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Higher Cefazolin Concentrations with Intraosseous Regional Prophylaxis in TKA

Simon W. Young FRACS, Mei Zhang PhD,
Joshua T. Freeman FRCPA, Kelly G. Vince MD,
Brendan Coleman FRACS

Abstract

Background Prophylactic antibiotics reduce the risk of deep infection after primary TKA. However, conventional systemic dosing may not provide adequate tissue concentrations against more resistant organisms such as coagulase-negative staphylococci. Regional intravenous administration of antibiotics after tourniquet inflation achieves far higher tissue concentrations but requires foot vein cannulation. The intraosseous route may offer a rapid and reliable method of regional administration.

Questions/Purposes We compared tissue concentrations of cefazolin achieved with systemic versus regional intraosseous administration.

Methods Twenty-two patients undergoing primary TKA were randomized into two groups. Group 1 received 1 g cefazolin systemically 10 minutes before tourniquet inflation. Group 2 received 1 g cefazolin intraosseously in 200 mL of normal saline through a tibial cannula after tourniquet inflation and before skin incision. Subcutaneous fat and femoral bone samples were taken at set intervals during the procedure and antibiotic concentrations measured using a validated technique involving high-performance liquid chromatography.

Results The overall mean tissue concentration of cefazolin in subcutaneous fat was 186 ug/g in the intraosseous group and 11 ug/g in the systemic group. The mean tissue concentration in bone was 130 ug/g in the intraosseous group and 11 ug/g in the systemic group. These differences were consistent across all sample time points throughout the procedure.

Conclusions Intraosseous regional administration can achieve concentrations of antibiotic in tissue an order of magnitude higher than systemic administration. Further work is required to determine if this translates into increased efficacy in preventing infection, particularly against coagulase-negative staphylococci.

S. W. Young (✉), B. Coleman
Department of Orthopaedics, Middlemore Hospital, Private Bag 93311, Otahuhu, Auckland 1640, New Zealand
e-mail: simonwyoung@gmail.com

K. G. Vince
Department of Orthopaedics, Whangarei Hospital, Whangarei, New Zealand

M. Zhang
Clinical Pharmacology, Department of Medicine, University of Otago—Christchurch, Christchurch, New Zealand

J. T. Freeman
Clinical Microbiology, Auckland City Hospital, Auckland, New Zealand

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Introduction

Deep surgical site infection is one of the most devastating complications of TKA. Despite concerted efforts to reduce infection rates, the reported incidence after primary TKA persists between 0.86% and 2.5% [1, 2, 20, 21]. Coagulase-negative staphylococci cause up to 49% of deep infections with evidence that the role of these organisms is increasing [1, 2, 20, 21].

The majority of early postoperative infections results from intraoperative contamination of the surgical site [10]. Even with a strict aseptic technique, bacterial contamination occurs in most if not all arthroplasty procedures [7]. Prophylactic antibiotics reduce the risk that contamination will progress to overt clinical infection, and in orthopaedic surgery, their efficacy is well established [4, 12, 14].

For antibiotic prophylaxis to be effective, the concentration of antibiotic in the tissues must exceed the minimum inhibitory concentration (MIC) of organisms that commonly cause infection for the period between skin incision and wound closure [3]. Coagulase-negative staphylococci (CoNS), one of the most common causes of infection post-TKA, have relatively high MICs against cephalosporins [28]. Conventional systemic dosing of prophylactic cephalosporins may therefore lead to inadequate tissue concentrations against these organisms [8, 28].

Regional administration of medication using a tourniquet achieves higher tissue concentrations than systemic administration by limiting distribution of the drug to the targeted limb. Some authors have used a foot vein cannula for administering prophylactic antibiotics in TKA. With this approach, substantially higher tissue concentrations of antibiotic can be achieved at the surgical site without systemic side effects [8, 9, 15, 17] (Table 1). However, cannulation of a foot vein is difficult, time-consuming, and may compromise sterility. An alternative means of regional administration is offered by intraosseous cannulation.

Since its first reported use over 70 years ago [16], the intraosseous route has gained popularity as a rapid and reliable method of accessing the circulation [26].

We therefore aimed to compare tissue concentrations of cefazolin achieved with systemic versus regional intraosseous administration.

