Intraosseous Regional Administration of Antibiotic Prophylaxis in Total Knee Arthroplasty

Disclosure – Financial support in relation to this study: Vidacare

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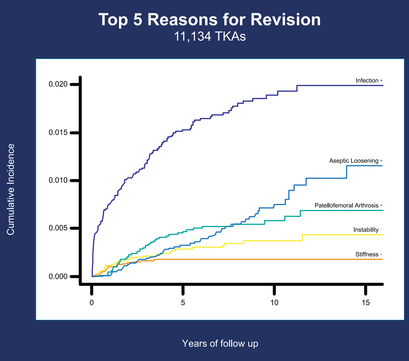
Introduction

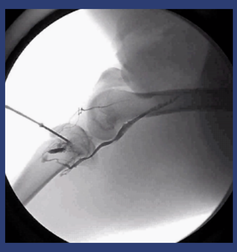
- Periprosthetic joint infection (PJI) is the most common reason for failure following Total Knee Arthroplasty (TKA)
- Many PJIs occur early after TKA, likely due to contamination during the surgery
- The principle of antibiotic prophylaxis is to have antibiotics present from incision to closure, when contamination is occurring
- 'Regional' administration involves injecting antibiotics into the vascular system **below an inflated tourniquet**
- Antibiotics are distributed only within the limb while the tourniquet is inflated, maximizing the tissue concentrations

(This method is commonly used with local anaesthetic in the upper limb, the so called "Bier's Block")

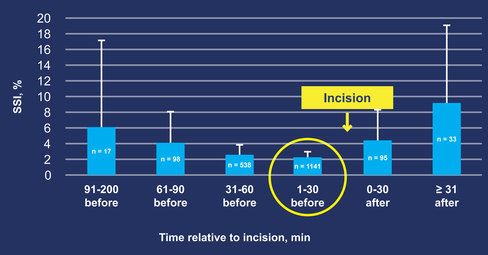


Deep infection is the primary cause of failure following knee arthroplasty, and often occurs early.

Reproduced from Koh CK, Zeng I, Ravi S, Zhu M, Vince KG, Young SW CORR. 2017



Following intraosseous injection, radio-opaque dye passes immediately into the vascular system. In IORA, an inflated tourniquet restricts distribution to the lower limb.



Surgical site infection (SSI) by antibiotic timing.

Rates are lowest when antibiotics are given immediately prior to skin incision, so concentrations are highest during the surgery.

Reproduced from van Kasteren ME et al Antibiotic prophylaxis following total hip arthroplasty: timely administration is the most important factor. Clin Infect Dis. 2007

- In the lower limb, regional administration typically requires injection into a foot vein.
- Cannulation of a foot vein is time consuming, and difficult in obese patients.
- Intraosseous injection is quicker and more reliable, and is equivalent to an intravenous injection.

This exhibit describes our work investigating intraosseous regional administration (IORA) of prophylactic antibiotics in TKA.

Technique of Intraosseous Injection in TKA

Choice of needle

Can use powered or manual insertion

Powered options require driver to be sterilized

Longer needles available for obese patients

Manual needles less expensive

Powered Driver and needles
(EZ-IO,Teleflex Corp, San Antonio, TX)

Manual IO Needle
(Cook Medical, Bloomington, IN)

Insertion technique

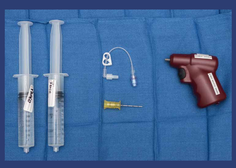
Medial border of proximal tibia

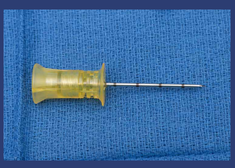
More proximal is optimal (2cm below joint line)
- Thinner cortex easier to penetrate
- Flow rates faster

In revision cases need to go more distal to avoid implant
- Usually need powered insertion as cortex thicker

Make small hole in adhesive drape to insert needle

Reseal with adhesive drape after injection





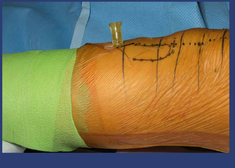
Injection Solution

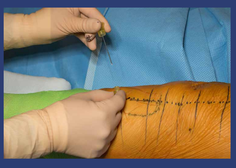
500mg Vancomycin
- Low dose prevents red man syndrome, if using cefazolin can use 1g
- We use 500mg Vanc IORA in addition to standard IV prophylaxis with 2g cefazolin. This ensures compliance with hospital guidelines.

