REVIEW ARTICLE

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Use of regional administration of prophylactic antibiotics in total knee arthroplasty

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Abstract

Prosthetic joint infection after total knee arthroplasty is an infrequent, yet serious complication. Antimicrobial prophylaxis plays an important role in reducing the rate of surgical site infections. To be effective as an antimicrobial prophylaxis, the serum, tissue and bone concentrations of the antibiotic must be greater than the target organism's minimum inhibitory concentration. As antibiotic resistance increases current intravenous prophylactic dosing has been shown to be subtherapeutic for some patients. Intravenous regional administration and intraosseous regional administration of prophylactic antibiotics are novel methods used to increase the antibiotic tissue concentrations, which may enhance the efficacy of prophylactic antibiotics in total knee arthroplasty. Currently, literature has shown both intravenous regional administration and intraosseous regional administration to be safe and effective techniques. However, there is no clinical evidence to show that it results in a reduction of prosthetic joint infection rates. This study summarizes the current knowledge base on the use of regional administration of prophylactic antibiotics in total knee arthroplasty.

Introduction

Prosthetic joint infection (PJI) after total knee arthroplasty (TKA) is a leading cause of arthroplasty failure and is a tremendous burden for patients as well as the healthcare industry. Despite rigorous efforts to reduce infection rates, the reported incidence after primary TKA persists between 0.86% and 2.5%.[1,2] Coagulase negative *Staphylococcus* (CoNS) and *Staphylococcus aureus* are the most common organisms, accounting for two-thirds of PJI infections.[2]

Prophylactic antibiotics have been shown to reduce infection rates in arthroplasty by providing protection against the bacteria most likely to cause contamination during surgery.[3] To be effective as an antimicrobial prophylaxis, the serum, tissue and bone concentrations of the antibiotic must be greater than the target organism's minimum inhibitory concentration (MIC).[4] Current intravenous (IV) antibiotic prophylaxis dosing has been shown to be sub therapeutic for some patients.[5] A novel technique to administer prophylactic antibiotics via an intraosseous regional administration (IORA) has recently been studied and described by Young *et al*.[5–7] His technique has been shown to provide significantly higher tissue concentrations around the knee which may provide better protection against sensitive bacterial strains.[5–8] The use of intravenous regional administration (IVRA) in TKA was analysed by de Lalla *et al*. The results of her studies demonstrated higher tissue concentrations, lower infection rates and no adverse effects as a result of regional administration.[9,10]

Current guidelines

Current literature recommends the IV administration of 2 g Cephazolin in adults under 120 kg and 3 g in adults over 120 kg undergoing joint replacements.[11] The use of cephalosporin as prophylactic antibiotics have been shown to reduce deep infection rates in joint arthroplasty to 0.7–0.9% in comparison to 3.3–7.6% with placebo.[12,13] Alternative regimes for those with cephalosporin hypersensitivity or at high risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infections include using Clindamycin, Teicoplanin or Vancomycin.[11] In clinical practice, however, there is a great variance in surgical antibiotic prophylaxis regimes for joint replacement surgery.[14]

Requirements for effective antibiotic prophylaxis

The MIC is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism.[15] Regular surveillance of MICs is required due to a continuing increase in antibiotic

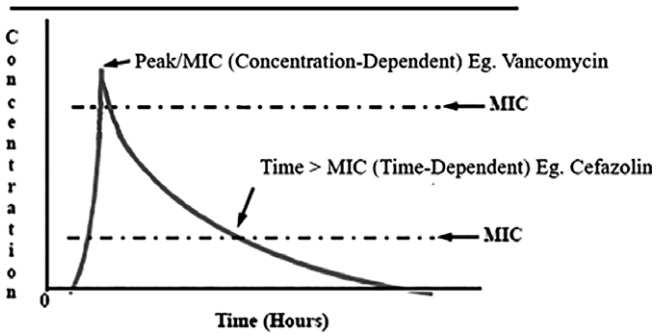

Fig. 1. Demonstrating how a higher MIC of bacteria affects concentration- and time-dependent killing of vancomycin and cefazolin. (Adapted from Quintiliani[16] with permission.)

resistance among pathogenic organisms. There is great variety in reported MIC between different sites and for different antibiotics.

