

# **A feasibility study of regional delivery of prophylactic antibiotics in total knee replacement via an intraosseous route**

## **Abstract**

### **Introduction and Aims**

Reported rates of deep infection following primary Total Knee Replacement (TKR) persist between 1-2.5%. Prophylactic antibiotics are effective in reducing this devastating complication, however conventional 'systemic' dosing may provide inadequate tissue concentrations against common causative organisms such as Coagulase negative staphylococci (CoNS) that have a high minimum inhibitory concentration against cephalosporins. Regional intravenous administration of antibiotics following tourniquet inflation provides tissue concentrations over 10 times higher than systemic dosing. However cannulation of a foot vein is difficult, time consuming, and may compromise sterility. Regional intraosseous cannulation is therefore an attractive alternative to intravenous regional administration, and the aim of this study was to assess its effectiveness in achieving adequate tissue concentrations of prophylactic antibiotics.

### **Methods**

22 patients undergoing primary total knee arthroplasty were randomised into two groups. Group 1 received 1g of cephazolin systemically 10 minutes prior to tourniquet inflation. Group 2 received 1g of cephazolin intraosseously in 200ml of normal saline via a tibial cannula (EZ-IO), following tourniquet inflation and prior to skin incision. Subcutaneous fat and femoral bone samples were taken at set intervals during the procedure, and antibiotic concentrations measured using a previously validated technique involving High Performance Liquid Chromatography (HPLC).

### **Results**

There were no significant differences in patient demographics, comorbidities, or physical parameters between groups. The overall mean tissue concentration of cephazolin in subcutaneous fat was 185.9ug/g in the intraosseous group and 10.6ug/g in the systemic group ( $p<0.01$ ). The mean tissue concentration in bone was 129.9 ug/g in the intraosseous group and 11.4ug/g in the systemic group ( $p<0.01$ ). These differences were consistent across all sample time points throughout the procedure. No complications occurred in either group.

### **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 CoNS.

## **Introduction**

Deep infections remain one of the most devastating complications of total knee arthroplasty (TKA). Despite efforts to reduce infection rates, the reported incidence following primary TKA persists between 0.86-2.5%.<sup>1-5</sup> Coagulase negative staphylococci (CoNS) cause up to 49% of deep infections, with evidence that the role of these organisms is increasing.<sup>3</sup>

It is believed that the majority of early post operative infections are due to intraoperative contamination of the surgical site.<sup>6</sup> Even with strict aseptic technique, most arthroplasty procedures show bacterial contamination within the operative field.<sup>7</sup> Prophylactic antibiotics reduce the risk that contamination will progress to overt clinical infection, and their efficacy in orthopedic surgery is well established.<sup>8-10</sup>

For antibiotic prophylaxis to be effective, the concentration of antibiotic in the tissues must exceed the minimum inhibitory concentration (MIC) of common causative organisms for the period between skin incision and wound closure.<sup>11</sup> CoNS, while tending to cause more indolent infections than other pathogens, frequently have higher MICs against many cephalosporins, leading to concerns that tissue concentrations achieved with conventional systemic dosing of cephalosporins may be inadequate to prevent infection with these organisms.<sup>12</sup>

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 utilized a foot vein cannula for administering prophylactic antibiotics in TKA. With this approach, significantly higher tissue concentrations of antibiotic can be achieved at the surgical site, without systemic side effects.<sup>12-14</sup> (Table I)

However cannulation of a foot vein is difficult, time consuming, and may compromise sterility. Intraosseous cannulation offers an alternative means of regional administration. Since its first reported use over 70 years ago<sup>15</sup>, the intraosseous route has gained popularity as a rapid and reliable method of

accessing the circulation.<sup>16</sup> The aim of this study was to assess the effectiveness of intraosseous regional administration in achieving adequate tissue concentrations of prophylactic antibiotics.

## **Materials and Methods**

### *Study Population*

Patients undergoing primary TKA at a single institution were eligible for enrolment into this prospective, randomised controlled trial. Inclusion criteria were age between 55-85 years and a primary diagnosis of osteoarthritis. Exclusion criteria included 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) <20 or >35.

