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CORR Insights®: Antibacterial Activity in Iodine-coated Implants Under Conditions of Iodine Loss: Study in a Rat Model Plus In Vitro Analysis

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Where Are We Now?

Periprosthetic joint infection (PJI) is a devastating complication of hip and knee arthroplasty. While the incidence remains low (0.5%-3%), the total annual numbers are growing as the frequency of both THA and TKA increases [4]. The resulting morbidity, mortality, and economic burden are substantial [1]. Methods to reduce the incidence of PJI have spanned the continuum of care from preoperative antibiotics to postoperative wound dressings. A particular area of interest involves the treatment of the prosthetic surface to create antimicrobial properties. These treatments can be broadly characterized as either surface modifications or coatings and can confer either bacteriostatic or bactericidal properties [3]. Dozens of various antibacterial macromolecules, antibacterial peptides, inorganic metal elements, and antibiotics have been utilized to render an implant surface anti-infective [2]. While many of these treatments appear promising in laboratory scenarios, for various reasons, few have been used in clinical practice. Questions remain regarding the feasibility of many of these treatments in large scale production, the length of time the treatment provides an anti-infective effect, and the effect of these treatments on osseointegration.

The study by Ueoka and colleagues [6] in this month's *Clinical Orthopaedics and Related Research*® evaluated the antibacterial activity of iodine-coated titanium implants using a rat model with additional in vitro analyses. Specifically, the authors sought to answer two important questions regarding the use of antibacterial implants: How much does the iodine content decrease over time, and what is the antimicrobial effect of the reduced iodine content? They found the iodine content decreased to 72% and 65% at 4 weeks and 8 weeks, respectively. But despite the decreased iodine content, the implants continued to confer an antimicrobial effect against methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *S. aureus*, and *P. aeruginosa*.

These data are promising for the development of anti-infective implants. While much work is still needed to bring this type of technology into the clinical arena, this type of research has the potential to significantly reduce one of the most dreaded complications of total joint replacement.

Where Do We Need To Go?

Orthopaedic implants for fracture fixation and some spinal implants are designed to bear a load for a short period of time and never achieve osseointegration. Others, like hip implants, are designed to achieve osseointegration and bear a load for the life of the patient. Implants designed to achieve osseointegration must be not only biocompatible, but also osteoconductive. For these implants, treatments designed to be bacteriostatic or bactericidal must not interfere with osseointegration. Ueoka and colleagues [6] have provided

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valuable information in the understanding of the antimicrobial properties of iodine-supported implants over time. But further questions will need to be addressed before this technology can be used in clinical practice. What is the effect of iodine on osseointegration? Does this method of iodine coating provide long-term antimicrobial effects? Are there consequences of iodine leaching over years? Will long-term exposure to iodine cause adverse effects to the local soft tissues? Will iodine exposure affect the wear characteristics of polyethylene? Is this type of treatment effective for short-term prophylaxis only or would this also prevent late hematogenous infections? Are these implants effective for managing established infections or only for prophylaxis? Is the cost associated with manufacturing these types of implants cost-effective? And, finally, what are the regulatory consequences of an implant that behaves as a drug?

How Do We Get There?

Further animal studies will be crucial to answer many of these questions. For instance, there are several well-described animal models to evaluate the effectiveness of osseointegration of various porous surfaces. A study to compare the push-out strength of porous-coated titanium implants with iodine coating to those without iodine will be necessary before one of these implants could be used in humans. A study like the one described by Ueoka et al. [6] could be performed to help determine the length of the antimicrobial effect of this type of iodine coating. Animal models will also help researchers determine the efficacy of this type of implant in treating an established infection versus as a prophylactic agent. By using a PJI model, some animals could have iodine-supported implants placed while others had traditional titanium implants placed to see if the iodine prevents the establishment of an infection. Additionally, an infection could be established to see if placing an iodine-supported implant was able to eradicate the infection. Previous publications [5] have demonstrated some efficacy of iodine-supported titanium implants in the prevention and treatment of musculoskeletal infections. The long-term effect of iodine leaching can also be performed using animal models. This type of study would likely require larger animals with longer life expectancy to study over the course of several years. A wear simulator could be used to assess whether there is a detrimental effect on polyethylene wear in the presence of iodine.

While animal studies are valuable, there are some questions that can only be answered with human trials. Patients with a PJI could be an early study cohort. Reinfection following a two-stage revision is higher than primary arthroplasty. A study comparing two-stage revisions for chronic PJI with either an iodine-supported implant or a standard titanium implant would likely provide early evidence for further study. Ultimately, randomized clinical trials will be necessary to establish efficacy in humans. Two cohorts of patients would be established, with one group receiving an iodine-supported implant and the other group receiving a standard implant. Short-term infection rates and complications will need to be the primary outcome. Finally, it will be important to assess the cost-effectiveness of these types of implants. This will require data on the number of infections prevented and how expensive the implants are to manufacture.

A final topic to be considered deals with the regulatory fallout of implants that behave like drugs. Current hip and knee implants are regulated by the FDA's Center for Devices and Radiological Health (CDRH). The FDA would need to determine whether an implant such as this would fall under the CDRH or the Center for Drug Evaluation and Research.

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