

Outcomes research and physician perceptions on antibiotic prophylaxis in total knee arthroplasty

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□ Introduction

Total knee arthroplasty is one of the major orthopedic surgeries, with approximately 70,000 performed every year in South Korea. Although post-operative satisfaction rate is more than 85% for advanced arthritis patients, various complications may occur because of insertion of a prosthesis. Especially, because the prosthesis is inserted into the body, deep infection can occur post-operatively. Consequently, complete resolution of infection using simple antibiotic treatment is very rare and, in most cases, further surgery is required. The subsequent distress and financial burden to the patient, and the socioeconomic costs, are significant.

Among the many preventative pre-surgical measures undertaken to prevent

infection, prophylactic administration of appropriate antibiotics is accepted as an effective measure. The prophylactic use of appropriate antibiotic prescription in total knee arthroplasty has been recommended in the scientific literature and in various clinical practice guidelines. However, adherence to clinical practice guidelines is very low and optimal use for antibiotic prophylaxis is still debatable.

□ Objective

The purpose of this study was to present the evidence for the use of prophylactic antibiotics for total knee arthroplasty, and to analyze the current state of antibiotic use and expert recognition in clinical practice.

□ Methods

To analyze the occurrence of infections, according to the use of prophylactic antibiotics in total knee arthroplasty, a retrospective cohort was constructed using health insurance claims data. New patients who had received a total knee arthroplasty between January 1, 2008 and December 31, 2015 formed the study cohort. Following a review of international guidelines, and Health Insurance Review & Assessment Service survey items that evaluated the appropriateness of prophylactic antibiotic treatment, prophylactic antibiotics were defined as 1st through 4th generation cephalosporin, streptomycin, other aminoglycosides, glycopeptide antibacterials, and intravenous antibiotics of the quinolone family. Prophylactic antibiotic groups were classified as follows: administration of prophylactic antibiotics for two days or less from the start of convalescence during hospitalization for total knee arthroplasty (adherent prophylactic antibiotic group), and administration of prophylactic antibiotics lasting longer than two days (non-adherent prophylactic antibiotic group). In the patient group used for sensitivity analysis, patients using 1st or 2nd generation cephalosporin antibiotics alone were classified into the prophylactic antibiotic adherence group, following the American Academy of Orthopedic Surgeons (AAOS)

guidelines. The overall risk of infection was summarized using a Kaplan-Meier plot without covariance corrections to analyze the infection risk, according to the method of total knee arthroplasty. The duration of infection was recorded in units of person-year, according to the method of total knee arthroplasty. Hazard ratios (HR) were estimated for the main analysis results using Cox's proportional hazard model, and 95% confidence intervals (CIs) and p-values were also presented.

Orthopedic surgeons were surveyed online from September 2 to November 22, 2017. Descriptive statistics and a variance analysis were performed on the results using a statistical package (IBM SPSS Statistics 23), and frequencies, percentages, and distribution differences were presented.

Focus group interviews were conducted with orthopedic surgeons who perform total knee arthroplasties, and they were divided into three groups as follows: a 'hospital director-orthopedic surgeon' group that comprised surgeons in charge of hospital administration, a 'professor-orthopedic surgeon' group that comprised surgeons involved in the teaching and training of students, and an 'appointed doctor-orthopedic surgeon' group that comprised surgeons employed at the hospital with a focus on surgery.

Focus group interviews were recorded and then coded by individual researchers and by all the researchers collectively. An analysis framework was completed through extracting meaningful categories and sub-categories from the coded data. Using the framework, analyses were performed for each group, and characteristics that emerged which were common to all groups and to the individual group characteristics were described after discussions among the researchers.

