A Randomize Control Trial between Fosfomycin and Cefuroxime as the Antibiotic Prophylaxis in Knee Arthroplasty

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Background: *Antibiotic prophylaxis is used in all patient underwent total knee arthroplasty to prevent post operative infection which produced poor outcome. The suitable drug should be safe and good efficacy.*
Objective: *To study safety and efficacy of fosfomicin and cefuroxime as antibiotic prophylaxis for total knee arthroplasty.*
Material and Method: *The control trial was performed to find out efficacy and safety of fosfomycin as an antibiotic prophylaxis comparing to cefuroxime. There were 112 patients, 14 male and 98 female, with their ages ranged between 57 and 86 years. They were randomly divided into two groups, the fosfomycin group, 56 patients and the cefuroxime group, 56 patients. All patients underwent elective knee arthroplasty by the authors. The scheduled antibiotics were given perioperatively for 24 hours and all patients were followed-up for 6 months. Physical examination, skin temperature of the operated knee, radiograph and blood tests were carried out in the patients to monitor post operative infection, renal and liver disturbance.*
Results: *One patient in the cefuroxime group had local wound infection which responded well to local treatment and administration of antibiotics. No patients had post operative infection at the 6 months follow-up. No patients had any complication and none had renal and liver function disturbance during the follow-up.*
Conclusion: *Comparing to cefuroxime, fosfomycin is safe and effective for the use as antibiotic prophylaxis in knee arthroplasty.*

Keywords: *Antibiotic prophylaxis, Wound infection, Fosfomicin, Total knee arthroplasty*

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Post operative infection after total knee arthroplasty has been reported between 2.9 and 4.4% of the patients[1-3]. These patients usually have poor functional outcome and a certain number of the patients might have permanent disability[4]. In order to minimize the infection, antibiotic prophylaxis is usually used in all patients who are going to have knee replacement[5,6]. The suitable antibiotics should be a safe and easy to be used drug. They should cover most common skin pathogenic bacterias including *Staphylococus aureus* and *Staphylococus epidermidis*. One of the common used medications for antibiotic prophylaxis in knee arthroplasty is cefuroxime[7]. It has less frequency of administration than other cephalosporins, 3 times a day, which can lessen the chance of missed timing of the drug[8]. Cefuroxime has good bone penetration and can be mixed in the bone cement for local application[9,10]. It has less side effects and toxicity than the other intra venous antibiotics[11,12]. However, there was a report of increasing the chance of anemia in the patients are administered it as prophylaxis in arthroplasty[13]. Sensitivity of cefuroxime on *Staphylococci* decreases significantly during the past couple years. Cefuroxime cannot inhibit methecillin resistant *Staphylococus aureus* (MRSA). Cefuroxime has cross drug hypersensitivity with penicillin, so should be avoided using as an antibiotic prophylaxis in the patients who have a history of penicillin allergy.

Fosfomycin, a synthetic antibiotic, was discovered in 1967. It molecule is similar to phosphoenolpyruvate which is the precursor of bacterial cell wall. It acts as a fault substrate in inhibiting bacterial cell wall synthesis at the early steps[14,15]. Fosfomycin can pass into bone and joint at a better rate than any cefarosporin, including cefuroxime[16]. Most common skin pathogenic bacterias, both grams positive and grams negative, including *Staphylococcus aureus*, particular MRSA, *Staphylococcus epidemidis, E. coli*, *Pseudomonas aeruginosa* and *Peptococci* are sensitive to fosfomycin[17]. Fosfomycin has been used in acute

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and chronic osteomyelitis with good results[18-20]. Fosfomycin has also been used as an antibiotic prophylaxis in orthopaedic trauma surgery, foot and ankle surgery and in immune deficiency patients who develop spinal infection[21,22]. Furthermore, fosfomycin can be mixed with bone cement or hydroxyl apatite and be used as a local antibiotic therapy in bone and joint infection[23].

It was the aims of the present study to find out the possibility to use fosfomycin as antibiotic prophylaxis for knee arthroplasty comparing to cefuroxime in terms of safety and efficacy.