Cephalosporins are time-dependent antibiotics. The effectiveness of the drug can be simplified to the time the serum/tissue concentration remains above the MIC during the dose interval (T > MIC) (Fig. 1).[16] Previously, the cefazolin MIC_{90} for CoNS has been reported at 0.5–1.0 μg/mL; however, as cephalosporin resistance among CoNS has increased there have been reports of MIC_{90} as high as 100 μg/mL.[17]

As antibiotic resistance increases the vast majority of MRSA and CoNS remains sensitive to vancomycin, leading it to be proposed as an alternative prophylactic agent.[2] Vancomycin exhibits concentration-dependent killing. The effectiveness of the drug can be simplified to the peak serum/tissue concentration above the MIC (peak/MIC) (Fig. 1).[16] Surveillance studies show that the vancomycin MIC is 1.0 μg/g for MRSA and 2.0 μg/g for CoNS.[18] Once concentrations are four to five times the MIC, further increases do not alter the killing rate.[19,20] This means the ability to achieve tissue concentrations of vancomycin four to five times the MIC is an important factor in reducing bacterial growth and joint infection.

Intravenous systemic antibiotics

Current guidelines for the administration of antibiotics prior to surgery are based on the assumption that those antibiotics reach tissue concentrations above the MIC. While serum antibiotic concentrations remain the standard practice for determining whether antibiotic exposures have been reached, the importance of bone concentrations and subcutaneous fat concentrations have been suggested to play a role in the development of deep surgical site infections.[17,21–23]

Recent research has shown that pathogenic organisms are becoming increasingly resistant to cephalosporin antibiotics and require a significantly higher MIC to prevent infections. A study by Yamada *et al*. assessed serum and bone concentrations of patients who had either 1 g or 2 g prophylactic IV dose of cefazolin prior to undergoing TKA or total hip arthroplasty. While all serum and bone concentrations exceeded the MIC for methicillin-sensitive *S. aureus*, no bone levels exceeded the MIC for cefazolin-resistant CoNS.[17] This study used several nationwide surveys that reported on cefazolin susceptibility of methicillin-sensitive *S. aureus* and CoNS in Japanese subjects to determine the variability of MIC for these pathogenic organisms. That data showed the MIC_{90} was 100 μg/g or greater in over half the reported species of CoNS.

Numerous studies have assessed bone or synovial concentrations of antibiotics with different IV prophylactic antibiotic protocols.[21,24,25] A study done by Sharareh *et al*. investigated antibiotic concentrations in the bone of patients undergoing TKA or total hip arthroplasty who received weight-based dosing protocols of cefazolin and vancomycin. The study had an average cefazolin bone concentration of 6.01 μg/mL and vancomycin bone concentration of 3.12 μg/mL for TKA. In this study 15% of the patients failed to reach an MIC of 2.0 μg/g in the cefazolin group and 20% of patients failed to reach an MIC of 2.0 μg/g in the vancomycin group.[21] Prats *et al*. investigated synovial tissue concentrations in patients receiving 2 g Cefonicid IV prior to TKA, this study established a reference value of 8 μg/g as the MIC based on previous literature. The mean tissue concentration was initially 23.16 μg/g at the start of the procedure and gradually declined to 15.45 μg/g by the end of the procedure.[24] Gergs *et al*. found the mean antibiotic concentrations in cortical and cancellous bone in patients undergoing TKA who were treated with 2 g ceftriaxone was below 20 and 12 μg/g, respectively.[25] This study does not identify MIC of ceftriaxone for CoNS or *S. aureus.*