□ Results

From 2008 to 2016, the total number of insurance claims for the first total knee arthroplasty was 473,034. Based on insurance claim data, the yearly number of surgeries rapidly increased 1.5 times, from 40,160 patients (50,758 cases) in 2008 to 59,599 patients (79,874 cases) in 2016. The average

days of antibiotic use per one total knee arthroplasty gradually reduced from 8.87 days in 2008 to 7.79 days in 2016. In 2016, the average number of days of antibiotic use by type per total knee arthroplasty for that year was similar for the 1st and 2nd generation cephalosporin at 7.79 and 7.7 days, respectively, which is approximately one day less when compared with 2008 at 8.7 and 8.6 days, respectively. In 2016, the average administration days of 4th generation cephalosporins was 8.36 days, followed with glycopeptide antibiotics (8.79 days), and quinolone (8.84 days), then 3rd generation cephalosporins (9.86 days), and aminoglycoside (10.3 days). The stronger the antibiotic, the longer the number of administration days involved, with the duration of antibiotic therapy being longer than the average days of administration days of all antibiotics.

To analyze the occurrence of infections according to the use of prophylactic antibiotics in patients who made claims for total knee arthroplasty, a retrospective cohort was constructed using health insurance claims data. The number of patients who had more than one total knee arthroplasty from January 1, 2008 to December 31, 2015 was 371,138. A total of 149,417 patients were selected as the analysis target, according to the study selection criteria. Among the selected patients, basic analysis was carried out on 6,922 patients in the group adhering to prophylactic antibiotic guidelines and 142,495 patients in the group nonadherent to prophylactic antibiotic guidelines. Sensitivity analysis was carried on 5,683 patients in the group adherent to prophylactic antibiotic guidelines, and on 143,734 patients in the group nonadherent to prophylactic antibiotic guidelines.

The analysis results using Cox's proportional hazard model for surgical site infection in all patients showed a nonsignificant difference (HR: 0.87, 95% CI: 0.68, 1.12, $p=0.27$) between the adherent and nonadherent groups. The analysis of subgroups according to age, type of antibiotic, type of medical care institution, and the number of antibiotic administration days per medical care institution also showed a nonsignificant difference in the total

number of surgical site infections between the groups. A sensitivity analysis conducted by defining the patients that had used 1st or 2nd generation cephalosporin alone as a group adhering to prophylactic guidelines, and all other patients as a nonadherent group, also showed a nonsignificant difference between the two groups (HR: 0.93, 95% CI: 0.72, 1.22, $p=0.62$).

A survey was undertaken to determine the orthopedic specialists' awareness level of clinical evidence and guidelines on the use of antibiotics and prophylactic antibiotics in total knee arthroplasty in actual clinical sites. The total number of participants in the survey was 203, of which 182 (89.7%) participants were members of the Korean Knee Society. The highest proportion of participants were between the ages of 30 and 39 years ($n=103$, 50.7%). Seventy-five participants (36.9%) were working at a general hospital, and the proportion of appointed survey-participating surgeons was high ($n=79$, 38.9%).

The number of survey-participating surgeons who administered intravenous prophylactic antibiotics prior to a total knee arthroplasty was 199 (98.0%), and the first antibiotics most frequently prescribed were the '1st generation cephalosporin family (such as cefazolin)', (154 surgeons, 77.4%).

Intravenous prophylactic antibiotics were administered for one week or less, post-operatively, by 192 surgeons (95.6%) among whom 29 surgeons (14.6%) administered them for one day or less (24 hours), post-operatively. In addition, for the appropriate number of days of intravenous administration of prophylactic antibiotics, 'use for one week or less (3-7 days) post-operatively' was the most prevalent (136 surgeons, 68.3%) followed by 'one day or less (24 hours) post-operatively' (31 surgeons, 15.6%), and 86% of the respondents were using a commercial bone antibiotic-embedded cement product when performing total knee arthroplasty.

Among the current prophylactic antibiotics guidelines, survey responses indicating a high level of agreement were 'chose 1st or 2nd generation cephalosporin family antibiotics as the primary prophylactic antibiotic', 'administer prophylactic antibiotics within one hour prior to incision', and

'combined administration of two or more prophylactic antibiotics is unnecessary'. Survey responses with a low level of agreement were 'administration of prophylactic antibiotics one hour prior to surgery is insufficient' and 'stop prophylactic antibiotic administration within 24 hours post-operatively'. Concerning the awareness of evidence-based clinical practice guidelines, there was a high level of agreement noted for the response: 'prophylactic antibiotic guidelines lack flexibility', while agreement on 'the latest guidelines are easily accessible' was low.

