Are Bone and Serum Cefazolin Concentrations Adequate for Antimicrobial Prophylaxis?

Koji Yamada MD, Kunihiro Matsumoto PhD,
Fumiaki Tokimura MD, Hiroshi Okazaki MD, PhD,
Sakae Tanaka MD, PhD

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Abstract

Background Antimicrobial prophylaxis is considered beneficial for preventing surgical-site infections in clean orthopaedic surgery. However, whether tissue concentrations of cefazolin achieve the minimum inhibitory concentration for the targeted contaminants have yet to be clarified.

Questions/purposes We asked whether 2 g of cefazolin would enable effective serum and bone concentrations

relative to the current minimum inhibitory concentration for cefazolin-resistant coagulase-negative Staphylococci and methicillin-sensitive Staphylococcus aureus.

Patients and Methods We enrolled 43 patients (THA, n = 16; TKA, n = 27) scheduled for primary THAs and primary TKAs. Subjects were given 2 g of cefazolin intravenously before incision. One blood sample and two bone samples were collected from each subject before tourniquet deflation before any additional dose. All samples were assayed at the same laboratory. Minimum inhibitory concentration values were defined based on nationwide surveys.

Results Mean ($\pm$ standard deviation) serum concentration was 170.3 ± 51.3 $\mu\text{g/mL}$ (range, 99.3–370.3 $\mu\text{g/mL}$). Mean bone concentration was 32.3 ± 15.2 $\mu\text{g/g}$ (range, 11.4–70.0 $\mu\text{g/g}$) in THA, and 16.0 ± 10.4 $\mu\text{g/g}$ (range, 6.3–46.3 $\mu\text{g/g}$) in TKA. All serum and bone concentrations exceeded the minimum inhibitory concentration for methicillin-sensitive S. aureus, but some serum levels were marginal and no bone levels exceeded the minimum inhibitory concentration for cefazolin-resistant coagulase-negative Staphylococcus.

Conclusions Our data suggest intravenous administration of 2 g of cefazolin achieves the minimum inhibitory concentration for methicillin-sensitive S. aureus in serum and bone, but not the minimum inhibitory concentration for cefazolin-resistant coagulase-negative Staphylococcus in bone, resulting in a potential risk of deep surgical site infections in THAs and TKAs.

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All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research* editors and board members are on file with the publication and can be viewed on request. Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained. This work was performed at Tokyo Metropolitan Tama Medical Center (Tokyo, Japan) and Tama-Hokubu Medical Center (Tokyo, Japan).

K. Yamada (✉), S. Tanaka
Department of Orthopaedic Surgery, Faculty of Medicine,
The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku,
Tokyo 113-0033, Japan
e-mail: forpatients2008@gmail.com

K. Matsumoto
Department of Medication Use Analysis and Clinical Research,
Meiji Pharmaceutical University, Tokyo, Japan

F. Tokimura
Department of Orthopaedic Surgery, Tokyo Metropolitan
Geriatric Hospital, Tokyo, Japan

H. Okazaki
Department of Orthopaedic Surgery, Tokyo Metropolitan
Tama Medical Center, Tokyo, Japan

Introduction

A surgical site infection (SSI) is a serious postoperative complication associated with increased morbidity and mortality. Patients with an infection are twice as likely to

die, twice as likely to spend time in an intensive care unit, and five times more likely to be readmitted after discharge [36]. Orthopaedic units are classified as high-risk areas because of the potentially serious consequences of infection, particularly among patients with prosthetic joints [33].

Antimicrobial prophylaxis is considered beneficial for preventing SSIs in clean orthopaedic surgery [9]. The World Health Organization (WHO) [36] and the Centers for Disease Control and Prevention (CDC) [19] have stated that microbial contamination during a surgical procedure is a precursor of a SSI. Use of prophylactic antibiotics with an antimicrobial spectrum that is effective against the pathogens likely to contaminate the procedure therefore is recommended for use in any clean surgical case [36].

