. PJIs were defined based on 2018 MSIS criteria and superficial SSIs were other infections that did not meet MSIS criteria. Antibiotic timing was separated into 15-min cohorts from 0 min before skin incision to over 45 min before incision. Further comparison between patients who received antibiotics within 30 min of incision with those who received antibiotics greater than 30 min prior was performed.

Results: Of the 2511 patients who underwent primary TKA, 19 were found to have post-operative infections. There were 7 SSIs, and 12 PJIs, 16 of the post-operative infections occurred when patients received antibiotics <30 min before incision. There was no significant difference in SSIs or PJIs between each 15-min time interval of antibiotic administration ($P = 0.45$) or between the 30-min time intervals ($P = 0.09$).

Conclusion: Our study demonstrates no difference in post-operative infection based on pre-operative antibiotic timing. As long as antibiotics are given within 60 min of incision, preferentially 30–60 min before incision, their timing does not have a significant effect on post-operative infection following TKA.

Keywords: Pre-operative antibiotics, periprosthetic joint infection, superficial skin infection, total knee arthroplasty, complications

Introduction

Total knee arthroplasty (TKA) is one of the most rewarding operations for patients, as it has some of the highest patient satisfaction rates. The number of TKAs performed per year continues to grow as the population continues to age, and it has been projected that nearly 3.5 million TKAs will be performed annually in the US by the year 2030 [1]. With this increase in caseload comes an increase in the total number of complications and infections. Although the rates of post-operative infections after hip and knee arthroplasty are notoriously low, they remain a costly burden to the healthcare system and can be devastating to patients [2]. Various efforts have been made to minimize the risk of infection, including the usage of antibiotic prophylaxis. This is accomplished through appropriately selected weight-based antibiotics administered in a timely fashion in the pre-operative period to achieve adequate tissue concentrations to reduce the risk of infection. However, there is significant variation within the literature regarding pre-operative antibiotic timing.

The success of the total knee arthroplasty relies not only on the technical aspects of the procedure but also more importantly, the standardized post-operative clinical pathways to expedite the rehabilitation process. However, there is a lack of

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standardization of the pre-operative protocols, specifically regarding antibiotic prophylaxis. In 2003, the Medicare National Surgical Infection Prevention Project released an advisory statement that concluded that the infusion of the first antimicrobial dose should begin within 60 min before surgical incision [3] which is the rationale behind today's principles of antibiotic timing. Studies have demonstrated inconsistent results in regard to the type of antibiotic, recommended dosages, and timing of administration, ranging from any time preoperatively to within 60 min or 120 min before skin incision [4,9].

The current clinical guidelines regarding antibiotic prophylaxis in total joint arthroplasty remains controversial and are concerning for patient care. This clinical variation may be contributing to suboptimal outcomes and possibly the development of post-operative infections if not appropriately studied and protocoled. Using a prospective cohort of patients who underwent primary TKA, this study aims to determine whether there is an association between the timing of pre-operative prophylactic antibiotic administration and post-operative infection after TKA.

Materials ans Methods

Study population

This investigation was approved by our institution's Institutional Review Board. Patients undergoing primary TKA were evaluated using a prospectively collected institutional database within our health system comprising 15 hospitals. Total knee arthroplasty patients were identified using ICD-10 diagnosis codes. We identified 2,511 patients who underwent primary TKA between March 1, 2020, and December 31, 2020. Patients were included if they were diagnosed with primary osteoarthritis, rheumatoid osteoarthritis, and post-traumatic arthritis. Patients who underwent revision TKA or simultaneous bilateral TKA were excluded from the study population.

Data on the following demographic and comorbidity variables were prospectively collected: Age, sex, body mass index (BMI), past medical history of anemia, malnutrition, diabetes mellitus (DM), myocardial infarction (MI), peripheral vascular disease (PVD), cerebrovascular accident (CVA), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), peptic ulcer disease (PUD), rheumatoid arthritis, tobacco use, anxiety, depression, end-stage renal disease (ESRD), hypertension, hyperlipidemia, pre-operative coronavirus 2019 (COVID-19), and post-operative COVID-19 (Table 1). The mean age of patients was 66.9 years (SD = 9.0, range 31-96), and there was a moderate female predominance (62.7%).

