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CORR Insights®: What is the Intraarticular Concentration of Tobramycin Using Low-dose Tobramycin Bone Cement in TKA: An In Vivo Analysis?

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Where Are We Now?

Infection following TKA is the most common cause for revision knee surgery in the United States [3] and the incidence is expected to rise steeply over the next 15 years [8]. Treatment of a patient with an infected

TKA can generate considerable morbidity and cost [10]. One strategy to reduce the occurrence of periprosthetic infections is to use antibiotic-laden bone cement (ALBC) at the time of primary TKA. This strategy remains controversial, as data from national registries, randomized clinical trials and meta-analyses suggest a protective effect of ALBC against infection when used in hips, but a variable effect in knees [1, 2, 4, 5, 9, 11]. It is not clear whether the inconsistent efficacy in TKA is related to the duration and quantity of locally elevated antibiotic levels in TKA as compared to that seen after THA. Although studies have looked at the elution of high-dose tobramycin from cement [6], as in

revision TKA for infection, to my knowledge, there have been no studies specifically addressing the intraarticular concentration of commercially available tobramycin impregnated cement when used in primary TKA. The current utilization of tobramycin ALBC in primary TKA is based solely on the results of studies in THA.

To better understand the value of using tobramycin ALBC in TKA, Vrabec and colleagues compared the intraarticular and serum levels of tobramycin in patients undergoing a primary TKA with commercially available, low-dose tobramycin impregnated antibiotic cement to those patients who received intravenous tobramycin and bone cement without antibiotics. The low-dose tobramycin impregnated bone cement provided short-term supratherapeutic local concentrations in the knee, while maintaining low and subtherapeutic serum tobramycin levels. In contrast, intravenous tobramycin resulted in subtherapeutic intraarticular levels in all cases. These findings mirror the

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previous findings seen with tobramycin ABLC used in primary THA [12].

Where Do We Need To Go?

Although the study by Vrabec and colleagues addressed the fundamental issue of whether or not a commercially available, low-dose tobramycin impregnated cement provided therapeutic intraarticular levels of antibiotics, like all good research, it has generated more questions that need to be understood prior to the routine use of tobramycin ABLC in primary TKA.

It has been well established that the elution of antibiotics from bone cement varies by the type of bone cement and by the mixing technique [7]. Furthermore, the time course and the amount of antibiotic that is released from the cement is dependent on factors inherent in the bone cement, such as porosity, as well as the overall quantity of cement used and the surface area of the bone cement exposed to the host tissues. Further studies are required to clarify each of these variables when using tobramycin ABLC in primary TKA.

Most importantly, and prior to its widespread use, it must be demonstrated that the use of low-dose tobramycin ABLC in primary TKA is effective and does not result in

complications. One must wonder why it is that the present study demonstrated a supratherapeutic level of tobramycin in the knees of patients undergoing primary TKA, yet the routine use of ABLC in primary TKA does not consistently decrease the risk of infection, although it seems effective in primary THA. Is this related to the thin cement mantle in TKA, the duration of action of the ABLC, or that the subsequent infection is caused by bacteria not sensitive to the antibiotic in the cement? The primary concerns regarding the routine use of antibiotic-loaded bone cement include the potential for detrimental effects on the mechanical strength of bone cement when antibiotics are admixed, allergic reactions to the specific antibiotic used, the development of drug-resistant bacteria and systemic toxicity such as renal failure [7]. The study by Vrabec and colleagues included only a small group of patients followed for 48 hours, so it could not specifically address these issues.

How Do We Get There?

While further studies can clarify the pharmacokinetics of tobramycin impregnated antibiotic cement *in vivo*, definitive clinical studies are needed to determine the long-term efficacy and safety of its use. Since periprosthetic

infections are multifactorial in nature, this would require a large study group that was stratified for patient risk and for the specific antibiotic cement used. Realistically, this may be most easily achieved through large hospitals, state databases, or through a trial organized by one of the large national arthroplasty organizations. Large hospital and organizational databases can overcome this deficiency and provide an insight into the long-term results with respect to infection and the bacteria involved, as well as the potential complications of ALBC such as premature loosening, allergic reactions, and renal failure. Although large, randomized multicenter trials are typically difficult to perform, such a trial by one of the national arthroplasty organizations would facilitate the recruitment of a large number of patients while controlling the other variables used for infection prophylaxis. Conversely, national registries have the advantage of analyzing the outcome of thousands of patients in a relatively short period of time, and may therefore be best suited to this type of study. Unfortunately, at the present time, the national registries lump all ABLC together, and most do not risk stratify the patients. If these obstacles could be overcome, the national registries would be the ideal resource to definitively clarify this issue.

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Periprosthetic infection remains a major complication following primary TKA. Vrabec and colleagues have provided an important insight into the ability of commercially available tobramycin impregnated bone cement to provide short-term supratherapeutic concentrations in the knee. It is now up to the orthopaedic community to expand on this knowledge and determine its clinical efficacy and safety for patients undergoing primary TKA.

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