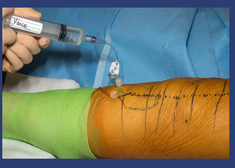
Make up antibiotic in 130-150ml Saline
- Volume ensures it distributes through the limb

Inject as a bolus after tourniquet inflated

Flow rates are variable, usually 1-2 minutes to inject







Antibiotic Tissue Concentrations with IORA

We first studied IORA of cefazolin in TKA in a randomised controlled trial, comparing tissue concentrations achieved with systemic versus regional intraosseous administration.

Inclusion criteria

Age >55 and <85

Exclusion criteria

Previous compartment syndrome
Allergy to antibiotics used in the study
Abnormal renal or liver function
BMI <20 or >35

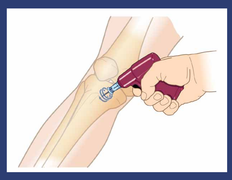
32 Patients assessed

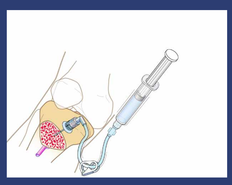
10 excluded
8 BMI >35
1 refused consent
1 on antibiotic treatment

22 Patients Enrolled

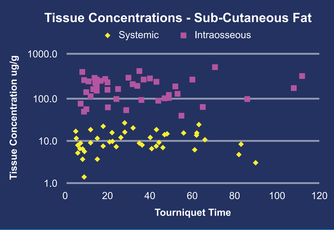
11 Systemic

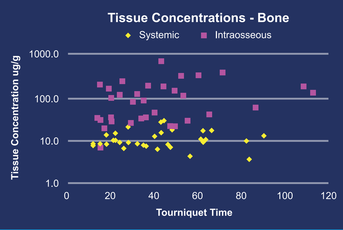
11 IORA





1 gram of Cephazolin
Subcutaneous fat and bone samples
Tissue Concentrations Analysed with High Performance Liquid Chromatography (HPLC)





Mean tissue concentration of cefazolin in subcutaneous fat was 186 µg/g in IORA group and 11 µg/g in systemic group (p<0.01)

Mean tissue concentration in bone was 130 µg/g in the IORA group and 11 µg/g in the systemic group (p<0.01).

Differences were consistent across all sample time points throughout the procedure.

Note scale is logarithmic.

- IORA provided antibiotic concentrations over 10x higher than systemic administration
- Insertion of an intraosseous needle was simple, rapid, and reproducible
- Previously, regional administration of prophylactic antibiotics in TKA required cannulation of a foot vein, which can be time-consuming and is not always successful.
- Intraosseous technique makes regional prophylaxis in TKA practical for routine use

IORA with Low–Dose Vancomycin

- Vancomycin covers resistant strains of Staphylococcus aureus and Coagulase-negative staphylococci, common causes of PJI.
- Prophylaxis with vancomycin in TKA is difficult; it requires prolonged administration to avoid red man syndrome, risks systemic toxicity and further antibiotic resistance, and patients are often underdosed
- IORA allows high tissue concentrations of Vancomycin even with a lower dose, avoiding toxicity and allowing bolus administration to optimise timing
- This RCT evaluated low-dose vancomycin prophylaxis via IORA

33 Patients assessed

3 excluded
2 Significant Cardiac disease
1 refused consent

30 Patients Enrolled

10 IV Systemic 1g Vanc

10 IORA 250mg Vanc

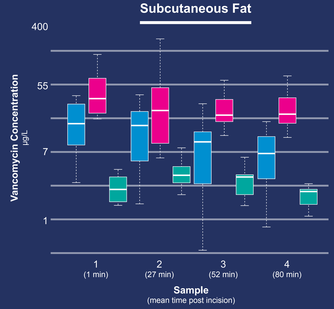
10 IORA 500mg Vanc

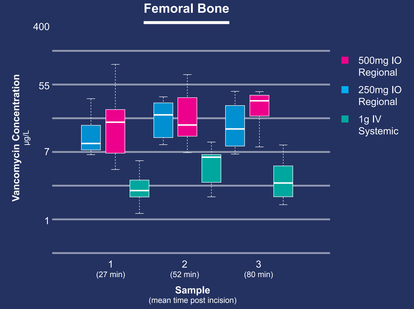
Why IORA Vancomycin?