Methicillin-sensitive *Staphylococcus aureus* (MSSA) and coagulase-negative *Staphylococci* (CoNS) are the most common organisms causing deep wound infections in clean orthopaedic surgery [9]. CoNS in particular is recognized as the most common contaminant obtained in cultures taken from surgical sites other than MSSA [2], and generally is accepted as being one of the most resistant pathogens worldwide [23]. The prevalence of methicillin resistance has been reported greater in CoNS than in *S. aureus*, with rates ranging globally from 75% to 90% during the 1990s [14]. Most resistance to oxacillin in staphylococci is mediated by the *mecA* gene, which codes for the production of a supplemental penicillin-binding protein, which has a low affinity for β -lactam antibiotics [22]. Thus, they are clinically considered cefazolin resistant [27, 34]. The existence of resistant CoNS seen on a patient's skin [30, 37] and the resistance seen in CoNS-infected joints [20, 21, 28] therefore must be given serious consideration.

Total joint arthroplasty is one of the most common surgeries performed by orthopaedic surgeons worldwide, with up to 600,000 operations annually in the United States [8]. According to the advisory statement from the National Surgical Infection Prevention Project (NSIPP), cefazolin is recommended as the first choice for antimicrobial prophylaxis for patients having THAs and TKAs [3]. To be effective as an antimicrobial prophylaxis, the serum and tissue drug levels must be greater than the minimum inhibitory concentrations (MICs) for the target organisms throughout the surgical period [3, 26]. Quintiliani and Nightingale [26] recommended the concentration of antibiotics be at least four times the MIC of the target organism in patients with normal host defenses, a recommendation others consider an adequate concentration for prevention of SSI [1, 11, 16].

Previous studies show bone and serum concentrations of cefazolin exceed these levels when given in doses of 1 or 2 g preoperatively [6, 11, 12, 31, 32, 35]. Several studies of bone concentrations of cefazolin, particularly against

CoNS [11, 35], suggest bone concentrations of 0.5 to 1 μ g/mL may be achieved, and these would reflect an MIC₉₀ of cefazolin for CoNS. However, these data do not consider the increasing resistance seen in CoNS. Thus, whether bone concentrations of cefazolin achieve the MIC and adequate concentrations have yet to be clarified.

The aim of this study was to examine whether (1) serum and (2) bone concentrations of cefazolin achieve the MICs and adequate concentrations for cefazolin-resistant coagulase-negative *Staphylococci* (CRCoNS) and MSSA based on current nationwide surveys in Japan.

Patients and Methods

This cross-sectional study was conducted in two general hospitals in Tokyo, Japan. Between September 2006 and June 2008, we screened all 54 patients scheduled to undergo primary THA or TKA for eligibility. We excluded patients who might have abnormal delivery of cefazolin to bone. Exclusion criteria in this study were: (1) patients undergoing revision procedures; (2) patients undergoing bilateral procedures; (3) patients with established joint infection at the time of surgery; (4) patients with abnormal laboratory data such as serum creatinine levels greater than 1.5 mg/dL, abnormal coagulation status (prothrombin time less than 10 seconds or greater than 14 seconds, or partial thromboplastin time greater than 40 seconds), hemoglobin levels less than 10 g/dL, hematocrit less than 30%, serum aspartate transaminase greater than 55 IU/L, serum alanine transaminase greater than 55 IU/L, or total bilirubin greater than 1.0 mg/dL before surgery; (5) patients who had received any antimicrobial agents during the week before surgery; (6) patients who were allergic to penicillin or cephalosporin; (7) patients receiving hemodialysis; (8) patients with a history of liver cirrhosis; (9) patients receiving surgery for fractures; (10) patients who received 1 g of cefazolin as the initial dose; and (11) patients who received additional doses of cefazolin before samples were taken. We screened 54 patients of whom 43 (THA, $n = 16$; TKA, $n = 27$) met the inclusion criteria. Patients who met the exclusion criteria had serum creatinine greater than 1.5 mg/dL on admission ($n = 1$); reoperation ($n = 2$); femoral neck fracture ($n = 1$); initial administration of 1 g of cefazolin ($n = 2$); and administration of additional cefazolin before specimens were taken ($n = 5$). The mean weight of patients in the total study population was 55.4 kg (range, 41–75 kg), and BMI was 24.3 (range, 17.7–31.6) (Table 1). There were no differences in the backgrounds of patients having THAs and those having TKAs. Diagnoses for patients having THAs were osteoarthritis ($n = 12$), osteonecrosis ($n = 3$), and rheumatoid arthritis ($n = 1$). Diagnoses of patients having TKAs were osteoarthritis

