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CORR Insights

CORR Insights®: How Long Does Antimycobacterial Antibiotic-loaded Bone Cement Have In Vitro Activity for Musculoskeletal Tuberculosis?

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Where Are We Now?

Osteomyelitis treatment is based on surgical débridement and systemic administration of antibiotics for prolonged time. However, intravenous therapy may not ensure adequate local concentration of antibiotics in necrotic bone tissue to eradicate biofilm-related infections, and it may cause systemic complications and toxicity. In the current study, Lee and colleagues investigated the in vitro antimycobacterial activity and elution characteristics of bone cement loaded with streptomycin or amoxicillin and clavulanate for the treatment of musculoskeletal tuberculosis. In a previous study, the authors demonstrated the in vitro antimycobacterial effectiveness of isoniazid when incorporated in bone cement [5]. However, the lack of a powder form of isoniazid limits its practical application as an antibiotic that can be used in depot form in bone cement.

Polymethyl methacrylate (PMMA) is still the cement of choice, but the method of mixing is affects the release of the antibiotics and the mechanical properties of cement. The preparation should be porous enough to facilitate the spread of the antibiotic, but not so porous that it weakens the structure of the cement itself. We know that manual preparation seems to reduce both the strength of the cement and the antibiotic's effectiveness compared to industrially prepared antibiotic-loaded cement [2, 10], and this needs to be considered when antibiotics are used either in spacers or for definitive reimplantation following treatment for periprosthetic joint infection.

Systemic toxicity related to antibiotic-loaded bone cement (ALBC) is rarely reported and generally involves patients with renal failure [9]. Studies evaluating local toxicity, with particular interest to the function of osteoblasts and osteocytes, found that osteoblast replication was reduced only when exposed to high local concentrations of antibiotics, well below

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those used clinically in bone cement [7, 8].

Where Do We Need To Go?

Although ALBC is increasingly used for treating osteomyelitis and periprosthetic infections, effectiveness of ALBC is remains controversial and doubts persist regarding the best method of preparation, the choice of the antibiotic, the effective release, and diffusion of the antibiotic in the surrounding tissues, and the mechanical properties of the cement [2, 13].

Treating musculoskeletal tuberculosis with ALBC is even-more controversial. The current study provided useful new data in terms of using ALBC with streptomycin, which is so important because first-line antituberculosis drugs are not available for this purpose; rifampicin is unsuitable for bone cement, and isoniazid has limited practical use because is unavailable in powder form. Whatever antibiotic we choose must be available in powder form, and each drug shows different elution kinetics and antimicrobial activity. These characteristics have been studied for the treatment of pyogenic osteomyelitis (sustained release and activity has been demonstrated for vancomycin, gentamicin, and tobramycin [2, 3]), but we know little about antituberculosis drugs in this regard, and future studies need to fill this gap.

The incidence of tuberculosis osteomyelitis has increased in the last decades [6], and the use of ALBC could be a powerful weapon in a multimodal treatment strategy. The ideal ALBC will provide sustained, prolonged elution, a high degree of antimicrobial activity, and adequate structural stability.

As observed by the authors, kanamycin is another second-line antituberculosis drug available in powder form and probably suitable for this use. New studies on kanamycin, as an alternative to streptomycin, are needed in order to identify the antibiotic of choice for clinical use. Further studies should also focus on the appropriate dosing of antibiotics for different clinical presentations of tuberculosis.

The development of new materials and preparation methods can enhance the effectiveness of ALBC. The use of PMMA enriched with tricalcium phosphate, barium sulfate, or porogens (compounds that create microcavities in the compact structure of bone cement, such as gelatin sponges and ceramic granules) improves the elution of antibiotics increasing the porosity of the cement. However, this may compromise the mechanical proprieties of the bone cement [4, 12]. Ayre and colleagues [1] developed a new preparation method based on a liposomal drug delivery system for PMMA bone cements using antibiotic-loaded nano-sized liposomes. This system increased the antibiotic elution without altering the mechanical properties of the cement. Another strategy to enhance the elution of the antibiotic can be the irradiation of bone cement with ultrasound and microbubbles-mediated ultrasound [11].

The effect of prolonged high local concentrations of antibiotic on the occurrence of antibiotic resistance needs further investigation. The importance of data on long-term antimicrobial activity is greater when treating chronic infections such as tuberculosis osteomyelitis.

Despite the expectations some have for ALBC, further clinical studies are needed to refine its use for the treatment of chronic osteomyelitis.

How Do We Get There?

Few antituberculosis drugs are suitable to be incorporated in ALBC, and in-vitro studies are needed to investigate the elution kinetics of second-line and third-line drugs in order to define the most-effective combination of antibiotics and the best doses. Moreover, the mechanical proprieties of

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bone cement should always be considered as important as the antimicrobial activity when testing new compounds if the cement will be used in a load-bearing way for a sustained period of time.

Therefore, observational cohort and case-control clinical studies with adequate followup are needed to evaluate the long-term performance of new ALBC combinations. Preparation methods that enhance the effectiveness of antibiotics without compromising the biomechanics should be promoted and clinically tested. Observational studies investigating the emergence of pharmacological resistance are also needed in order to define the appropriate combination with systemic therapy.

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