Among the survey participants, 166 surgeons (81.8%) stated that a South Korean prophylactic antibiotics guideline was necessary, and 'training should be conducted by a discipline-specific professional society' recorded the highest response (179 surgeons, 89.1%).

In terms of infection prevention, more than half of the respondents were satisfied with their hospital operating room environment, and those surgeons working in the Seoul metropolitan area and its vicinities (Seoul, Incheon, and Geongi), and who performed 200 or more total knee arthroplasties per year showed a higher ratio of satisfaction with their operating room environment.

To identify factors that affect the intention of orthopedic surgeons to adhere to prophylactic antibiotics guidelines, the theory of planned behavior, which explains intention and behavior using psychosocial factors, was used. The results of regression analysis, performed to identify the effect on the intention to adhere to prophylactic antibiotic guidelines, showed that the intention to adhere to guidelines was higher for hospital directors ($B=.960$, $\beta=.189$, $p < .05$) than for appointed surgeons, and the higher the ($B=.493$, $\beta=.415$, $p < .001$), the higher the intention to adhere to guidelines. It was also found that the stronger ($B=.340$, $\beta=.245$, $p < .01$) to guidelines, the higher the intention to adhere to guidelines. That is, the variable that had the greatest effect on guideline adherence was the intention to adhere to guidelines followed by institutional adherence related to guidelines and the position held within the hospital.

Orthopedic surgeons' awareness of guidelines for antibiotics use in total knee arthroplasty, identified through in-depth interviews, showed that the prophylactic antibiotic guidelines proposed by the government are being gradually accepted by medical professionals, and future antibiotic prescriptions are expected to be based on the guidelines. Doctors who prescribe antibiotics were aware of the guidelines and used them as an important reference, but their use did not accurately match the guidelines. The application of the guidelines was accompanied not only by government guideline proposals but was also informed through implementation efforts derived from various diverse supporting medical and educational institutions. In addition, hospital organization was found to be the key to implementation and adherence to antibiotic guidelines. Because of a gradual convergence concerning understanding and acceptance of the guidelines by orthopedic surgeons, and the effect and speed of implementation of government-led guidelines involving top-down proposal methods, the interactions and feedback processes between the government and medical doctors has been perceived as overpowering. Furthermore, hospitals made efforts to control the use of antibiotics through setting up their own standards concerning preoperative prophylactic antibiotic prescription on which the guidelines were focused, and the hospitals considered that there had been little positive feedback or differential compensation for their compliance efforts, but rather coerciveness and institutional pressure in applying government guidelines. Improvements in operating room environments, such as investment in hospital operating room facilities alongside the guidelines have been recognized as an important factor that can control infection issues and lead to successful surgery together with antibiotic use, as recommended in the guidelines.

□ Conclusions

This study identified a significant gap between the use of prophylactic antibiotics in actual domestic medical sites and international literature and

guidelines. Moreover, the biggest gap was seen between the opinions of domestic medical specialists and guideline recommendations in terms of the duration of prophylactic administration. However, the use of prophylactic antibiotics over recent years has gradually converged towards the guideline recommendations, and the awareness of medical specialists is moving towards accepting guideline recommendations rather than the findings of previous studies. Since deep infection at the surgical site does not increase when prophylactic antibiotics are administered according to the guidelines, these evidence-based guidelines are expected to lead domestic medical specialists to appropriately use prophylactic antibiotics according to the guidelines in future. A one-sided policy of monitoring and disciplining expert medical groups can bring about adverse effects such as hostility and distrust among expert medical groups. Whereas, if the establishment and implementation of policies in the future is based on the evidence derived from the domestic environment, such as the results of the present study, medical behavior can be led in a more desirable direction. Various types of evidence need to be gathered on the use of prophylactic antibiotics through additional research in the future. Surgical site infections are not simply determined through prophylactic antibiotic administration but occur through complex interactions among varying factors involving patients, medical staff, and the hospital operating environment. The non-significant difference in the risk of deep infection between the adherent and nonadherent groups also signifies that prophylactic antibiotics alone cannot prevent all surgical site infections. Therefore, to induce the appropriate use of prophylactic antibiotics while reducing surgical site infections, policy investment and support for other areas, such as the operating room environment and medical staff training, is recommended.

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