Table 1. Patients' baseline characteristics and clinical findings

Variable	Overall	THA	TKA	p Value [†]
Numbers of participants	43	16	27	
Age* (years)	74.8 ± 7.9	73.4 ± 8.1	75.6 ± 7.8	0.392
Sex				0.780
Male	7	3	4	
Female	36	13	23	
Height* (cm)	151.1 ± 7.0	152.1 ± 8.1	150.5 ± 6.4	0.483
Weight* (kg)	55.4 ± 8.2	54.1 ± 8.1	56.2 ± 8.2	0.419
BMI*	24.3 ± 3.4	23.4 ± 2.9	24.9 ± 3.5	0.164
Amount of administration* (mg/kg)	36.9 ± 5.5	37.8 ± 6.2	36.3 ± 5.2	0.386
Duration of operation (minutes)	158 ± 43	158 ± 60	158 ± 31	0.993
Blood examination				
Creatinine* (mg/dL)	0.7 ± 0.2	0.6 ± 0.1	0.8 ± 0.3	0.117
Total protein* (g/dL)	7.6 ± 0.6	7.7 ± 0.6	7.5 ± 0.5	0.322
Albumin* (g/dL)	4.2 ± 0.4	4.4 ± 0.5	4.2 ± 0.4	0.085
Hemoglobin* (g/dL)	12.7 ± 1.3	12.9 ± 1.4	12.6 ± 1.3	0.539
Hematocrit* (%)	38.4 ± 3.8	38.4 ± 4.0	38.4 ± 3.8	0.988
Platelets* (10 ³ /μL)	249 ± 69	240 ± 64	254 ± 73	0.546
Prothrombin time* (seconds)	11.0 ± 0.5	11.0 ± 0.6	11.0 ± 0.5	0.634
PT/INR*	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.437
Activated partial thromboplastin time* (seconds)	27.2 ± 2.8	27.4 ± 3.0	27.0 ± 2.7	0.724
Blood sugar* (mg/dL)	107.8 ± 28.9	99.2 ± 7.6	112.9 ± 35.3	0.134
GOT* (IU/L)	23.3 ± 6.7	25.3 ± 6.7	22.1 ± 6.6	0.130
GPT* (IU/L)	18.1 ± 8.5	19.2 ± 5.8	17.5 ± 9.9	0.542
Total bilirubin* (mg/dL)	0.6 ± 0.2	0.6 ± 0.2	0.5 ± 0.2	0.140

* Values = mean and standard deviation; [†]Fisher's exact test was used for dichotomous data, and unpaired Student's t-test was used for continuous data; PT/INR = prothrombin time/international normalized ratio; GOT = serum glutamic-oxaloacetic transaminase; GPT = glutamic-pyruvic transaminase.

(n = 21), osteonecrosis (n = 2), and rheumatoid arthritis (n = 4). A total of 86 bone specimens were obtained throughout the study period. Successfully screened patients provided written informed consent. All data were collected prospectively. This study was approved by the local medical research ethics committee.

THAs and TKAs were performed using uncemented and cemented implants, respectively. Minimally invasive surgery was not performed during the study period. The antimicrobial prophylaxis protocol in our study followed NSIPP recommendations [3]. Two grams of cefazolin in 100 mL normal saline was administered intravenously in 15 minutes (400 mL/hour) before incision (THA), and before inflation of the tourniquet (TKA). Two grams of cefazolin was administered initially throughout the study period for its advantage in obese patients [10]. No additional dose was administered before bone and serum samples were taken. Cancellous bone specimens were obtained from the femoral neck and the trochanteric region in patients undergoing THAs (Fig. 1), and from the posterior femoral condyle and tibial plateau in those

undergoing TKAs (Fig. 2). Bone specimens taken from the femoral neck were obtained using a bone saw and rongeur, whereas samples from the trochanteric region were obtained using box osteotomy. Bone specimens taken from the posterior femoral condyle and tibial plateau were obtained using the bone saw before tourniquet deflation. Bone specimens were washed with normal saline to remove the surface blood clot in an aseptic manner, and sampling times were recorded. The intervals were calculated between cefazolin administration and the sample collection. Specimens were immediately frozen and stored at −20 to −80°C until assay. Specimens were transported to the same laboratory and assayed as soon as possible. Cartilage and cortical bone were excised carefully using a rongeur, so the remaining cancellous bone specimens were used for analysis. Blood samples were collected concurrently with bone collection, and sera were stored at −20°C and analyzed at the same laboratory site.