After providing informed consent, patients were randomized into two groups using computer-generated random allocations placed in numbered, opaque, sealed envelopes. Patients were randomised in the preoperative area to allow appropriate setup in the operative room.

### *Technique*

All patients received 1g of systemic cefuroxime between 10-30 minutes prior to tourniquet inflation. All patients underwent limb exsanguination and tourniquet inflation to 300mmHg prior to routine prep and draping. The tourniquet remained inflated for the entire procedure.

Patients in the Systemic group were given 1g of cefazolin systemically via a forearm vein between 10-30 minutes prior to tourniquet inflation. Intraosseous group patients received 1g of cefazolin via an EZ-IO (Vidacare, San Antonio, Texas) intraosseous cannula, placed into the medial aspect of the proximal tibia, after draping and prior to skin incision. The cephazolin was administered as a bolus in 200ml of normal saline following the recommendations of Waisman et al.<sup>17</sup>

During the procedure samples of subcutaneous fat and femoral cancellous bone were taken at set steps of the procedure and the times recorded. The first subcutaneous fat sample was taken immediately following skin incision, then both bone and fat samples at the time of the distal femoral cut, trialling of components, and immediately prior to closure.

#### *Laboratory procedures*

Samples were rinsed in normal saline to remove excess blood and stored at -90C before undergoing analysis using a validated technique involving high performance liquid chromatography (HPLC), which has been published elsewhere.<sup>18</sup> 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 h at 4°C. The fat samples were finely cut with a scalpel, and then treated in a 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 min. The supernatant was transferred to a clean tube and perchloric acid was added to precipitate the proteins. After centrifugation at 15,000 g for 5 min, 50 µl of clear supernatant was injected into the HPLC system. All the samples were analysed in duplicate.

#### *Statistical analysis*

Based on the published data of Hoddinott et al<sup>14</sup> for regional cephalosporin concentrations, a priori power analysis calculated that 11 patients in each arm would provide > 80% statistical power to detect the expected difference in subcutaneous fat concentrations between two groups at 5% significant level. Similarly, this sample size also provided adequate statistical power (> 90%) to detect the difference in mean bone concentrations.

Means, standard deviations, and the 95% confidence limits were calculated for the cephalosporin concentrations in the different samples. Different tissue samples were pooled according to the surgical steps at which they were taken. Coefficient of variations (CV) of concentration levels were also summarized at each surgical step for the comparison between two drug administration routes. Repeat measure analysis of variance was used to compare the average level of cefazolin

across time between groups adjusted by BMI, age, and length of surgical procedure; Shapiro-Wilk test was applied to assess the normality of the residuals.

## Results

From March to August 2010 32 patients aged between 55-85 undergoing primary total knee arthroplasty for osteoarthritis were assessed for enrolment. Ten patients were excluded (8 patients BMI >35, 1 refused consent, 1 patient on oral antibiotics for recent nasal infection) leaving 22 patients who were randomised into systemic and intraosseous groups. Patient demographics are given in Table I. There were no significant differences in patient demographics, comorbidities, physical parameters, or procedure lengths between groups.

The mean tissue concentrations of cefazolin in subcutaneous fat at difference collection intervals ranged from 175.3 ( $\pm 110$ ) to 206.3 ( $\pm 127$ ) ug/g in the intraosseous group; and from 7.2 ( $\pm 4.3$ ) to 12.8 ( $\pm 6.6$ ) ug/g in the systemic group (Table III). The mean tissue concentration in bone ranged from 75.4 ( $\pm 74.2$ ) to 165.6 ( $\pm 216.1$ ) g/g in the intraosseous group; and ranged from 9.2 ( $\pm 2.6$ ) to 14.1 ( $\pm 8.2$ ) g/g in the systemic group. These differences were consistent across all sample time points throughout the procedure. Sample concentrations are demonstrated graphically in Figures 1 and 2.

The measured concentration was noted to be more variable with the intraosseous route for both subcutaneous fat (coefficient of variability range 0.62-0.71 vs. 0.37-0.56) and the bone samples (coefficient of variability range 0.7-1.0 vs. 0.3-0.6). The repeat measure analysis of covariance showed no association between concentration level and age, BMI, gender, and length of procedure. No complications were seen in either group either in the early post operative period or at one year follow up.