Material and Method

The present study was carried out as a control trial comparing safety and efficacy in the prevention of infection in knee arthroplasty between fosfomycin, the trial and cefuroxime, the control with 6 months follow-up. The numbers of the enrolled patients of the present study was calculated indirectly which based on Ishizaki's study[24] and the proposed formula,

$$n = \frac{2 (Z_{\alpha} + Z_{\beta})^2 p(1 - p)}{\Delta^2}$$

Each group should consist of 52 patients. The authors recruited 56 patients in each group to compensate attrition. Chi-square test and Fisher's exact test were used to analyze the discrete data and Student t-test was used to analyze the continuous data.

The present study was carried out which all patients were operated by the authors at the department of orthopaedic surgery, Faculty of Medicine Siriraj Hospital, Mahidol University. The proposal was approved by Siriraj Ethic Committee, No 001/2552. Inclusion criteria were 1) primary osteoarthritic patients who were scheduled for elective knee arthroplasty, 2) all patients had no source of infection in the other systems which were ruled out by physical examination, 3) patients who underwent single knee arthroplasty and 4) all patients had to agree to be enrolled in the present study and signed in the consent form after they had enough information. Exclusion criteria were 1) immune compromised patients, including diabetes mellitus, gouty arthritis and autoimmune diseases, 2) patients who might have any technical error during the operation, 3) patients who could not be followed-up as per the schedule and 4) patients who had history of allergy to cephalosporins or fosfomycin. There were 112 patients in the present study. The enrolled patients were randomized by using of computer program with blocks of two so that the numbers of the patients in each group were similar. There were 56 patients in group I, fosfomycin group and 56 patients in group II, cefuroxime group.

All patients underwent standard peri-operative management as ordinary patients who underwent arthroplasty, except for the prophylaxis antibiotics. The type of anesthesia to be used in the present study was spinal anesthesia, with patients controlling the analgesia after the operation. In the group I, the patients received 2 doses of 2 grams of fosfomycin by 15 minute intravenous dripping. The 1st dose was given at one hour before skin incision and the 2nd dose was given at 12th hour after the first dose. In the group II, three intravenous bolus doses of cefuroxime were given intravenously. The 1st dose, 1.5 grams of cefuroxime, was given to the patient at one hour before skin incision. The 2nd dose, 750 milligrams of cefuroxime, was given at the 8th hour and the 3rd dose, 750 milligrams of cefuroxime, was given to the patient at 16th hour after the first dose.

Surgical technique

After spinal anesthesia, the patient was placed in supine position and pneumatic tourniquet was applied at the upper thigh of the operating side. Povidone iodine scrubbing for 10 minutes was performed on the leg and the area of scrubbing starting from the thigh to the foot. Then, the patient's leg was draped and supported at 45 degrees hip flexion and 90 degrees knee flexion on the operating table. Medial parapatellar approach was carried out and the LPS-flex and PFC sigma instrumentation (Zimmer, Warsaw, USA and Depuy, Warsaw, USA) was used for joint replacement. Bone cement without antibiotic was used to fix the components. The wound was sutured in layers. Closed vacuum system was used for wound drainage. Then, bulky pressure dressing cooperating with posterior slab was applied on the operated knee at full extension.

Conventional post operative care was carried out in all patients of both groups except the post operative antibiotic administration for 24 hours. No patient of either group received any antibiotic after the 24th hour after the first dose of antibiotic prophylaxis if there was no sign of infection. Patient control analgesia was administered to all patients. Wound drainage was removed on the 2nd day. At the 3rd post operative day, the dressings were removed and light dressing was applied. Passive continuous range of motion exercise was applied to the patient. Progressive weight bearing and active range of motion exercise were carried out. The patient was discharged on the 8th to 10th day after

the operation. The sutures were removed after the 10th day after the operation. The patient was followed-up at 1, 3 and 6 months after the operation. During the follow-up, the patient was interviewed about pain and improvement of function of the operated knee. Physical examination of all systems and measurement of vital signs were carried out. At the operated knee, sign of inflammation, point of tenderness, skin temperature compared to the non-operated knee, stability and range of motion were evaluated. Infrared thermometer camera Fluke TiR was used to measure skin temperature. At the 3rd and 6th month follow-up, plain radiograph of the operated knee, screening blood test for CBC, ESR, C reactive protein, renal and liver function tests were also carried out.