All serum and bone samples were assayed in the same laboratory. Cefazolin concentrations were determined using the method described by Irie et al. [15] with minor

Fig. 1 Cancellous bone specimens were taken from the femoral neck and the trochanteric region during THA.

Fig. 2 Cancellous bone specimens were taken from the posterior femoral condyle and tibial plateau in patients having TKAs.

Table 2. Cefazolin susceptibility of MSSA and CoNS in Japanese subjects

Study	Bacteria (number of species investigated)	Strains	MIC ₉₀ * (μg/mL)	Range of MIC (μg/mL)
Kimura et al. [17]	MSSA	117	0.78	0.39–1.56
	CoNS (4)	174	0.78, 12.5, 100, > 100	0.39–> 100
Kimura et al. [18]	MSSA	89	0.78	0.39–1.56
	CoNS (7)	207	0.78, 1.56, 6.25, 50, 100, > 100, > 100	0.2–> 100
Yoshida et al. [38]	MSSA	84	0.78	0.1–25
	CoNS (8)	311	0.39, 0.39, 0.78, 1.56, 100, 100, > 100, > 100	0.1–> 100
Fujimura et al. [13]	MSSA	76	1	0.25–2
	CoNS (5)	104	Not reported	Not reported

* MIC₉₀ = minimum inhibitory concentrations of each species; MSSA = methicillin-susceptible *Staphylococcus aureus*; CoNS = coagulase-negative *Staphylococci*.

modification. The frozen bone specimens were first milled. After adding 0.067 mol/L phosphate buffer (pH 7.0) and centrifuged, the remaining supernatants were examined. Briefly, after adding 50 μL of 0.1 mg/mL coumarin-3-carboxylic acid, the mixture was evaporated under an N₂ gas stream at 50°C, applied to Bond Elut C18 (Varian Inc, Lake Forest, CA, USA) to eliminate substances that would interfere with the assay, washed with 500 μL of extra-pure water containing 8.5% phosphoric acid and 5% CH₃OH/8.5% phosphoric acid, and eluted with 1 mL of 10 mmol/L acetate buffer (pH 3.2)/CH₃OH. Finally, 50 μL of the eluate was applied to high-performance liquid chromatography (HPLC). The conditions of HPLC were as follows:

mobile phase, 10 mmol/L acetate buffer (pH 3.2)/CH₃OH = 70/30 (v/v); flow rate, 0.8 mL/minute; column, Inertsil ODS-3 (5 μm, 4.6 × 250 mm) (GL Sciences Inc, Tokyo, Japan); and column temperature, 40°C; detector, ultraviolet (262 nm).

MICs were defined using the results obtained from several nationwide surveys (Table 2) [13, 17, 18, 38]. The MIC₉₀ of MSSA was defined as 1 μg/mL as results were consistently 0.78 to 1 μg/mL in the surveys. For CoNS, we chose the highest MIC₉₀ level for comparison, as all species had the chance of contamination during the procedures [29]. There were no data regarding how much more than 100 μg/mL they were, and the overall MIC₉₀ for CRCoNS

Table 3. Bone and serum concentrations in THA and TKA

Type of operation	Serum				Bone			
	Number of samples	Mean concentration (µg/mL)	Range (µg/mL)	Mean sampling time* (minutes)	Number of samples	Overall mean concentration (µg/g)	Range (µg/g)	Overall mean sampling time* (minutes)
THA	16	177.2 ± 68.1	99.3–370.3	40 ± 9	32	32.3 ± 15.2 [†]	11.4–70.0	64 ± 33 [†]
TKA	26	166.0 ± 38.5	109.8–258.2	54 ± 12	50	16.0 ± 10.4 [‡]	6.3–46.3	63 ± 19 [‡]
Total	42	170.3 ± 51.3	99.3–370.3	49 ± 13	82	22.4 ± 14.8	6.3–70.0	63 ± 25