Covers resistant organisms

Pharmacokinetics benefit more from higher concentrations

Bolus injection solves problems of systemic vancomycin:
- Optimizes timing
- Prevents systemic toxicity
- Minimizes promotion of further resistance





Mean tissue concentration of vancomycin in subcutaneous fat was 14ug/g in the 250mg IORA group, 44ug/g in the 500mg IORA group, and 3.2ug/g in the 1g systemic group (p<0.01)

Mean concentration in bone was 16ug/g in the 250mg IORA group, 38ug/g in the 500mg IORA group, and 4.0ug/g in the 1g systemic group (p<0.01).

Note scale is logarithmic.

No clinical signs of red man syndrome were seen in any patient undergoing IORA; including aftersigns were seen after tourniquet deflation.

- IORA technique provided very high tissue concentrations even when low-dose vancomycin was used
- We recommend the use of 500mg IORA dose as no red man syndrome was seen in any patient

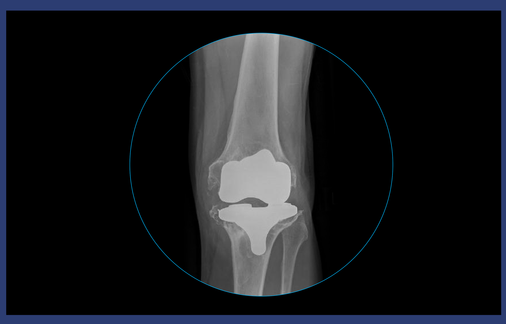
IORA in High Risk Patients – Revision TKA

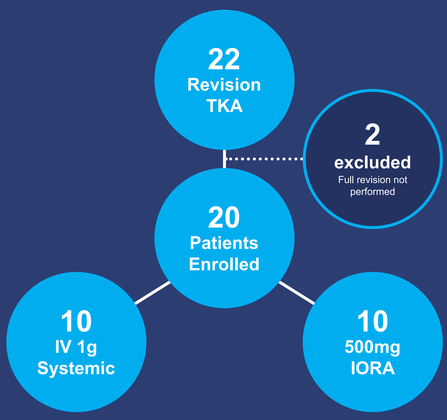
The use of IORA prophylaxis may be more clinically important in patients at greater risk of PJI, such as those undergoing Revision TKA.

This RCT evaluated two questions regarding IORA prophylaxis in revision TKA:

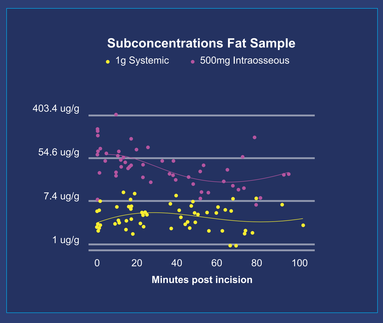
1) Does the presence of a tibial implant compromise IO injection?

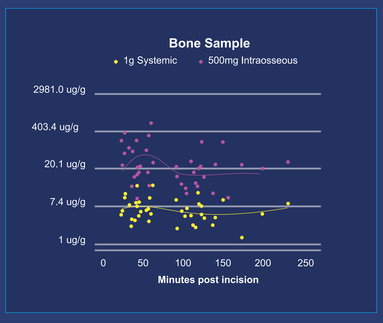
2) Does a period of tourniquet deflation during these prolonged procedures lower tissue concentrations?

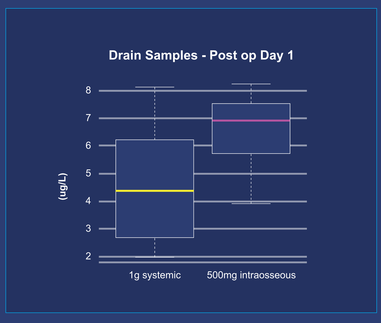




	Systemic 1g n=10	IORA 500mg n=10
Males	5	3
Females	5	7
Age (years)	67.4 (54-82)	69.3 (43-83)
BMI	32.6 (22-42)	32.3 (26-42)
1st Tourniquet time (minutes)*	94 (85-108)	91 (89-96)
Tourniquet Deflation time (minutes)*	37 (15-88)	61 (18-109)
2nd Tourniquet time (Cementation - minutes)*	35 (25-48)	35 (21-52)
Total Procedure Time (minutes skin to skin)	212 (177-282)	219 (167-263)
ASA Score (range)	2.4 (2-3)	2.7 (2-3)







- IORA administration of vancomycin is effective in revision TKA
- Vancomycin concentrations 5-20 times higher than systemic IV administration (p<0.01)
- High concentrations maintained throughout the procedure, despite a period of tourniquet deflation.