The criteria of post operative infection were 1) pain and tenderness at the area which the patient did not experience before[25], 2) skin temperature of the operated knee was 5 degrees Celsius higher than the skin temperature of the non operated one[25], 3) significant high C-reactive protein at the 3rd and 6th month follow-up[26], 4) significant high or sustained high ESR at the 3rd and 6th month follow-up[27] and 5) osteolytic area around the prosthesis wider than 2 mm. For the patient who might have infection, joint aspiration was done and the fluid was sent for smear and stain and bacterial culture to confirm the diagnosis.

Results

There was no statistically significant difference in terms of biographic data, pathology, severity of knee arthrosis, sides, deformities and present of limb edema before the operation between the two groups (Table 1). Length of operative time of both groups was also similar. No patient had positive MRSA culture from nasal swab. No error of timing of antibiotic administration was found during the present study. No patient in either group had post-operative infection, except for one patient in the group II, cefuroxime group (Table 2). The patient had superficial wound infection at the operated knee. *Staphylococcus aureus* was the causative agent. Incision and drainage with prolonged

Table 1. Biographic data for the patients

	Group I (Fosfomycin) (n = 56)	Group II (Cefuroxime) (n = 56)	p-value
Sex			
Male	8 (14.3%)	6 (10.7%)	0.568
Female	48 (85.7%)	50 (89.3%)	
Age (yrs)			
Mean (SD)	68.02 ± 8.54	70.70 ± 8.51	0.099
Range	57-86	54-86	
Underlying conditions			
No	21 (37.5%)	17 (30.4%)	0.550
Yes	35 (62.5%)	39 (69.6%)	
Diabetes	10	11	
Hypertension	31	37	
Heart Disease	7	4	
Site			
Left	25 (44.6%)	22 (39.3%)	0.566
Right	31 (55.4%)	34 (60.7%)	
Deformity			
Genu varus	54 (96.4%)	53 (94.6%)	0.999
Genu valgus	2 (3.6%)	3 (5.4%)	
Radiographic classification			
Alhback III	44 (78.6%)	41 (73.2%)	0.902
Alhback IV	12 (21.4%)	15 (26.8%)	
Edema			
Yes	9 (16.1%)	9 (16.1%)	0.999
No	47 (83.9%)	47 (83.9%)	
Length of surgery (min)			
Mean (SD)	98.75 ± 34.61	91.88 ± 23.26	0.220
Range	40-240	50-155	

Table 2. Overall clinical efficacies of the drugs

	Effective	Ineffective	p-value	95% CI of Effective rate	Difference in Effective rate (FOS-CEF)
Follow-up 1 mo					
Group I (n = 56)	56 (100%)	0	0.313[a]	94.79%-100%	1.8%
Group II (n = 56)	55 (98.2%)	1 (1.8%)		90.45%-99.95%	
Follow-up 3 mo					
Group I (n = 56)	56 (100%)	0	-	94.79%-100%	0%
Group II (n = 56)	56 (100%)	0		94.79%-100%	
Follow-up 6 mo					
Group I (n = 56)	56 (100%)	0	-	94.79%-100%	0%
Group II (n = 56)	56 (100%)	0		94.79%-100%	

Z-test
[a] Fisher's exact test: p-value = 0.999

use of oral antibiotics have been carried out. There was no sign of superficial or deep infection at the 3rd and 6th month follow-up. During the follow-up, the patients of both groups had no statistically significant differences in terms of pain, range of motion, skin temperature, C-reactive protein and ESR, (Table 3 and 4). All patients were satisfied with the results of arthroplasty. There was no statistically significant difference in terms of blood tests for CBC, renal and liver function tests between the groups (Table 5).