Patients and Methods

Patients undergoing primary TKA at a single institution were eligible for enrollment into this prospective, randomized controlled trial. Inclusion criteria were age between 55 and 85 years and a primary diagnosis of osteoarthritis. We excluded patients with previous compartment syndrome, allergy to an antibiotic used in the study, abnormal renal or liver function, recent (< 1 week) antibiotic treatment, or a body mass index (BMI) > 35 kg/m^2. From March to August 2010, we assessed 32 patients undergoing primary TKA for osteoarthritis for enrollment. Ten patients were excluded (eight patients BMI > 35 kg/m^2, one refused consent, one patient on oral antibiotics for recent nasal infection) leaving 22 patients who were randomized into systemic and intraosseous groups using computer-generated random allocations placed in numbered, opaque, sealed envelopes (Table 2). We randomized patients in the preoperative area to allow appropriate setup in the operative room.

Based on the published data of Hoddinott et al. [15] showing an average mean fat tissue cephalosporin concentration across five time points of 88 ug/mL with SD 88 (regional administration) versus 11 ug/mL with SD 9 (systemic), a priori power analysis calculated that 11 patients in each arm would provide > 80% statistical power to detect the expected difference of 77 ug/mL in subcutaneous fat concentrations between two groups at the 5% significance level. Similarly, this sample size also

Table 1. Articles investigating regional administration of prophylactic antibiotics in TKA

Authors	Comparison	Outcomes
Hoddinott et al. [15]	Compared 1000 mg IV cefamandole versus 750 mg regional cefuroxime through the foot vein in the same 5 patients	Mean cefuroxime bone (133 mg/L) and fat (88 mg/L) higher than cefamandole bone (9 mg/L) and fat (10 mg/L); p < 0.001
de Lalla et al. [8]	RCT in 24 patients comparing 800 mg IV teicoplanin 2.5 hours preoperatively versus 400 mg teicoplanin through the foot vein	Tissue samples (skin, subcutaneous tissue, bone, synovium) 2–10 times higher through regional route
de Lalla et al. [9]	Clinical study 160 patients (205 knees) undergoing TKA, 400 mg teicoplanin through the foot vein	One superficial infection; no deep infections at 2-year followup
Lazzarini [17]	Five patients with 800 g IV teicoplanin 2.5 hours preoperatively versus 15 patients 200 mg teicoplanin through the foot vein	Tissue samples (skin, subcutaneous tissue, bone, synovium) 2 times higher through regional route

IV = intravenous; RCT = randomized controlled trial.

provided adequate statistical power (> 90%) to detect a difference in mean bone concentrations between the two groups (assuming the average mean bone concentration is 133 ug/mL [SD 101] versus 11 ug/mL [SD 9] in regional and systemic administration, respectively). As discussed later, it is difficult to quantify what clinical effect such a difference would have on infection rates. However, antibiotic concentrations below an organism's MIC are unlikely to provide effective prophylaxis against that organism [3]. CoNS causes up to 49% of TKA infections [20], and at our institution, over 68% of CoNS isolates have an MIC > 32 ug/mL against cefazolin. Assuming distribution similar to the cephalosporins used in the study of Hoddinott et al. [15], such isolates would therefore not

be covered by the tissue concentrations seen with systemic dosing (11 ug/mL); tissue concentrations with regional dosing (88–133 ug/mL) would however provide effective prophylaxis against such isolates, suggesting the differences used in our power analysis are clinically relevant.

Patients in both groups received 1 g systemic cefuroxime between 10 and 30 minutes before tourniquet inflation. All patients underwent limb exsanguination and tourniquet inflation to 300 mmHg before routine preparation and draping. The tourniquet remained inflated for the entire procedure. Patients in the systemic group were given 1 g cefazolin systemically through a forearm vein between 10 and 30 minutes before tourniquet inflation. Intraosseous group patients received 1 g cefazolin through an EZ-IO (Vidacare, San Antonio, TX, USA; FDA-approved) intraosseous cannula, placed into the medial aspect of the proximal tibia, after draping and before skin incision. The cefazolin was administered as a bolus in 200 mL of normal saline following the recommendations of Waisman et al. [27]. In the intraosseous group, incision occurred immediately (< 1 minute) after antibiotic injection.