## Discussion

In 1908, Bier first reported on the regional delivery of medications.<sup>19</sup> Although his technique is most commonly applied to local anaesthetic agents, in principle, the technique can be used for any medication.

There are a number of potential advantages to regional administration of prophylactic antibiotics in TKA. Firstly, tissue concentrations of antibiotic can reach far higher levels at their site of action - the open surgical wound - thus maximising their effectiveness. In contrast, the tissue concentrations that can be achieved with systemically administered antibiotics are limited by the risk of dose-dependent toxicity to other organs. Although the possibility of local toxic effects on osteocytes must be considered,<sup>20,21</sup> regionally administered prophylaxis may also allow the use of low doses of antibiotics not usually considered for systemic prophylaxis due to their systemic toxicity profile.<sup>22</sup>

Secondly, regional administration may make surgeons more comfortable with single dose prophylaxis, as concentrations greater than the MIC have been reported in drain fluid for up to 21 hours following the procedure,<sup>14</sup> presumably secondary to the high initial tissue concentrations achieved by this route. While it is known prolonged antibiotic treatment for many days confers no additional benefit,<sup>8</sup> many authors continue administration for 24 hours following surgery,<sup>6,8,23</sup> at significant economic cost.<sup>24</sup>

Finally, by requiring injection following prep and draping, it places responsibility for perhaps the single most effective measure in preventing infection in the hands of the surgeon. In a study of 34,133 Medicare surgical inpatients, Bratzler et al.<sup>25</sup> found only 55.7% of eligible patients received antibiotics within one hour prior to incision, a finding confirmed in other studies.<sup>26,27</sup> Although the reasons for incorrect timing of antibiotic prophylaxis in these studies are not fully understood, it seems logical that if the intraosseous injection became part of the standard surgical routine leading up to the incision, then a greater proportion of patients undergoing TKA would receive appropriately timed prophylaxis.

Intraosseous administration has become popular in emergency and intensive care settings.<sup>28-32</sup> It provides rapid access to the venous circulation via the network of venous sinusoids in the medullary cavity, which with its surrounding bone provides a non-collapsible entry point to the central venous circulation. The technique has been more popular in paediatric patients because intravenous access is more difficult; however intraosseous administration is equally as effective in adult patients. Both fluids and medications can be given, with pharmacokinetics similar to peripheral or central intravenous administration.<sup>16</sup>

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 systems kits offer consistent and rapid access.<sup>32</sup> The average time for cannulation and injection in this study was under 2 minutes, and thus minimal difference in overall tourniquet time was seen between the two groups.

While regional intraosseous antibiotic has been successfully reported in the treatment of equine limb infection,<sup>33-35</sup> only one study has investigated the use of regional intraosseous medications in humans. Waisman<sup>5</sup> reported on 109 patients who were given local anaesthetic in 140mls of saline through the regional intraosseous route, prior to both upper and lower limb surgery. The procedure provided successful anaesthesia in 106 of 109 patients, with 3 failures. In one patient the needle was incorrectly positioned, and two patients had inadequate anaesthesia that the authors attributed to an insufficient volume (80mls) infused in these patients. No other complications were reported. In our study we used a volume of 200mls, as during regional administration the circulation in the limb has effectively ceased; therefore distribution of the medication relies on this volume of fluid to 'push' through the vasculature of the limb. This novel mode of drug administration may also have other applications, allowing 'surgical site delivery' of medication, while minimising systemic side effects.

Similar to previous studies of regional prophylaxis, we saw more variability in tissue concentrations when compared to the systemic route. Patency of venous

valves, the limb size, effectiveness of the tourniquet, and individual venous anatomy could all theoretically influence antibiotic distribution and may explain the increased range of concentrations seen.

Complications with intraosseous infusions are reported mainly in emergency medicine literature. They include fluid extravasation and compartment syndrome related to incorrect needle placement,<sup>16</sup> a situation less likely to arise in the controlled environment of theatre than an emergency setting. Infection is rare and correlates to the length of time the needle is left in situ. Subclinical fat emboli have been seen histologically in animal studies<sup>36</sup>, but no cases of fat embolism following intraosseous infusion have been reported in humans.