Discussion

Although the most important factor influencing post surgical infection is surgeon awareness[28], antibiotic prophylaxis is also a very effective tool in the prevention of the infection[29]. However, bacteria resistant to the common used antibiotics including cefazolin, cefamandole and cefuroxime, is now frequently reported[30,31]. From the recent study, not only are methicillin resistant *Staphylococcus aureus* (MRSA) and coagulase negative staphylococci are the common pathogens in post arthroplasty infection, but polymicrobial organisms including gram negative *bacilli* and *enterococcus* are also commomly found[31]. Changing surgical antibiotic prophylaxis to the other medication or combination of glycopeptides and cefazolin has been recently proposed[31]. There is no strong evidence to support the routine use of dual drugs for antibiotic prophylaxis in arthroplasty[32]. On the other hand, combined drug therapy might increase the chance of drug side-effects and increase rate of drug resistant. Antibiotic prophylaxis by the use of single drug which can cover most common pathogens is still more popular than the combined drugs. Some antibiotics which can destroy MRSA such as fusidic acid and vancomycin are still not recommended for prophylactic use in primary THA and TKA, even in institution where MRSA and MRSE exceed 25% of orthopedic infections, as they are not cost effective and bacterial resistance to these medication might be rapidly developed[33]. Fosfomycin can cover most common pathogenic bacterias which have been found in common surgical infection[34]. Thus, it was used as the trial drug in the present study.

From our data, both antibiotics, fosfomycin and cefuroxime, are effective drugs to be used an antibiotic prophylaxis in knee arthroplasty. Short duration of antibiotic prophylaxis with good results in the present study also confirmed that they should not be used longer than 24 hours to lessen chance of drug resistance. Both of them were similar in term of safety as there was no significant difference in any clinical signs and blood tests.

Many authors reported errors of timing of antibiotic prophylaxis which could be a factor of post surgical infection[8,35,36]. The antibiotics with short half lives usually require more frequencies in administration. Use of them might have more common errors in timing of medication administration and unstable blood level than the medication with longer half lives[37]. Fosfomycin needs only 2 times of drug administration a day which is less than cefuroxime[14]. However, in the present study as we provided a check list for the residents and the nurses in charge and no error of timing of antibiotic prophylaxis was found. In clinical practice fosfomycin might provide lower chance of timing error

Table 3. Number of the patients who had normal and abnormal C- reactive protein levels during the study

	Pre Op		p-value	Post Op 3 mo		p-value	Post Op 6 mo		p-value
	Group I (n = 56)	Group 2 (n = 56)		Group I (n = 56)	Group 2 (n = 56)		Group I (n = 56)	Group 2 (n = 56)	
C-reactive protein									
Normal (< 3.0 mg/L)	37 (66.1%)	37 (66.1%)	0.999	35 (62.5%)	34 (60.7%)	0.846	37 (66.1%)	44 (78.6%)	0.139
Abnormal (≥ 3.0 mg/L)	19 (33.9%)	19 (33.9%)		21 (37.5%)	22 (39.3%)		19 (33.9%)	12 (21.4%)	

Table 4. ESR value during the study

	Pre Op		p-value	Post Op 3 mo		p-value	Post Op 6 mo		p-value
	Group I (n = 56)	Group 2 (n = 56)		Group I (n = 56)	Group 2 (n = 56)		Group I (n = 56)	Group 2 (n = 56)	
ESR (mm/hr)	33.14 ± 16.84	30.66 ± 17.16	0.442	36.57 ± 16.4	36.73 ± 17.89	0.961	32.29 ± 17.09	33.09 ± 19.74	0.818

One-way repeated ANOVA

Table 5. Results of screening renal and liver function tests during the study

	Pre Op	Post Op3 mo	Post Op6 mo
BUN (mg/dl)			
Group I (n = 56)	16.70 ± 5.16	16.66 ± 5.32	16.37 ± 4.49
Group II (n = 56)	18.27 ± 7.09	16.73 ± 5.54	17.07 ± 5.99
Creatinine (mg/dl)			
Group I (n = 56)	0.88 ± 0.25	1.23 ± 2.43	1.21 ± 2.57
Group II (n = 56)	0.98 ± 0.44	0.95 ± 0.32	0.97 ± 0.42
AST (U/L)			
Group I (n = 56)	26.48 ± 19.68	24.95 ± 15.04	23.63 ± 7.58
Group II (n = 56)	24.16 (7.27)	22.93 (8.11)	24.09 (9.48)
ALT (U/L)			
Group I (n = 56)	21.16 ± 8.97	19.59 ± 10.10	19.95 ± 9.75
Group II (n = 56)	22.20 ± 13.36	19.36 ± 11.64	20.39 ± 12.97
Alkaline phosphatase (U/L)			
Group I (n = 56)	75.93 ± 22.66	77.50 ± 20.89	74.75 ± 19.11
Group II (n = 56)	76.64 ± 63.98	73.39 ± 18.25	75.00 ± 22.69

Student t-test $p > 0.05$

than cefuroxime.