Table 1: Demographics and comorbidities

	Infection (n = 19) (%)	No Infection (n = 2,492) (%)	P-value
Age (years)	63.0 ± 7.2	66.8 ± 9.0	0.07
BMI (kg/m^2)	31.8 ± 6.3	32.2 ± 6.4	0.78
Sex			
Male	11 (58)	924 (37.1)	0.06
Female	8 (42)	1,568 (62.9)	
Obesity	6 (31.5)	808 (32.4)	0.94
Anemia	6 (31.5)	332 (13.2)	**0.02**
Renal Failure	1 (5.3)	183 (7.3)	0.59
Malnutrition	1 (5.3)	6 (0.2)	**0.05**
Diabetes	2 (10.6)	462 (18.5)	0.29
MI	0 (0.0)	23 (0.9)	0.67
PVD	0 (0.0)	28 (1.1)	0.64
CVA	0 (0.0)	32 (1.3)	0.62
CKD	0 (0.0)	20 (0.8)	0.7
COPD	0 (0.0)	57 (2.3)	0.51
Peptic Ulcer Disease	0 (0.0)	18 (0.7)	0.71
Rheumatoid Arthritis	0 (0.0)	56 (2.2)	0.51
Smoking	8 (42.1)	787 (31.6)	0.33
Anxiety	6 (31.6)	293 (11.8)	**0.01**
Depression	5 (26.3)	252 (10.1)	**0.02**
ESRD	0 (0.0)	3 (0.1)	0.88
Hypertension	12 (63.2)	1,104 (44.3)	0.1
Hyperlipidemia	10 (52.6)	796 (31.9)	**0.05**
Pre-operative COVID	0 (0.0)	29 (0.9)	0.64
Post-operative COVID	0 (0.0)	10 (0.3)	0.78

Variables

The primary variable of interest was the time, in minutes, between the intravenous administration of pre-operative antibiotics and surgical incision. Most patients had an antibiotic administration time of <30 min before skin incision (n = 1,668, 70.5%), and nearly all patients were given antibiotics within 60 min before the skin incision (n = 2,273, 96.1%).

The primary outcome of interest was the incidence of post-operative infection following primary TKA. Post-operative infections were classified as either superficial surgical site infections (SSIs) or periprosthetic joint infections (PJIs). SSIs were defined by a clinical diagnosis of infection (presence of any combination of redness at the surgical site, constitutional symptoms, and elevated white blood cell count) that was treated with a course of oral antibiotics. PJIs were defined by the 2018 Musculoskeletal Infection Society (MSIS) criteria [5].

Data analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) Version 26.0 for Windows (International Business Machines (IBM), Armonk, New York). The criterion for statistical significance was set at $\alpha = 0.05$. A two-proportion z-test was used to compare the incidence of post-operative infection to that of prior studies. Independent sample t-tests were used to identify continuous variables that were predictive of post-operative infection in univariate analysis. Similarly, Chi-square and Fisher's exact tests were employed to identify categorical predictors of post-operative infection. Predictor variables found to be

Table 2: Infection frequency

Type of infection	Frequency (%)
Superficial SSI	7 (0.28)
Deep SSI	12 (0.48)
Total	**19 (0.76)**

statistically significantly associated with post-operative infection were subsequently included in multivariate logistic regression modeling.

Results

The incidence of post-operative infection following primary total knee arthroplasty was found to be 19 (0.76%). In total, there were 7 SSIs (0.37%) and 12 PJIs (0.63%). Of the 2511 patients, 2281 were treated preoperatively with cefazolin (91%), 165 with vancomycin (6.6%), 63 with clindamycin (2.5%), and 2 with daptomycin (0.08%). All 19 of the post-operative infections in this study were found to be in the group who was treated with cefazolin.

Table 1 demonstrates the demographics and comorbidities among the patient population, separated by those who were diagnosed with a post-operative infection and those who were not. Univariate analysis showed a significant difference in infection incidence between those with and without anemia (P = 0.02), malnutrition (P = 0.05), anxiety (P = 0.01), depression (P = 0.02), and hyperlipidemia (P = 0.05).