In summary, we report on a technique of intraosseous regional administration that can achieve tissue levels of prophylactic antibiotic 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 CoNS.

## **Acknowledgements**

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**Table I.** Papers investigating regional administration of prophylactic antibiotics in TKA

<b>Authors</b>	<b>Comparison</b>	<b>Outcomes</b>
Hoddinott et al <sup>1</sup> 1990	Compared 1000mg IV cefamandole versus 750mg regional cefuroxime via foot vein in same 5 patients	Mean cefuroxime bone (133mg/L) and fat (88mg/L) higher than cefamandole bone (9mg/L) and fat (10mg/L) p<0.001
De Lalla et al <sup>2</sup> 1993	RCT in 24 patients comparing Teicoplanin 800mg IV 2.5hours pre operatively versus Teicoplanin 400mg via foot vein	Tissue samples (skin, subcutaneous tissue, bone, synovium) 2-10 times higher via regional route
De Lalla et al <sup>3</sup> 2000	Clinical study 160 patients (205 knees) undergoing TKR, 400mg Teicoplanin via foot vein	One superficial infection. No deep infections at 2 year follow up.
Lazzarini et al <sup>4</sup> 2003	5 patients with 800g Teicoplanin IV 2.5 hours preoperatively versus 15 patients 200mg Teicoplanin via foot vein	Tissue samples (skin, subcutaneous tissue, bone, synovium) 2 times higher via regional route

**Table II.** Patient Demographics. Values given as mean with range in parentheses. No statistically significant differences were seen for any variable.

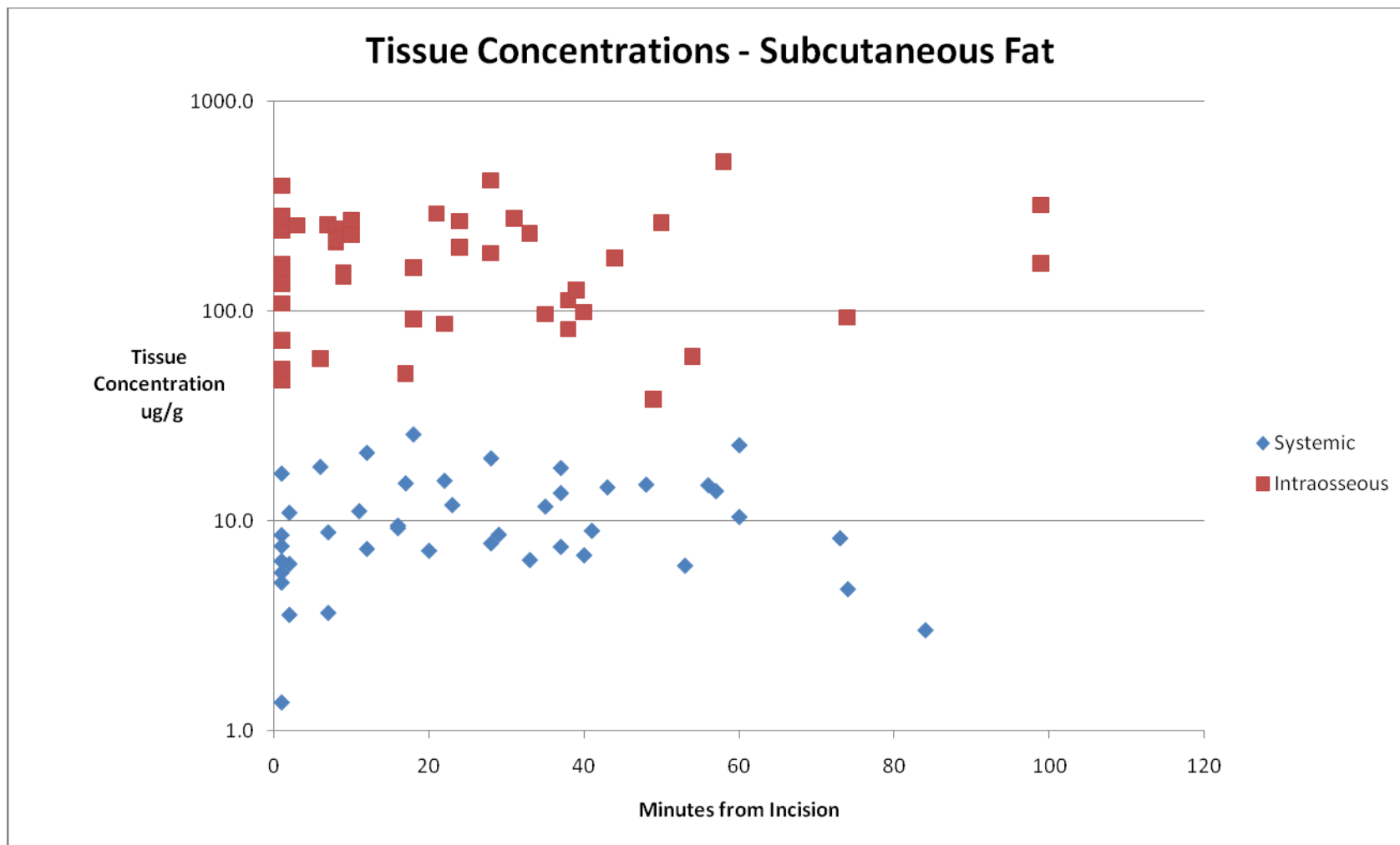
	<b>Intraosseous Group</b> n=11	<b>Systemic Group</b> n=11
<b>Males</b>	6	4
<b>Females</b>	5	7
<b>Age</b>	71.8 yrs (56-87)	65.3 yrs (48-83)
<b>BMI</b>	27.7 (22.1-35)	29.1 (23.1-35)
<b>Tourniquet time (minutes)</b>	84 (44-135)	82 (43-113)
<b>Procedure Length (minutes skin to skin)</b>	74 (37-122)	76 (39-110)
<b>ASA Score</b>	2.2	2.1