Recent studies reported good results in the use of fosfomycin as a combined therapy, with some antibiotics such as tobramycin and colistin, for the treatment of a particular resistant strains of Pseudomonas and MRSA. Fosfomycin could enhance the active transport of tobramycin in Pseudomonas aeruginosa[38]. Furthermore, fosfomycin has be used in the combination with colistin for the treatment of carbapenem-resistant Pasudomonas aeruginosa[39]. Fosfomycin in the combination with other antibiotics revealed success in the inhibition of MRSA[40,41]. On the other hand, cefuroxime has no synergistic effect on other antibiotics.

Conclusion

Fosfomycin can be used as an antibiotic prophylaxis for knee arthroplasty. Its safety and efficacy can be compared with the common use antibiotic, cefuroxime.

Potential conflicts of interest

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การศึกษาเปรียบเทียบการใช้ยาปฏิชีวนะฟอสโฟมัยซินและเซฟฟูรอกซีมเพื่อป้องกันการติดเชื้อจากการผ่าตัดเปลี่ยนข้อเข่าเทียม

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วัตถุประสงค์*: เพื่อศึกษาความปลอดภัยและประสิทธิภาพของยาฟอสโฟมัยซินในการป้องกันการติดเชื้อหลังการผ่าตัดเปลี่ยนข้อเข่าเทียมเปรียบเทียบกับยาเซฟฟูรอกซีม*

วัสดุและวิธีการ*: ศึกษาผลการใช้ยาฟอสโฟมัยซินทางคลินิก ในการป้องกันการติดเชื้อหลังการผ่าตัดเปลี่ยนข้อเข่าเทียมในผู้ป่วย 122 ราย เป็นชาย 14 ราย และเป็นหญิง 98 ราย อายุผู้ป่วยอยู่ระหว่าง 57 และ 86 ปี เปรียบเทียบกับยาเซฟฟูรอกซีม ซึ่งเป็นยาที่นิยมใช้เพื่อการป้องกันการติดเชื้อหลังการผ่าตัดเปลี่ยนข้อ แบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มใช้ยาฟอสโฟมัยซิน 56 ราย และกลุ่มยาเซฟฟูรอกซีม 56 ราย การประเมินอาการติดเชื้อและความปลอดภัยใช้วิธีการตรวจร่างกาย การวัดอุณหภูมิผิวหนังข้างที่ผ่าตัดเปรียบเทียบกับข้างที่ไม่ได้ผ่าตัด ภาพถ่ายรังสีและผลการตรวจเลือด โดยตรวจการทำงานของตับและไตและการตรวจร่องรอยการติดเชื้อจาก ESR และ C-reactive protein*

ผลการศึกษา*: ไม่พบการติดเชื้อรุนแรงหลังการผ่าตัดยกเว้นกลุ่มที่ใช้ยาเซฟฟูรอกซีม มีผู้ป่วย 1 ราย เกิดการติดเชื้อที่ผิวหนัง ซึ่งตอบสนองดีต่อการผ่าตัดนำหนองออกและการใช้ยาปฏิชีวนะ ไม่พบการติดเชื้อในทั้ง 2 กลุ่ม เมื่อติดตามผลการศึกษาที่ 6 เดือน ไม่พบภาวะแทรกซ้อนใดๆในผู้ป่วยทั้ง 2 กลุ่ม*

สรุป*: ยาฟอสโฟมัยซินเป็นยาปฏิชีวนะที่ปลอดภัยสามารถนำมาใช้ในการป้องกันการติดเชื้อระหว่างการผ่าตัดเปลี่ยนข้อเข่าเทียม*