These studies demonstrate the range of antibiotic tissue concentrations sampled from around the joint in patients receiving IV antibiotics. While vancomycin levels reached the target MIC, its tissue concentration is not optimal for reducing bacterial growth, which requires concentrations four to five times the MIC.[19,20] Furthermore, Cephalosporin dosing regimens may not reach high enough concentrations to exceed the MIC for certain cephalosporin-resistant CoNS.[17]

Regional antibiotics

Due to concerns that conventional intravenous systemic antibiotic administration may not provide adequate tissue concentrations, regional administration techniques have emerged as alternative techniques to deliver prophylactic antibiotics.[6,17] There are two methods of regional administration of antibiotics, each of which are not routinely used in primary TKA or outlined for use in prophylactic antibiotic guidelines. Both techniques require the use of a tourniquet to provide an antibiotic 'bier's block' within the limb. The antibiotics are administered via IVRA, with foot vein cannulation; or IORA, via the proximal tibia (Table 1).

Intravenous regional administration

Since 1908, it has been recognized that injection of drugs into a vein of a limb isolated by a tourniquet above, achieves higher tissue concentrations than the same drug administered systemically.[26] IVRA for patients undergoing TKA involves prophylactic antibiotics being given into a foot vein after tourniquet inflation. Studies have measured the bone and tissue concentrations in patients undergoing TKA after IVRA to evaluate its efficacy.[10,27,28] Hoddinott *et al*. was the first to demonstrate that IVRA into a foot vein was effective in achieving and maintaining higher tissue concentrations

Table 1 Advantages of regional administration versus disadvantages of IVRA and IORA

Advantages of regional administration	Disadvantages of IVRA	Disadvantages of IORA
Higher antibiotic tissue concentrations Lower antibiotic dosing Reduced systemic side effects May have the potential benefit of reducing prosthetic joint infections	Potentially challenging and time consuming foot vein cannulation Requires tourniquet No current guidelines	Risk of compartment syndrome due to extravasation of fluid Risk of fat emboli Require Tourniquet No current guidelines

IORA, intraosseous regional administration; IVRA, intravenous regional administration.

in patients undergoing TKA than in those receiving conventional systemic prophylaxis.[27] A study by de Lalla *et al*. compared tissue concentrations in patients undergoing TKA following 800 mg teicoplanin administered IV 2.5 h preoperatively versus 400 mg teicoplanin through a foot vein prior to incision. The tissue concentrations from the samples (skin, subcutaneous tissue, bone and synovium) obtained from patients undergoing IVRA were found to be 2–10 times higher than those achieved following systemic prophylaxis.[10] A follow up study by de Lalla *et al*. investigated the efficacy and safety of using IVRA of 400 mg teicoplanin in patients undergoing TKA. The study followed 160 patients (205 knees) for a minimum of 2 years. The results were one superficial infection of the primary site which was attributable to intraoperative contamination. This is in comparison to the institutions infections rates prior to IVRA which ranged from 1% to 1.5% for deep infections and 1–2% for superficial infections following TKA. None of the patients experienced any local or systemic adverse effects.[9]

IVRA of antibiotics has also been studied in other elective lower and upper limb surgeries, namely foot and elbow.[29–31] These studies all identified that the delivery of regional antibiotic prophylaxis achieved higher antibiotic tissue concentration than those achieved with standard systemic delivery. None of these studies identified any local or systemic adverse effects.

Complications of IVRA

While the studies that look at IVRA of antibiotics do not mention any specific complication, the difficulties may be that cannulation of the foot vein can be challenging and time consuming. Complications classically associated with the use of IV access such as hematoma, extravascular injection, phlebitis and thrombophlebitis are unlikely to be of any consequence due to the short duration of cannulation. These are the same potential complications that can arise from systemic administration of IV antibiotics via cannulation of the upper limb.

Intraosseous regional administration

Intraosseous (IO) techniques for fluid resuscitation were originally developed for paediatric patients but its use in adults is increasing as an alternative choice for vascular access in emergency situations. IORA of antibiotics has been used for some time in veterinary medicine for the treatment of equine infections.[32–35] Recently, it has gained attention in orthopaedics as a method to deliver prophylactic antibiotics to the limb as a 'bier's block'.