Timing of pre-operative antibiotic administration was separated into four different groups for analysis, in 15-min intervals from 0 to 15 min, 16 to 30 min, 31 to 45 min, and more than 45 min before incision. A total of 478 patients received antibiotics 0-15 min before skin incision, two of whom went on to develop a post-operative infection (0.42%). A total of 1263 patients received antibiotics 16-30 min before skin incision, and 14 of those patients went on to develop a post-operative infection (1.1%). A total of 548 patients received antibiotics 31-45 min before skin incision, and 3 of those patients went on to develop a post-operative infection (0.55%). There were 222 patients who received antibiotics more than 45 min before skin incision and none of those patients went on to develop a post-operative infection (Table 2).

Table 3: Patient distribution of antibiotic administration before incision

	0-15 min (%)	16-30 min (%)	31-45 min (%)	> 45 min (%)
n (%)	478 (19)	1,263 (50.3)	548 (21.8)	222 (8.9)

Table 4: Infection distribution within each time frame

	0-15 min (%)	16-30 min (%)	31-45 min (%)	> 46 min (%)	*P*-value
Number of infections (frequency)	2 (0.42)	14 (1.1)	3 (0.55)	0 (0.0)	0.45

Most of the 19 infections occurred in those patients who received antibiotics in the 0-30-min pre-incision cohort (Table 3 and 4), so a comparison of patients receiving antibiotics 0-30 min pre-incision and greater than 30 min pre-incision was performed (Table 5). A total of 1741 patients (69.3%) received antibiotics within 30 min of incision and 16 (0.91%) developed post-operative infections, while 770 patients (30.7%) received antibiotics greater than 30 min before incision with 3 (0.39%) who developed post-operative infection. The difference in infection rate between these two groups did not reach significance (P = 0.09).

In multivariate analysis, the timing of pre-operative antibiotics was not significantly associated with the development of post-operative infection after total knee arthroplasty.

Table 5: Infection distribution and comparison for 30-min pre-incision

	0-30 min (%)	>30 min (%)	*P*-value
n (%)	1741 (69.3)	770 (30.7)	
Number of infections (frequency)	16 (0.91)	3 (0.39)	0.09

Discussion

Recommendations for the timing of pre-operative antibiotics in total knee arthroplasty vary by major organizations. For example, the Musculoskeletal Infection Society's 2013 International Consensus on Periprosthetic Joint Infection recommends administering antibiotics within 1 h before surgical incision [6], whereas the WHO recommends a 2-h pre-incision timeframe [7] the and Center for Disease Control Guidelines for Prevention of SSI reports pre-operative antibiotic timing as an uncertain/unresolved issue based on clinical outcomes [8].

In our analysis, we grouped patients based on the timing of pre-incision antibiotic administration and evaluated the distribution of post-operative infections. The results of this study showed that antibiotic timing did not have a significant effect on the combined rate of post-operative infection in patients undergoing primary total knee arthroplasty. This was the case in two separate analyses: One grouped based on 15-min intervals within the 60 min before incision, and another grouped based on greater than or <30 min before incision. There was a difference in infection rates when comparing 30 min time intervals, but it did not reach significance. While antibiotic timing is only one of the multiple factors that can contribute to the development of infection after joint arthroplasty, it is a topic that has been explored in the literature with some consensus.

In a seminal study of antibiotic timing, Classen et al. looked at 2847 patients who underwent "clean" or "clean

contaminated" surgery at a single community hospital over the course of a 12-month period. While this study looked at all surgeries done at the hospital, 11% of the total surgeries were total hip or total knee arthroplasty. Study participants were divided and four groups based on timing of antibiotics: (1) early (>2 h pre-incision), (2) pre-operative (0-2 h pre-incision), (3) peri-operative (0-3 h post-incision), (4) late (>3 h post-incision) [9]. They found that the risk of SSI was significantly lower for patients in the pre-operative group (0.6%) compared to those in the early group (3.8%) or late group (3.4%). The infection rate in the pre-operative group was lower than the peri-operative group (1.4%), but the difference was not significant. While this would lay the groundwork for future studies, it is interesting to note that the SSI rate for patients receiving antibiotics within 2 h of incision is very similar to the rate in our study. Other studies surrounding the effects of prophylactic antibiotic timing that include, but are not limited to, arthroplasty have found similar conclusions. Steinberg et al. found that infection rates were significantly lower when antibiotics were administered <30 min before incision when compared to administration 31-60 min before surgery [10]. In addition, their models found that infection risk increased as time between antibiotic administration and the beginning of surgery increased.