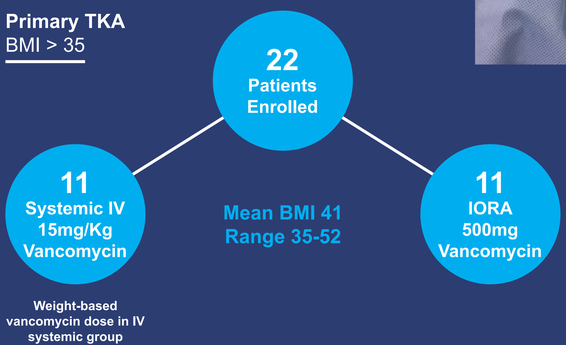
IORA in High Risk Patients - High BMI

High BMI patients are at high risk of PJI

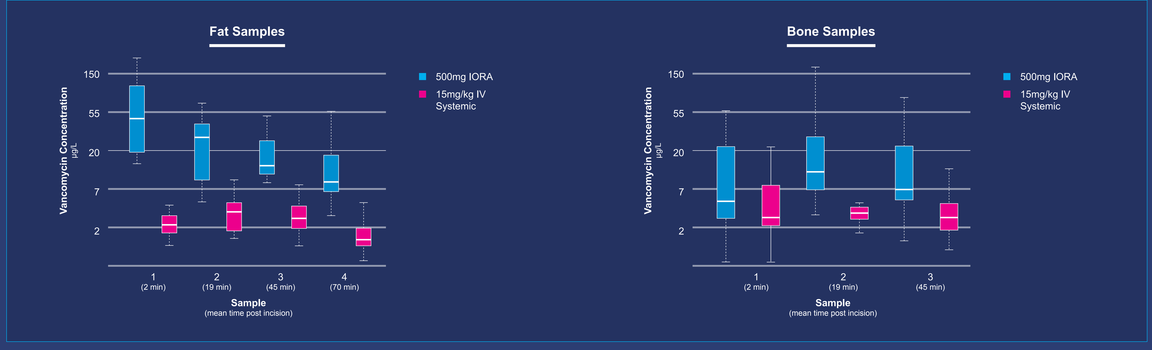
This RCT evaluated two questions regarding IORA prophylaxis in high BMI patients:

1) Does the higher volume of distribution diminish tissue levels?

2) Are there technical difficulties with IO insertion due to soft tissue depth?



Longer Needle used



- IORA Vancomycin Prophylaxis is Effective in High BMI patients
- IORA gave 4-8x higher antibiotic concentrations than systemic administration (p<0.01)
- Targeted option in this high-risk group