The current literature assessing IORA of prophylactic antibiotics in humans is led by Young *et al*.[5–7] The delivery technique described by Young *et al*. is via an IO cannula placed into the medial aspect of the proximal tibia at the level of the tibial tuberosity, after draping and before skin incision. The needle *in situ* allows injection of antibiotics, occurring after tourniquet inflation.[5] Their studies demonstrated that antibiotics delivered via IORA provided higher tissue concentrations in bone and subcutaneous fat samples compared to IV administration.[5,6] Antibiotic tissue concentration in subcutaneous fat and femoral bone samples were analysed from patients receiving the same dose of cefazolin via systemic IV administration or IORA. The results showed a 10–15-fold increase in the tissue concentrations from the group receiving antibiotics via IORA. The mean subcutaneous fat tissue concentration was 186 μg/g in the IO group versus 10.6 μg/g in the systemic group. The mean tissue concentration in the bone was 130 μg/g in the IO group and 11.4 μg/g in the systemic group.[6] This demonstrates that IORA achieved tissue concentrations above the required MIC_{90} of 100 μg/mL reported among cephalosporin-resistant CoNS.[17]

Similar results were demonstrated with IORA of vancomycin. Patients who received 250 mg IORA had a higher mean tissue concentration of vancomycin in their subcutaneous fat and bone than those randomized to receive 1 g IV. The difference in tissue concentrations were 14 μg/g in the 250 mg IORA group versus 3.2 μg/g in the systematic group in subcutaneous fat and 16 μg/g in the 250 mg IORA group versus 4.0 μg/μg in the systemic group.[5] This study demonstrated that low-dose IORA of vancomycin resulted in higher tissue concentrations than systemic administration. Importantly as vancomycin exhibits concentration-dependent killing the ability of IORA to reach higher tissue concentrations should provide more effective antibiotic prophylaxis. The study identified further benefits of IORA, including optimized timing of vancomycin administration and the potential for the lower-dose to reduce side effects such as red-man syndrome.[5]

A similar study was recently published by Young *et al*. examining vancomycin tissue concentrations using IORA in revision TKA.[7] The study compared 1 g systemically administered versus 500 mg via IORA. The tissue concentrations were found to be 5–20 times higher in the group of patients who had their antibiotics delivered by IORA despite lower dose and a period of tourniquet deflation during surgery. The study did not identify problems with IO administration resulting from the previous tibial implant.

To determine whether the higher antibiotic tissue concentrations provided more effective prevention against surgical site infections, Young *et al*. used a mouse model to test the hypothesis. Mice were randomized to one of six prophylaxis regimes followed by surgical

implantation of a k-wire and wound inoculation with *S. aureus*. The prophylactic regimes were control, systematic cefazolin, IORA cefazolin, high-dose systematic vancomycin, subtherapeutic low-dose systematic vancomycin and IORA vancomycin. Bacterial loads 4 days post-surgery showed mice treated with high-dose systemic vancomycin, IORA of vancomycin or IORA of cefazolin had lower *in vivo S. aureus* burdens. The results of the study indicated that IORA was more effective than same-dose antibiotics given systematically in reducing *S. aureus* colony forming units in samples taken from the prosthesis in the knee tissue.

There is no current standard of practice for how IORA of antibiotics is to be given or guidelines around dosages. In the studies by Young *et al*. participants received antibiotics through an EZ-IO (Vidacare, San Antonio, TX, USA; FDA approved) IO cannula, placed into the medial aspect of the tibia, after draping and prior to skin incision. Antibiotic dosages were then delivered in a 200 mL saline bolus.[5,6]

Complications of IO

The potential issues with IORA are unknown. An equine case study identified osteomyelitis and osteonecrosis following IO perfusion with gentamicin.[36] However, complications with IO access for fluid resuscitation are uncommon, between 0.3% and 1% of insertions.[37,38] Compartment syndrome due to extravasation of fluid from incorrect needle placement is the most common complication.[38] Other serious complications include osteomyelitis, cellulitis and skin abscesses which are all linked to prolonged IO access use which is not the case with IORA for antibiotic prophylaxis.[39]

