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Review

Local antibiotic therapy strategies in orthopaedic trauma: Practical tips and tricks and review of the literature

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ABSTRACT

The use of local antibiotics for the prevention of infection in the setting of open fractures and as part of the treatment of osteomyelitis is well established. Antibiotics are most commonly incorporated into polymethylmethacrylate (PMMA) cement, which can then be formed into beads, moulded to fit a bone defect or used to coat a guide wire or IM nail. Newer delivery vehicles and techniques are being evaluated to improve upon these methods. Many factors influence how local antibiotics are applied. Treatment strategies are challenging to standardise due to the variability of clinical presentations. The presence of hardware, upper versus lower extremity, healed versus non-healed fracture and quality of soft tissues overlying the affected bone, as well as patients' comorbidities all need to be considered.

Despite the accepted use of local antibiotic therapy in orthopaedic trauma, high-quality evidence regarding the use of local antibiotics is lacking. Indications, techniques, dosages, types of antibiotics, elution properties and pharmacokinetics are poorly defined in the clinical setting. The purpose of our manuscript is to review current strategies and provide practical tips for local application of antibiotics in orthopaedic trauma. We focus on delivery vehicles, types of antibiotics, dosage recommendations when mixed with PMMA and indications.

Contents

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Introduction

Musculoskeletal infection is a challenging complication for both orthopaedic surgeons and patients alike. The orthopaedic trauma literature lags behind the arthroplasty research on the topic. However, in recent years, more clinical and research attention has been given to this costly condition. However, progress and innovations that make clinical differences and change practice are scarce. The variability of presentations, patients' comorbidities, patient populations affected, surgical history with presence or absence of hardware and anatomical location makes the topic challenging to study prospectively in a meaningful way [1]. The armamentarium to prevent or treat deep infections in orthopaedic trauma includes local application of antibiotics. There is some science behind the topic, albeit controversial and often criticised by our infectious disease colleagues. The aim of this strategy is to increase local concentration of antibiotics in the zone of injury without the risk of systemic toxicity.

Combining antibiotics with polymethylmethacrylate (PMMA) cement for application in a wound with an established infection or at risk of becoming infected has been shown to reduce infection rates in both animal and clinical studies [2]. The technique of coating intramedullary nails with antibiotic impregnated cement has the added advantage of providing stability and it may improve the outcomes of infected non-unions of long bones [3]. However, these custom-made combinations of antibiotics and carriers/implants are not approved by the FDA and by definition cannot be studied prospectively.

New vehicles for the delivery of antibiotics are being developed and studied [4]. These absorbable carriers have the ability to release high local concentrations of antibiotics, without the need of additional surgery to remove them.

In this review, we summarise the use of local antibiotics in orthopaedic trauma. We review antibiotic types and delivery vehicles as well as pharmacokinetics of antibiotics when they are mixed with polymethilmethacrylate (PMMA). We seek to provide evidence for the doses of antibiotics when combined with PMMA and describe our preferred strategies to manufacture carriers in the operating room. Finally, we propose future direction for research on this topic.

General principles

Antibiotic options

Various antibiotics have been used to deliver high local concentrations in the setting of open fractures and osteomyelitis. Essential properties of the selected antibiotic(s) include activity against the causative organism (if known or suspected), a form that can be incorporated into the delivery vehicle, and thermo-stability to prevent denaturation during the exothermic reaction that occurs during polymerisation of the cement [5]. Aminoglycosides and Vancomycin fulfil those criteria and are therefore most commonly used. In addition, these antibiotics have a broad spectrum of efficacy and have extremely low rates of anaphylaxis.

Aminoglycosides, such as tobramycin and gentamicin, are bactericidal and active against aerobic gram-negative bacilli. They can also exhibit synergistic activity against gram-positive bacteria such as *Staphylococcus* and *Enterococcus* [6]. Aminoglycosides have been studied in both animal and clinical trials with few reports of systemic toxicity [7,8].

Vancomycin is a glycopeptide that is active against gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*. As Gram-positive bacteria are the most common cause of osteomyelitis, vancomycin should be considered for most cases of long bone osteomyelitis. Excellent elution properties from PMMA cement and calcium sulfate are well established [9]. Other antibiotics such as cephalosporins have been described in combination with PMMA and thermo-stability has been demonstrated by several in vitro studies [10].

Safe doses of antibiotics to use when combined with PMMA

Antibiotic cement preparation can be divided into low dose and high dose categories. In general, low dose cement contains less than 2 gm of antibiotics per 40 gm of cement and high dose contains greater than 3.6 gm of antibiotics per 40 gm of cement. Commercially available antibiotic cement has been available in the United States since 2003, but is only available in low-dose form. Low dose antibiotic cement is used for prophylaxis in primary joint replacement and hemi-arthroplasty [11]. High dose antibiotic cement is preferred for the treatment of established infections. Total dosages as high as 10.5 gm of vancomycin and 12.5 gm of tobramycin have been described without system toxicity [12]. Others have recommended using 4 gm of vancomycin and 3.6 gm of tobramycin per 40 gm of PMMA cement for open fractures and treatment of osteomyelitis [13].

Delivery vehicles

PMMA cement is the most commonly used substance to deliver antibiotics to the affected region. This polymer has many advantages including controlled release over time as well as a structural integrity to manage dead space or bone loss. PMMA is easy to mix and form into various shapes and sizes, depending on the clinical needs. While there are commercially available choices with pre-mixed antibiotics that have been approved by the FDA, the dosage of these is typically not sufficient for the treatment of established infections [14]. Most commonly, beads are formed and incorporated onto a wire or non-absorbable suture. The main disadvantage of PMMA is its lack of biodegradability with the need of surgical removal. This raises the concern that the cement can act as a foreign body, harbouring infection in cases of resistant organisms or once antibiotic concentrations are below the minimum inhibitory concentration (MIC).

A number of alternative delivery vehicles have been developed to obviate the detrimental aspects of PMMA cement. Modern carriers are biodegradable, thereby alleviating the need for surgical removal. Bone grafts and bone graft substitutes have been used successfully in conjunction with local antibiotics [15]. The advantage of this strategy is that the treatment of infection and bone loss occurs simultaneously. Substances that have been investigated include calcium sulfate [16], calcium hydroxyapatites [17], calcium phosphate [18], bioactive glasses [19], and demineralised bone [20]. However, the cost of these combination products is a concern without prospective clinical evidence of efficacy in the prevention or treatment of infection [4].