**Table III.** Mean Tissue concentrations of Cefazolin at each sample point. Times are given as minutes post surgical incision.

	<b>Intraosseous</b>			<b>Systemic</b>		
	<b>Time</b> Minutes ( $\pm$ SD)	<b>Mean Concentration</b> $\mu\text{g/g}$ ( $\pm$ SD)	<b>95% CI</b> ( $\mu\text{g/g}$ )	<b>Time</b> Minutes ( $\pm$ SD)	<b>Mean Concentration</b> $\mu\text{g/g}$ ( $\pm$ SD)	<b>95% CI</b> ( $\mu\text{g/g}$ )
<b>Subcutaneous Fat 1</b>	1.2 (0.6)	<b>175.3</b> (110)	102-250	1.3 (0.4)	<b>7.2</b> (4.3)	4.2-10.3
<b>Subcutaneous Fat 2</b>	11 (5.1)	<b>193.0</b> (79.8)	140-247	14 (6.6)	<b>12.8</b> (6.6)	8.4-17.2
<b>Subcutaneous Fat 3</b>	30 (11.1)	<b>206.3</b> (127)	121-292	35 (12.3)	<b>11.2</b> (4.1)	8.4-14.0
<b>Subcutaneous Fat 4</b>	56 (23.2)	<b>169.1</b> (120)	88-250	54 (17.3)	<b>11.3</b> (6.2)	7.1-15.4
<b>Bone Sample 1</b>	11 (5.1)	<b>75.4</b> (74.2)	26-125	14 (6.6)	<b>9.2</b> (2.6)	7.4-10.9
<b>Bone Sample 2</b>	30 (11.1)	<b>165.6</b> (216)	21-311	35 (12.3)	<b>14.1</b> (8.2)	8.6-19.6
<b>Bone Sample 3</b>	56 (23.2)	<b>148.8</b> (105)	79-219	54 (17.3)	<b>10.8</b> (4.6)	7.7-13.8

Differences in mean tissue concentrations between the two groups were statistically significant ( $p < 0.001$ ) for all comparison points.

**Figure 1.** Tissue Concentrations of cephazolin in subcutaneous fat for each sample. Note the scale is logarithmic.



**Figure 2.** Tissue Concentrations of cephalosporin in subcutaneous fat for each sample. Note the scale is logarithmic.

