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CORR Insights®: Regional Intraosseous Administration of Prophylactic Antibiotics is More Effective Than Systemic Administration in a Mouse Model of TKA

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Where Are We Now?

Despite the best preoperative and intraoperative practices, contamination of the surgical

site may be unavoidable due to air-borne or skin bacteria. Prophylactic antibiotics can help inhibit or kill contaminating bacteria, thereby preventing bacterial adherence to the arthroplasty implants, biofilm formation, and infection [7]. Additionally, systemic antibiotic prophylaxis has been shown to reduce infections in orthopaedic procedures [5, 6] and is part of well-established guidelines [2]. However, optimal antibiotic selection remains unclear. Cefazolin and cefuroxime are the recommended antibiotics, unless the patient has β -lactam allergy, in which case clindamycin or vancomycin should be used [2]. The increasing prevalence of infections by resistant microorganisms, such as methicillin resistant *Staphylococcus aureus* (MRSA), has raised the

question whether prophylaxis with vancomycin is necessary. No definite criteria exist, but vancomycin should be considered for patients at high risk for infection, such as patients colonized with MRSA or treated in institutions with recent MRSA outbreaks [7].

The protective effect of antibiotics depends on achieving adequate local tissue levels, but systemic administration of high doses of antibiotics may be limited by associated adverse effects. For this reason, local antibiotic delivery becomes an attractive option that could achieve high local levels while avoiding systemic toxicity. Antibiotic-impregnated cement has been widely employed in arthroplasty procedures and has been shown to reduce revisions due to infection in total hip arthroplasty [4, 5]. On the other hand, the benefit of adding antibiotics to the cement in TKA has not been conclusively demonstrated [1].

Intraosseous regional administration (IORA) of antibiotics was recently

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evaluated in two randomized controlled trials [10, 11], which convincingly demonstrated that IORA achieved significantly higher bone and subcutaneous fat levels of cefazolin and vancomycin compared to systemic administration. Mean cefazolin levels in bone were 12 times higher following IORA [11] and mean vancomycin levels in bone were four times higher following IORA of low-dose vancomycin [10]. However, it remains unclear whether such high tissue levels of antibiotics will result in increased efficacy and infection prevention.

In an effort to resolve this, Young and colleagues elegantly demonstrated in a murine model of TKA that IORA of cefazolin and vancomycin was more effective than the same dose administered IV at reducing the burden of contaminating bacteria in both tissue and implants. These findings appear to be promising and may have useful clinical implications.

Where Do We Need To Go?

However, an important question remains unanswered; will IORA of antibiotics help reduce postoperative infections in patients undergoing TKA? The findings of the current paper may not necessarily translate in improved prophylaxis in the clinical setting because of several factors, and

these point to some potentially important avenues for future inquiry: (1) In vivo animal models of antimicrobial strategies cannot reliably predict clinical efficacy [8], (2) the bacterial inoculum in intraoperative contamination would be expected to be much lower than the one used in the study, (3) the use of antibiotic-impregnated cement in the clinical setting may contribute in infection prevention, and (4) very high tissue levels of antibiotics may not necessarily offer additional benefit. For example, β -lactam antibiotics and vancomycin do not exhibit concentration-dependent killing and concentrations higher than four to five times the minimum inhibitory concentration do not increase the killing rate. Instead, time above minimum inhibitory concentration is the pharmacokinetic/pharmacodynamic parameter that correlates with therapeutic efficacy [3].

Furthermore, IORA of antibiotics needs to be clinically evaluated for potential complications, such as fat embolization or fluid extravasation with compartment syndrome following incorrect needle placement.

How Do We Get There?

We need well-designed, multicenter randomized controlled trials to evaluate the efficacy and safety of

prophylactic IORA of antibiotics compared to systemic administration in patients undergoing TKA. It is important that such studies use well-established criteria for the definition of infection [9], control for the presence of factors associated with infection, such as patient comorbidities, and have adequate followup.

Because of the low infection rate in TKA, demonstrating an overall reduction in postoperative infections may be a difficult task requiring extremely large sample sizes. However, if similar efficacy can be demonstrated, an improved safety profile of IORA might still make it a better alternative to systemic administration. Careful analysis of patient subgroups in these studies will be required to identify the optimal prophylaxis strategy. For example, IORA of antibiotics may help prevent infections only in patients at high risk of infection, such as patients with comorbidities or a previously treated infection; or IORA may improve safety compared to systemic administration of a specific antibiotic but not others. This important information can still be derived from well-conducted studies and will help us improve clinical practice.

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