During the procedure, we took samples of subcutaneous fat and femoral cancellous bone at the following four steps of the procedure and the times were recorded. The first subcutaneous fat sample was taken immediately after skin incision, then both bone and fat samples at the time of the distal femoral cut, trialing of components, and immediately before closure. Times were recorded for each sample (Table 3), which were approximately 0.5 to 1 cm^2.

Table 2. Patient demographics

Demographic	Intraosseous group (n = 11)	Systemic group (n = 11)
Males	6	4
Females	5	7
Age (years)	71.8 (56–87)	65.3 (48–83)
Body mass index (kg/m^2)	27.7 (22.1–35)	29.1 (23.1–35)
Tourniquet time (minutes)	84 (44–135)	82 (43–113)
Procedure length (minutes skin to skin)	74 (37–122)	76 (39–110)
American Society of Anesthesiologists score	2.2	2.1

Values given as mean with range in parentheses.

Table 3. Mean tissue concentrations of cefazolin at each sample point

	Intraosseous			Systemic		
	Time (minutes; ± SD)	Mean concentration (μg/g; ± SD)	95% CI (μg/g)	Time (minutes; ± SD)	Mean concentration (μg/g; ± SD)	95% CI (μg/g)
Sample point						
Subcutaneous fat 1	1.2	175.3	102–250	1.3	7.2	4.2–10.3
	(0.6)	(110)		(0.4)	(4.3)	
Subcutaneous fat 2	11	193.0	140–247	14	12.8	8.4–17.2
	(5.1)	(79.8)		(6.6)	(6.6)	
Subcutaneous fat 3	30	206.3	121–292	35	11.2	8.4–14.0
	(11.1)	(127)		(12.3)	(4.1)	
Subcutaneous fat 4	56	169.1	88–250	54	11.3	7.1–15.4
	(23.2)	(120)		(17.3)	(6.2)	
Bone sample 1	11	75.4	26–125	14	9.2	7.4–10.9
	(5.1)	(74.2)		(6.6)	(2.6)	
Bone sample 2	30	165.6	21–311	35	14.1	8.6–19.6
	(11.1)	(216)		(12.3)	(8.2)	
Bone sample 3	56	148.8	79–219	54	10.8	7.7–13.8
	(23.2)	(105)		(17.3)	(4.6)	

Times are given as minutes postsurgical incision. Differences in mean tissue concentrations between the two groups were statistically significant (p < 0.001) for all comparison points.

We rinsed samples in normal saline to remove excess blood and stored them at −90°C before undergoing analysis. Bone samples were crushed with pliers, finely cut further with a scalpel, then weighed, and immersed in phosphate-buffered saline pH 7.3 for 15 hour at 4°C. The fat samples were finely cut with a scalpel and then treated in the same way as the bone samples. The immersed bone or fat tissue suspension was vortexed for 30 seconds and centrifuged at 15,000 g for 10 minutes. We transferred the supernatant to a clean tube and perchloric acid was added to precipitate the proteins. After centrifugation at 15,000 g for 5 minutes, 50 µL of clear supernatant was injected into the high-performance liquid chromatography (HPLC) system. A validation study was carried out of the extraction and HPLC technique using bone and tissue samples spiked with known concentrations of cefazolin. We analyzed all samples in duplicate.

Means, SDs, and the 95% confidence limits were calculated for the cefazolin concentrations in the different samples. Different tissue samples were pooled according to the surgical steps at which they were taken. Coefficients of variation (CVs) of concentration levels were also summarized at each surgical step for the comparison between two drug administration routes. We used repeated-measures analysis of variance to compare the average level of cefazolin across time between groups adjusted by BMI, age, and length of the surgical procedure; the Shapiro-Wilk test was applied to assess the normality of the residuals.