* Time between cefazolin administration and sample collection; [†]overall mean (± SD) of femoral neck and trochanteric region; [‡]overall mean (± SD) of posterior femoral condyle and tibial plateau.

was 100 µg/mL from the available data. Therefore, we defined the MIC₉₀ as 100 µg/mL for CRCoNS. We chose CRCoNS for comparison to know the upper end of the predominant contaminant, as MRSA usually is not reported as a contaminant in clean orthopaedic surgeries [2, 7, 24, 37]. Thus, we focused on CRCoNS. Adequate concentration levels were defined as four times the MIC₉₀, as reported in previous studies [1, 11, 16]. The bioactivity of cefazolin in fresh frozen bone reportedly has an inhibitory effect against *Staphylococcus aureus* using an agar disc diffusion bioassay [4]. One blood sample, two samples of posterior femoral condyles, and two samples of tibial plateaus were excluded because the sampling times were missing.

The primary endpoint was to ascertain whether bone and serum concentrations of cefazolin achieved the MIC₉₀ and adequate concentration for MSSA and CRCoNS, as derived from the domestic national surveys [13, 17, 18, 38]. The primary endpoint was concealed from investigators performing the cefazolin assay. No feedback was given to the patients during the study.

Analyses of the demographic data comparing THAs and TKAs were performed. Fisher's exact test was used for dichotomous data and unpaired Student's t-test was used for continuous data. We used SAS version 9.1.3 (SAS Institute, Cary, NC, USA) for all analyses.

Results

The mean (± SD) serum concentration of cefazolin was 170.3 ± 51.3 µg/mL (range, 99.3–370.3 µg/mL) (Table 3). All serum samples were greater than the MIC₉₀ of cefazolin for MSSA (Fig. 3), whereas some serum samples were at a marginal level for CRCoNS (Fig. 3). All serum samples were greater than the adequate level for MSSA (Fig. 3), but none exceeded the adequate level for CRCoNS (Fig. 3).

Mean bone concentrations in each group were 32.3 ± 15.2 µg/g (range, 11.4–70.0 µg/g) for THAs and 16.0 ± 10.4 µg/g (range, 6.3–46.3 µg/g) for TKAs

Fig. 3 A scatter plot of the cefazolin serum concentrations for patients having THAs and TKAs is shown. The lines represent the predicted MIC₉₀ and adequate concentrations: Line a = MIC₉₀ of methicillin-sensitive MSSA based on recent domestic nationwide surveys; Line b = the adequate concentration for MSSA (four times the MIC₉₀ of MSSA); Line c = MIC₉₀ of cefazolin-resistant CoNS (CRCoNS) based on recent domestic nationwide surveys; and Line d = adequate concentration for CRCoNS (four times the MIC₉₀ of CRCoNS).

(Table 3). For THAs, the mean bone concentrations were 40.8 ± 15.2 µg/g (range, 13.9–70.0 µg/g) at the femoral neck and 23.8 ± 9.7 µg/g (range, 11.4–43.8 µg/g) for the trochanteric region. All bone specimens exceeded the MIC₉₀ (Fig. 4A) and the adequate level (Fig. 4A) for MSSA. However, no bone specimens exceeded the MIC₉₀ (Fig. 4A) or adequate level (Fig. 4A) for CRCoNS. For TKAs, the mean bone concentrations were 16.0 ± 9.7 µg/g (range, 6.3–37.8 µg/g) at the posterior femoral condyle and 16.1 ± 11.2 µg/g (range, 7.5–46.3 µg/g) at the tibial plateau. All specimens were greater than the MIC₉₀ (Fig. 4B) and adequate level (Fig. 4B) for MSSA, but were

Fig. 4A–B Scatter plots of the cefazolin bone concentration for patients having (A) THAs and (B) TKAs are shown. The lines represent the predicted MIC₉₀ and adequate concentrations: Line a = MIC₉₀ of MSSA based on recent domestic nationwide surveys; Line b = adequate concentration for MSSA (four times the MIC₉₀ of MSSA), and Line c = MIC₉₀ of cefazolin-resistant CoNS based on recent domestic nationwide surveys.

mostly at a lower level compared with THAs (Fig. 4B). None exceeded the MIC₉₀ or the adequate level for CRCoNS (Fig. 4B).

