Authors: Simon W. Young, Kelly Vince

QUESTION 1: Is there a difference in the bioavailability of vancomycin when administered through the intravenous route or intraosseous regional route in total knee arthroplasty (TKA)?

RECOMMENDATION: Yes. Tissue concentrations of vancomycin and other antibiotics are significantly higher when given via intraosseous regional administration for prophylaxis in TKA. Currently, it is unclear whether these higher concentrations will lead to a reduction in prosthetic joint infection (PJI) rates.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 91%, Disagree: 2%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Prophylaxis via intraosseous regional administration (IORA) in TKA involves injection of antibiotics into an intraosseous tibial cannula after tourniquet inflation and immediately prior to skin incision [1]. Intraosseous injection is equivalent to intravenous injection [2] but is more rapid than cannulation of a foot vein. As the tourniquet is inflated prior to injection, the antibiotic distribution is restricted "regionally" to the lower limb, similar to the manner of a "Bier's block" used in anaesthesia [3]. It allows tissue concentrations of the antibiotic to be maximized during the TKA procedure before decreasing once the tourniquet is deflated.

Earlier studies investigated the use of intravenous regional administration (IVRA) of prophylactic antibiotics via cannulation of a foot vein [4–7] and demonstrated tissue concentrations two to ten times higher than systemic administration (Table 1). The advantage of IORA is the more rapid and reliable placement of an intraosseous cannula into the proximal tibia, compared to the foot vein cannulation required for IVRA.

Vancomycin in particular may be suited for use with IORA. It covers resistant organisms commonly causing PJIs, such as coagulase-negative staphylococci and methicillin-resistant S*taphylococcus aureus* (MRSA) [8,9]. However, when given systemically it requires a prolonged infusion time [10] and can cause systemic side effects such as nephrotoxicity [10,11]. Vancomycin can be given by IORA as a bolus injection, ensuring optimal timing of prophylaxis. As distribution of the antibiotic is limited by the tourniquet, a lower vancomycin dose can be used, potentially reducing systemic side effects.

Four clinical studies have investigated the use of IORA in TKA (Table 2). One study compared 1 gm systemic cefazolin vs. 1 gm IORA cefazolin in 22 patients, reporting tissue concertation ten times higher with IORA [1]. A second study randomized 30 patients to receive either 250 mg or 500 mg of vancomycin by IORA or 1 gm of vancomycin systemically [12]. Tissue concentrations were four to ten times higher in the IORA groups. As no complications such as red man syndrome were seen on tourniquet deflation in the IORA groups, the authors recommended the use of the higher 500 mg IORA dose.

A third study randomized 22 patients undergoing revision TKA to 500 mg IORA vancomycin or 1 gm systemic prophylaxis [8]. Because revision TKA has a higher PJI rate, it was unclear if IORA prophylaxis would be effective in this setting. The presence of a tibial implant could compromise intraosseous (IO) injection, and the tourniquet is often deflated during prolonged revision procedures. The study found tissue concentrations of vancomycin 5 to 20 times higher in the IORA group and these were maintained throughout the procedure despite a period of tourniquet deflation. Concentrations from drain samples taken the next morning were similar between the groups. A fourth study randomized 22 obese patients (body mass index (BMI) > 35) undergoing TKA to 500 mg IORA vancomycin or a weight-adjusted 15 mg/kg systemic vancomycin prophylactic dose. Mean BMI was 41.1 and 40.1 (range 35 to 52) in the two groups. Tissue concentrations were five to nine times higher in the IORA versus systemic group.

It is unclear whether the higher tissue concentrations seen with IORA will reduce the incidence of PJIs. Pharmacodynamically, vancomycin's effect correlates with the area under the concentration-time curve (AUC) divided by the minimum inhibitory concentration (MIC) (AUC/MIC ratio) [9], thus greater tissue concentrations may be expected to increase efficacy. An animal study comparing six prophylaxis regimes in a murine model of TKA found IORA of both cefazolin and vancomycin to be more effective than systemic prophylaxis [13], but clinical data is lacking. As PJIs are rare, a randomized trial of IORA with PJI as the endpoint is unlikely to be feasible; larger cohort studies may offer further insights.

TABLE 1. Studies investigating the use of IVRA prophylaxis in TKA via foot vein cannulation

Study	Study Design	Patients	Findings
Hoddinott (1990) [4]	Comparative Cohort	5 patients, 1,000 mg IV cefamandole vs.750 mg IVRA cefuroxime via a foot vein in same 5 patients	Mean concentrations of cefuroxime in bone (133 mg/L) and fat (88 mg/L) were higher than those of cefamandole in bone (9 mg/L) and fat (10 mg/L); $p < 0.001$
de Lalla (1993) [5]	RCT	24 patients comparing 800 mg IV teicoplanin 2.5 hours preoperatively vs.400 mg IVRA teicoplanin via foot vein	Tissue samples (skin, subcutaneous tissue, bone, synovium) 2–10 times higher through the regional route

de Lalla (2000) [6]	Cohort	Clinical study of 160 patients (205 TKAs), 400 mg IVRA teicoplanin via foot vein	One superficial infection; no deep infections at 2-year follow-up
Lazzarini (2003) [7]	Comparative Cohort	5 patients 800 mg IV teicoplanin 2.5 hours preoperatively vs.15 patients 200 mg IVRA teicoplanin via a foot vein	Tissue samples (skin, subcutaneous tissue, bone, synovium) 2 times higher through the regional route

IV, intravenous; IVRA, intravenous regional administration; RCT, randomized control trial; TKA, total knee arthroplasty

TABLE 2. Studies investigating the use of IORA prophylaxis in TKA

Study	Study Design	Patients	Findings
Young (2013) [1]	RCT	22 Primary TKA patients, 1 g systemic cefazolin vs. 1 gm IORA	Mean cefazolin subcutaneous fat concentrations: 11 ug/gm systemic vs.186 ug/gm IORA, mean bone concentrations: 11 ug/gm vs.130 ug/g IORA
Young (2014) [12]	RCT	30 Primary TKA patients, 1 gm Systemic vancomycin vs.250 mg and 500 mg IORA	Mean vancomycin fat concentrations: 3.2 ug/g systemic group, 14 ug/gm 250 mg IORA group, 44 ug/gm 500 mg IORA group. Mean bone concentrations: 4.0 ug/g systemic, 16 ug/gm 250 mg IORA, 38 ug/gm 500 mg IORA
Young (2017) [8]	RCT	20 Revision TKA patients, 1 gm systemic vancomycin vs. 500 mg IORA	Mean vancomycin concentrations fat: 3.7 ug/gm systemic vs.49.3 ug/gm IORA, mean bone concentrations: 6.4 ug/gm vs.77 ug/gm IORA
Chin (2018) [14]	RCT	22 Primary TKA patients with BMI > 35, 15 mg/kg systemic vancomycin vs.500 mg IORA	Mean vancomycin concentrations fat: 4.4 ug/gm systemic vs. 39.3 ug/gm IORA, mean bone concentrations: 6.1 ug/gm vs. 34.4 ug/gm IORA
Young (2015) [13]	Animal Model	42 mice, 6 prophylaxis regimes compared	IORA of vancomycin and cefazolin more effective than systemic in preventing PJI in murine model of TKA infection

BMI, body mass index; IORA, intraosseous regional administration; TKA, total knee arthroplasty; RCT, randomized controlled trial

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