Results

The mean tissue concentrations of cefazolin in subcutaneous fat at different collection intervals ranged from 175 (± 110) to 206 (± 127) ug/g in the intraosseous group and from 7.2 (± 4.3) to 12.8 (± 6.6) ug/g in the systemic group (Fig. 1; Table 3). The mean tissue concentration in bone ranged from 75 (± 74) to 165.6 (± 216) g/g in the intraosseous group and ranged from 9.2 (± 2.6) to 14.1 (± 8.2) µg/g in the systemic group (Fig. 2). The overall mean tissue concentration of cefazolin in subcutaneous fat was 186 ug/g in the intraosseous group and 10.6 ug/g in the systemic group (p < 0.01). The mean tissue concentration in bone was 130 ug/g in the intraosseous group and 11.4 ug/g in the systemic group (p < 0.01). The concentration was noted to be more variable with the intraosseous route for both subcutaneous fat (CV range 0.62–0.71 versus 0.37–0.56) and the bone samples (CV range 0.7–1.0 versus 0.3–0.6). The repeated-measures analysis of covariance showed no association between concentration level and age, BMI, sex, and length of procedure.

No complications were seen in either group in the early postoperative period nor by 1-year followup.
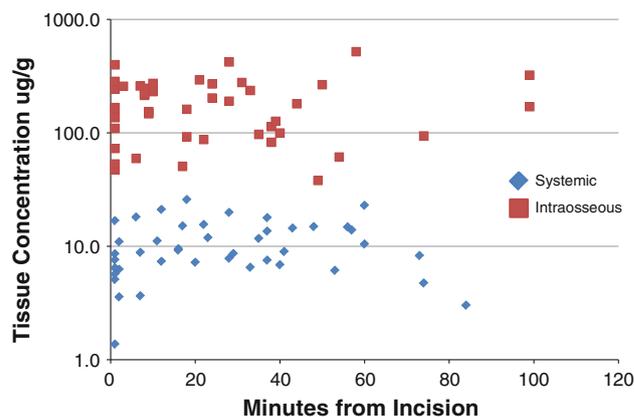
Fig. 1 Tissue concentrations of cefazolin in subcutaneous fat for each sample.
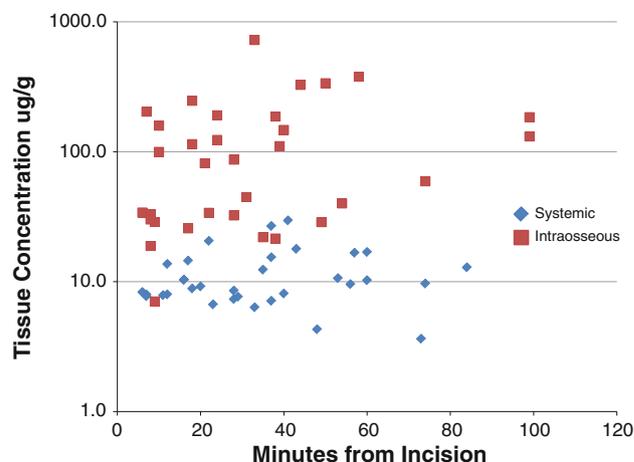
Fig. 2 Tissue concentrations of cefazolin in femoral bone for each sample.

Discussion

Early studies on systemic cefazolin for surgical prophylaxis reported adequate bone and soft tissue concentrations to prevent infection [6, 11, 24] and assumed MIC_{90} levels for CoNS of 0.5 to 1.0 ug/mL. Over recent decades, however, resistance to cephalosporins among CoNS has increased markedly, and current MIC_{90} is as high as 100 ug/mL in half of reported species [28]. This increase in resistance coincides with clinical data reporting a rise in the number of CoNS deep prosthetic infections [20]. Regional delivery of antibiotics may offer better protection against CoNS by achieving higher tissue concentrations (Table 1), but cannulation of a foot vein cannulation is difficult, time-consuming, and may compromise sterility. We aimed to investigate whether the more convenient intraosseous route could be used in regional delivery of prophylaxis.

There are a number of limitations to our study. First, although the intraosseous route is reported to have pharmacokinetics for both fluids and medications similar to intravenous administration [26], its use for regional administration is not as well studied. The tissue concentrations of cephalosporins in our study are comparable to those seen with intravenous regional administration [15], suggesting the two routes are similar. Second, we excluded patients with high BMIs to minimize the effect of this variable and because many authors recommend a higher systemic cefazolin dose in heavier patients [28]. Because we used a relatively high cutoff of BMI > 35 kg/m^2, some of our systemic patients may have been underdosed. However, in patients undergoing TKA (mean BMI 25 kg/m^2) given 2 g cefazolin systemically, Yamada [28] found a mean bone concentration of only 16 ug/g suggesting a higher systemic dose would be unlikely to alter our findings. A higher intraosseous dose could be considered for obese patients, but given the smaller volume of distribution in regional administration, 1 g is still likely to provide extremely high tissue levels. Finally, although we saw no complications with this technique in our study, the number of participants was small. Potential complications with intraosseous infusions include fluid extravasation with compartment syndrome related to incorrect needle placement in emergency situations [26]. Needle site infection has been reported rarely [26] and correlates with the length of time the needle is left in situ. Subclinical fat emboli have been seen histologically in animal studies [13], but no cases of fat embolism after intraosseous infusion have been reported in humans.