When these types of studies are applied to arthroplasty, similar trends appear without establishing a definitive consensus on the exact effect of timing. In a study looking at the effects of various factors, including antibiotic timing, on the development of SSI in 1922 elective total hip arthroplasties performed at 11 Dutch hospitals, van Kasteren had an overall superficial and deep SSI rate of 2.6%. There was no significant difference in rates of infection when pre-operative antibiotics were administered within 200 min of incision, whether pre-operative time intervals were grouped into 30-min intervals or 60-min intervals. The lowest infection rate was in the 0-30 min before incision group and the highest odds ratio of infection was in the group receiving antibiotics during or after incision, but no significance was reached [11]. These results are similar to this study, which found no significance in infection rate based on timing of pre-operative antibiotic administration within smaller time intervals 60 min before incision.

However, significant differences have been found in more recent literature. Badge et al. performed a study looking at 1838 total hip and knee arthroplasties performed in 19 Australian centers. They found that receiving pre-operative antibiotics within 60 min before incision and more than 60 min before incision were both significantly associated with reducing the rate of any SSI or deep SSI compared to intraoperative or post-operative administration [13]. These results align with ours, showing no significant difference in SSI rate for antibiotic administration for various time intervals, although their study had a wider pre-operative timeframe for antibiotic administration. Interestingly, this study found that starting antibiotics more than 60 min before incision had a greater effect on SSI reduction than starting within 60 min. In a study similar to ours, Wu et al. looked retrospectively at 3152 patients who underwent primary total knee arthroplasty and received pre-operative antibiotics within 60 min before incision. They found that administration of antibiotics within 30 min of incision was associated with a higher risk of developing deep SSI when compared to administration 30-60 min before incision [12]. Although significance was not reached in our study, our results similarly suggest that administration of antibiotics within 30 min of incision may actually be harmful. These studies show that the timing of antibiotics can make a difference in SSI but deviate slightly from the direction of previous literature. Restricting pre-operative administration within 60 min, and even suggesting that being closer to incision time is better, may not be as important as it once was thought to be. Our results suggest that adherence to this 60 min pre-operative does not have an effect on post-operative infection, but suggests that administration between 30 and 60 min before incision may be preferential.

At present, there is no definitive evidence for appropriate pre-operative antibiotic timing for primary TKAs, which is reflected in the variable guideline recommendations. Our study addresses two major issues that limit the reliability of these guidelines: Lack of specificity for primary TKAs and wide time intervals. The results of our analysis suggest that pre-operative antibiotic timing is not significantly associated with the incidence of post-operative infections for primary TKAs, although there was a higher rate of infections for patients who received antibiotics 30 min or less before incision. This implies that the threshold for antibiotic administration may be safely adjusted to start at a minimum 30 min before surgery.

There are some limitations to this study. Since it is retrospective in nature, the distribution of the data is influenced by proper information, including exact timing, being present in the medical record. The retrospective nature also leads to influence from existing protocols. Administration of antibiotics within 60 min of incision for arthroplasty is strongly suggested by both the American Academy of Orthopedic Surgeons [14] and the international consensus on periprosthetic joint infection [4]. This makes it a common part of the protocol, as it is part of the protocol at the centers in our study. This resulted in data being skewed toward patients receiving antibiotics earlier, rather than later.

Conclusion

This study shows that timing of pre-operative antibiotics is not associated with post-operative infection after TKA. We did not identify a more ideal timing for antibiotic administration. As long as antibiotics are given within 60 min of incision, preferentially 30-60 before incision, their timing does not have a significant effect on post-operative infection following TKA. Future studies are required to understand the ideal timing for pre-operative antibiotics.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Conflict of Interest: NIL; **Source of Support:** NIL

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