Discussion

Previous studies showed bone and serum concentrations of cefazolin exceeded MIC₉₀ and an adequate concentration for preventing CoNS and MSSA SSIs [6, 11, 12, 31, 32, 35]. However, the MIC₉₀ used in those studies were 0.5 to 1 µg/mL for CoNS [11, 35], with no consideration of the increasing resistance. Thus, the aim of our study was to examine whether (1) serum and (2) bone concentrations of cefazolin, with 2 g administered intravenously, achieved the MICs and adequate concentrations for CRCoNS and MSSA based on current nationwide surveys.

We note limitations to our study. First, we followed the guidelines of Quintiliani and Nightingale [26], who proposed that a concentration of antibiotic approximately four times the MIC should be achieved in patients with normal host defenses. With this assumption, concentrations of 4 µg/g of cefazolin for MSSA and 400 µg/g for CRCoNS were considered adequate. Although their assumption is not based on any large prospective studies [26], it has been used in previous studies as the definition of adequate cefazolin concentration [1, 11, 16]. The necessity for antibiotic tissue concentrations at this level to accomplish SSI prevention remains controversial and needs to be clarified by additional investigations. However, the finding that bone concentrations were not even beyond the MIC₉₀ of CRCoNS is noteworthy, given that this is the minimal level needed to establish effective antimicrobial prophylaxis. Second, the definition of MIC₉₀ was not directly derived from bacteria cultured from surgical sites in our

patients. In a previous study, we observed that CoNS was the predominant pathogen cultured from patients' surgical sites, in the same study period [37]. Currently, 80% of CoNS strains are reportedly methicillin-resistant [25]. According to domestic surveys [13, 17, 18, 38], resistance to cefazolin is seen in many CoNS species, with a MIC₉₀ of 100 µg/mL or greater in approximately half of the reported species (Table 2). In contrast, in Japan the MIC₉₀ for MSSA has not changed markedly during the last few decades, ranging from 0.78 to 1 µg/mL. As these data were based on very large studies involving nationwide facilities [13, 17, 18, 38], we considered these as the most reliable data representing increasing resistance in these pathogens. We therefore defined 100 µg/mL as the MIC₉₀ for CRCoNS and 1 µg/mL as the MIC₉₀ for MSSA in the current study. Moreover, the MIC₉₀ for methicillin-resistant CoNS was reported as 64 µg/mL [5] in 1990. Considering the increasing resistance worldwide [14, 17], we believe the MIC level we defined for CRCoNS could be acceptable. Although the assumptions made were based on several large nationwide surveys [13, 17, 18, 38], discrepancies might have existed in the MIC₉₀ for species actually contaminating surgical sites and those derived from the surveys. This issue needs to be clarified in further investigations.

In previous studies, the estimated serum concentrations at approximately 60 minutes after 1 g intravenous cefazolin administration were approximately 50 to 70 µg/mL [6, 11, 12, 31, 35] (Table 4). We found an estimated serum concentration of approximately 130 µg/mL with 2 g of cefazolin administered intravenously. The serum concentrations exceeded the MIC₉₀ of cefazolin in 40 of the 42 (95%) samples and 42 of the 42 (100%) samples for CRCoNS and MSSA, respectively (Fig. 3). All were greater than the adequate level for MSSA. However, in

Table 4. Bone and serum cefazolin concentrations (comparison of current data with previously published results)