We found intraosseous regional administration of prophylactic antibiotics in TKA provides tissue concentrations 10 to 15 times higher than systemic administration. Our findings are similar to previous studies of TKA that used intravenous regional administration of other cephalosporins (Table 1). Hoddinott [15] compared 1 g intravenous regional cefuroxime to 1 g systemic cefamandole and found tissue concentrations five to 30 times higher with regional administration. During elbow surgery, Miller et al. [19] reported bone cefazolin concentrations 41 times higher and fat concentrations 133 times higher than systemic dosing, reflecting the smaller regional volume of distribution in the upper limb.

Do such high levels lead to increased efficacy? Nickinson et al. [20] reported 49% of TKA infections were the result of CoNS, and over 55% of CoNS strains were methicillin-resistant. In 1990 Friedman et al. [11] reported an MIC$_{90}$ of 64 ug/mL against cefazolin for resistant strains of CoNS, and in 2011, Yamada et al. [28] reported an MIC$_{90}$ of 100 ug/mL. Similar to previous studies [6, 11, 24], we found systemic dosing gave tissue concentrations of cefazolin (mean 10.6 ug/g fat and 11.4 ug/g in bone) well below these levels. In contrast, the regional intraosseous route provided mean cefazolin concentrations of 185.9 ug/g in fat and 129.9 ug/g in bone. Such levels have a plausible theoretical advantage by providing greater activity against organisms with typically high cefazolin MICs such as CoNS.

Whether such high cefazolin levels improve efficacy against more sensitive (lower MIC) bacterial strains is less clear. Although antibiotics such as aminoglycosides and fluoroquinolones exhibit concentration-dependent killing, for β-lactam antibiotics such as cefazolin, time above MIC is the most important factor. Cephalosporin treatment in animal models of infection suggests saturation of the killing rate occurs at concentrations four to five times the MIC [5]. By definition, the highest MIC$_{90}$ for cefazolin-sensitive CoNS is 8 ug/g [28]; so although the intraosseous regional route will ensure tissue concentrations are at least five times this level, any clinical advantage may well be small. However, higher β-lactam concentrations (64 times MIC) are known to lead to an earlier initiation of bacterial killing [5], which may be more important for prophylaxis against infection where the goal is to prevent initial bacterial adherence and colonization.

Regional intraosseous antibiotic administration is used in the treatment of equine limb infection [18, 22, 23]; however, only one study has investigated the use of regional intraosseous medications in humans. Waisman et al. [27] reported on 109 patients given local anesthetic in 140 mL of saline through the regional intraosseous route before both upper and lower limb surgery. Two patients had inadequate anesthesia that the authors attributed to an insufficient volume (80 mL) infused in these patients. In our study, we chose a higher volume of 200 mL, because during regional administration, the circulation has effectively stopped and distribution relies on the volume of fluid to push the medication through the vasculature of the limb. We believed this volume would ensure the antibiotic is present in the tissues at incision, which occurs immediately after intraosseous injection. Our data showed very high antibiotic levels in first tissue sample, and it is possible a smaller volume may be adequate.

For regional delivery of antibiotics in TKA, the main advantages of intraosseous over foot vein cannulation are reliability and speed. The proximal tibia is already exposed during TKA, and modern intraosseous cannulation system kits offer rapid access [25]. The average time for cannulation and injection in this study was under 2 minutes, and thus a minimal difference in overall tourniquet time was observed between the two groups.

In summary, we describe a technique for administering intraosseous, regional antimicrobial prophylaxis before TKA that can achieve tissue levels an order of magnitude higher than with systemic administration. Further work is required to confirm whether this translates into increased efficacy in preventing infection, particularly against CoNS.

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