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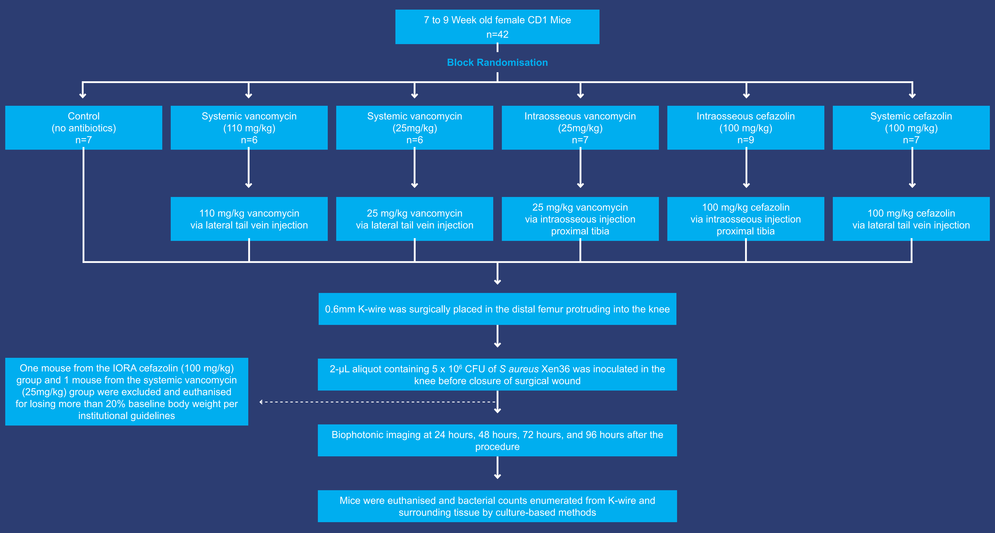
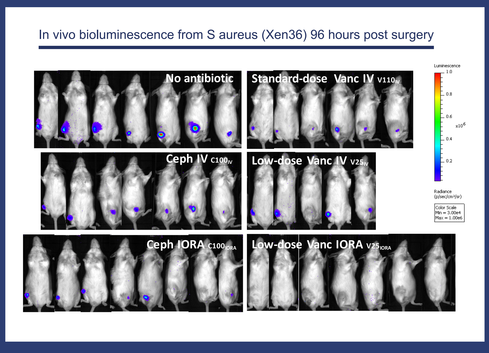
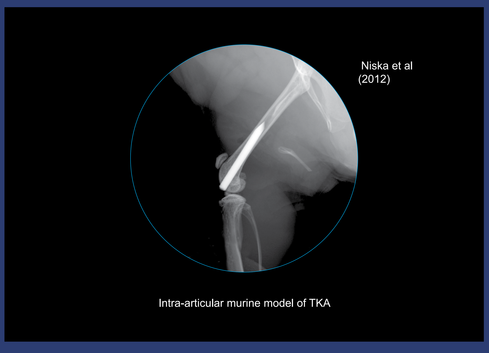
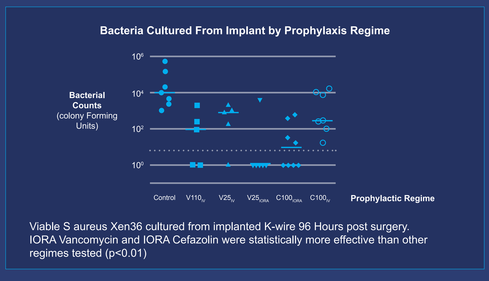
Does IORA Lower PJI Rates?

IORA gives higher tissue concentrations of vancomycin and cefazolin than conventional systemic prophylaxis
However it is difficult to adequately power a clinical trial to prove IORA prophylaxis lowers PJI rates
This study compares 6 different prophylaxis regimes in a mouse model of TKA

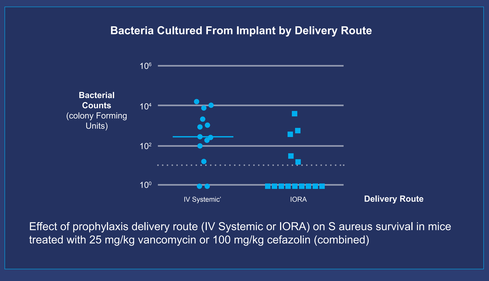








Viable S aureus Xen36 cultured from implanted K-wire 96 Hours post surgery. IORA Vancomycin and IORA Cefazolin were statistically more effective than other regimes tested ($p<0.01$)



Effect of prophylaxis delivery route (IV Systemic or IORA) on S aureus survival in mice treated with 25 mg/kg vancomycin or 100 mg/kg cefazolin (combined)

IORA of prophylactic cefazolin and vancomycin was more effective than systemic administration
The effectiveness of vancomycin in particular was enhanced by IORA, despite using a lower dose.

Conclusion

Intraosseous Regional Administration of prophylactic antibiotics achieves markedly higher tissue concentrations in TKA

Applicable in high risk settings such as elevated BMI and revision TKA

Intraosseous Regional Administration of vancomycin allows bolus administration and optimises prophylaxis timing

Provided more effective prophylaxis in an animal model of TKA

"Antibiotics must be present in the tissues at sufficient concentration from the time of incision until the time of closure"

Burke 1961, Journal of Surgery