Currently, no articles report a direct involvement of IO perfusion in fat emboli syndrome in humans.[40] Although in an animal study microscopic pulmonary fat and marrow emboli were found in the lungs of animals after IO access and cardiopulmonary resuscitation. Interestingly, fat emboli were also found in lungs of animals with cardiopulmonary resuscitation and no IO access. This study concluded that the use of IO did not increase the risk of fat embolization in the animal model; however, more research into the risk of fat embolization was needed.[41] As fat emboli syndrome is a recognized nonsurgical complication following TKA it is difficult to identify if the fat emboli is from IO fluid administration or from the tibial and femoral canal being instrumented.[42–44]

Discussion

PJIs are one the most devastating complications of TKAs. As antibiotic resistance increases, updates of the antibiotic prophylactic guidelines and identification of novel prophylactic strategies needs to occur. Current evidence suggests that the administration of IV Cephazolin could be subtherapeutic in its ability to treat cephalosporin-resistant CoNS and this could be a potential issue as half of all PJIs are caused by CoNS.[17] The regional administration of antibiotics is a novel technique to provide higher tissue concentrations, which may enhance the efficacy of prophylactic antibiotics in TKA.[5,6,8]

The only current clinic evidence to show that using IVRA results in a reduction of PJI rates is from de Lalla *et al.*[9] However, as PJI rates after primary TKA are low the results are not of statistical significance. Further prospective randomized trials comparing IVRA versus standard systemic prophylactic antibiotics would be required.

There is currently no clinical evidence to show that using IORA results in a reduction of PJI rates. As PJI rates after primary TKA are low, it is difficult to conduct an appropriately powered prospective randomized control trial to compare IV versus IO prophylactic antibiotics.

It may be difficult for surgeons to start adopting regional administration of prophylactic antibiotics into their clinical practice, as current guidelines do not support this method. While the current literature has shown regional administration to be a safe and effective technique, it is unlikely that exclusive use would be approved in many health services. Despite this there is reasonable evidence to support abandoning IV administration if using regional administration. Further research demonstrating a reduction in PJI rates as a result of either IVRA or IORA compared to IV prophylactic antibiotics is required for the technique to become recommended in clinical practice guidelines. For surgeons wishing to adopt IORA of prophylactic antibiotics, a pragmatic approach is required to integrate this technique into their clinical practice. To maintain compliance with current guidelines, surgeons could administer IO antibiotics in addition to conventional IV prophylactic antibiotics. While this would result in patients receiving a higher total dose of perioperative antibiotics, the therapeutic safe range for first generation cephalosporins would not be breached. Alternatively, additional low dose vancomycin could be administered via the IO route. Young *et al*. identified the potential benefits of using IO vancomycin as the systemic dosage can be reduced; thereby reducing systemic side effects such as nephrotoxicity, ototoxicity or red man syndrome.[5] The routine administration of vancomycin and using double antibiotics for prophylaxis does go against antibiotic stewardship guidelines and raises the potential issue of bacterial resistance. A change in guidelines and practice is an ideal time to audit both the benefits and complications of the chosen method and compare them to either consultants in the same hospital or historical controls. If the guidelines are not changed enabling IVRA and/or IORA then a change in practice by using double antibiotics will never provide data to change the guidelines in the future and these novel methods will always be contra to current guidelines.

It will be important for surgeons who do adopt regional administration of prophylactic antibiotics to keep clinical data on this technique, not only demonstrate clinical efficacy, but to also report on potential complications.

Intravenous and IORA of prophylactic antibiotics in TKA is a novel way to increase the tissue concentrations of prophylactic antibiotics. Current evidence suggests this technique has the potential to reduce PJI rates and support a change in guidelines, though further research is required to establish clinical efficacy.

Conflicts of interest

None declared.

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