Study	Serum		Bone		Number of samples	Mean time after cefazolin administration (minutes)	Type of operation	Sampling sites	Cefazolin dosage		Mean body weight (kg)
	Estimated concentration at 60 minutes after cefazolin administration ($\mu\text{g/mL}$)	Mean concentration ($\mu\text{g/g}$)	Mean concentration ($\mu\text{g/g}$)	Mean time after cefazolin administration (minutes)					Initial dose	Additional dose before sample taken	
Schurman et al. [31]	~70	5.7	5.7	45	39	45	THA	Femoral head	1 g	NA	NA
Sørensen et al. [32]	~70	5.5	5.5	41	8	41	TKA	Femoral condyles	1 g	NA	NA
	NA	12	12	45	1	45	Osteosynthesis	Medial supracondylar region of femur	1 g	None	NA
Cunha et al. [6]	~60	NA	NA	NA	31	NA	THA	Femoral head	1 g	NA	NA
Friedman et al. [11], Friedrich et al. [12]	~50–70	~3	~3	~65	24	~65	TKA	Distal femur	1 g	NA	90–98
Williams et al. [35]	~50	6.9	6.9	69*	17	69*	THA	Femoral head	1 g	NA	NA
	~90	4.7	4.7	51*	6	51*	TKA	Femoral condyle	2 g		
Current study	~130	18.4	18.4				THA	Femoral head	2 g		
		7.8	7.8				TKA	Femoral condyle			
		40.8	40.8	35	16	35	THA	Femoral neck	2 g	None	54.1
		23.8	23.8	93	16	93	THA	Trochanteric region			
		16.0	16.0	51	25	51	TKA	Posterior femoral condyle			
		16.1	16.1	75	25	75	TKA	Tibial plateau			

* Mean time of THA and TKA bone samples; NA = not available.

some patients, the concentration was already at a marginal level of the MIC₉₀ for CRCoNS at approximately 40 minutes after administration, with none exceeding the adequate level for CRCoNS (Fig. 3).

Compared with previous studies in which 1 g intravenous cefazolin was used, the bone concentration in our patients seemed to be greater (Table 4). There are several problems, however, when interpreting these data. First, none of the previous studies reported the exact sampling sites. This is important owing to the potential differences in bone concentrations at different sampling sites [35]. Second, the mean weight of the study populations was not available in most studies [6, 31, 32, 35]. Third, the only data available for 2 g of cefazolin were those for six patients with a mixture of THAs and TKAs [35]. Our data suggest the bone concentrations would be adequate for protection against MSSA (Fig. 4). The concentrations were mostly adequate for the highest MIC₉₀ available for cefazolin-sensitive CoNS (8 µg/g) [34]. However the concentrations seemed insufficient compared with the MIC₉₀ for CRCoNS for THAs and TKAs (Fig. 4), with none exceeding the adequate level, even with higher bone concentrations.

The WHO [36] and CDC [19] have recommended prophylactic use of antibiotics against the pathogens likely to contaminate the procedure. Bernard et al. [2] reported CoNS as the predominant pathogen obtained in intraoperative swab cultures collected from 1036 patients undergoing clean orthopaedic surgeries. As similar results have been reported in subsequent studies [7, 24], CoNS must be considered an important pathogen for targeting in antimicrobial prophylaxis. Moreover, CoNS has been recognized as the predominant causative organism for prosthetic joint infections [20, 21, 28], and globally one of the most resistant [14, 25]. Moran et al. [20] reported that 47% of causative organisms for prosthetic joint infections were CoNS, 60% of which were methicillin-resistant, followed by MSSA. These findings suggest CoNS, especially with established resistance, is an important pathogen in orthopaedic infection in addition to MRSA, therefore, we focused on CoNS with resistance to cefazolin—the most recommended antimicrobial prophylaxis [3].

Our data showed intravenous administration of 2 g of cefazolin achieved the MIC₉₀ and adequate concentration for MSSA in serum and bone, but that neither the MIC₉₀ nor the adequate concentration for CRCoNS were achieved in bone, resulting in a potential risk of deep SSI. Just because the range may at its upper border exceed the attainable bone or even serum concentrations does not mean that for a majority of patients, cefazolin prophylaxis would not be adequate. However, concerns remain owing to the increasing antibiotic resistance observed among human pathogens, which is an important issue in directing

future recommendations for surgical antibiotic prophylaxis [25]. Institutions using cefazolin as a first-choice agent for antimicrobial prophylaxis for patients having THAs and TKAs, with CoNS as the main pathogen of SSI, should be aware of the possible failure using cefazolin as described in this study. We believe it would be important to identify better techniques to reduce surgical contaminants or to provide more effective antimicrobial prophylaxis against the contaminants. Additional investigations are required to guide recommendations and solutions to this particular issue.

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