Antibiotic-loaded cement in revision joint replacement

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The infected joint replacement remains a difficult clinical challenge. Antibiotic-loaded cement provides one therapeutic solution that combines mechanical stability and antibiotic delivery.

Infection in total joint replacement continues to affect 1% of total hip replacements and 1–2% of total knee replacements (Sculco, 1993). The effects of infection are devastating, with patients often requiring prolonged hospital treatment including antibiotic suppression, surgical debridement, single stage, two stage or multiple stage revision, arthrodesis or amputation.

Following implantation of a prosthetic joint, there is a race for the surface of the implant between the host cells and bacterial colonization (Gristina et al, 1988). The surface of the prosthesis is contaminated by bacteria at the time of implantation. Bacteria are derived from airborne colony-forming units, from contamination of the surgical wound at the skin margin, from surgical gloves and instruments, along wound drains or from haematogenous spread. Ultra clean airflow theatres, scrupulous attention to surgical preparation, draping and no touch technique, good theatre discipline, exhaust suits and prophylactic antibiotics have contributed to reducing bacterial contamination, and may swing the balance towards the host body winning the race for the surface of the prosthesis. Patient factors including nutritional status, diabetes, rheumatoid arthritis, previous sepsis and concurrent illness may swing the balance in favour of the contaminating bacteria.

There is an acute inflammatory response to surgery that causes the secretion of local and systemic proteins such as fibronectin and C reactive protein (CRP). These proteins opsonise the implant, allowing the host cells, including immune cells, to adhere to the surface. Bacterial cells have a variable ability to produce a polypeptide or polysaccharide glycocalyx that also opsonises the surface of the implant encouraging bacterial adhesion and protecting the bacteria from cellular attack.

The surface of any implanted prosthetic material interacts with the host. The mode of interaction will depend on the type of material, its surface finish and the mechanical environment at the interface.

TYPES OF MATERIAL

Polymethylmethacrylate (PMMA) bone cement without antibiotics is an implant material that allows bacterial colonization, whereas titanium inhibits bacterial growth (Insall et al, 1983; Humphrey et al, 1998). PMMA inhibits the ability of leucocytes to both phagocytose and kill bacteria (Petty, 1978). Materials with a rough surface are more easily colonized by bacteria than those with a smooth surface. Instability at the implant–host interface promotes infection. Stability allows the bone to grow on to the surface. The initial stability gained by using PMMA cement, as well as the addition of antibiotics, offsets some of the unfavourable material characteristics of PMMA that encourage bacterial colonization.

The host reaction to implanted bone cement is a complex one. PMMA polymerization is an exothermic reaction that can cause thermal damage to the interface bone. The thickness of thermally damaged bone is dependant on the temperature of the polymerizing PMMA bone cement, which in turn is dependant on the formulation of the PMMA, the thickness of the cement, the temperature of the monomer, how vigorously it is mixed, and the ability of the prosthesis and bone to absorb the heat produced. The cement will flow into the interstices of the bone to varying degrees depending on the viscosity of the PMMA (Stone et al, 1996), the pressurization of the cement at implantation and the openness of the pore size between bone trabeculae including the presence of blood or debris at the bone surface.

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PMMA can also be used as a slow release carrier for antibiotics, for structural support, or for both. Antibiotics are added as a prophylaxis against the common infecting organisms and for treatment of established infections. High local concentrations of antibiotic can be achieved by adding them to a carrier that allows elution to the local tissues.

ANTIBIOTIC CHOICE

Antibiotic choice is constrained by the thermal stability of the antibiotic, the availability of the antibiotic in a powder formulation and the antibiotic elution characteristics. Many antibiotics can be added to cement. The rate and pattern of release has been documented by both in-vitro and in-vivo studies. Commonly used antibiotics include aminoglycosides (gentamicin (powder), tobramycin, amikacin), the glycopeptides (vancomycin, teicoplanin), and others such as clindamycin (powder) and ciprofloxacin (Bucholz and Engelbrecht, 1970; Hoff et al, 1981; Insall et al, 1983; DiMaio et al, 1992). Penicillins and cephalosporins can be used but are rarely the antibiotic of choice because of risks of allergenicity. An unusual application of this technique has been described using amphotericin B added to bone cement to treat *Candida albicans* osteomyelitis (Marra et al, 2001).

Chloramphenicol and tetracycline are inactivated and some penicillins are partially inactivated by the heat of polymerization. Antibiotics supplied as an aqueous solution such as gentamicin and clindamycin interfere with the polymerization process, and rifampicin produces a black tacky composite that does not harden for several days.

Antibiotic combinations added to cement have the potential to minimize the development of antibiotic resistance, and combinations with different elution characteristics may optimize the therapeutic effect. The combination of tobramycin, which has rapid elution, and vancomycin, which has a slower elution, produces an initial high peak tobramycin concentration followed by prolonged protection from the vancomycin. This combination improves the elution characteristics of vancomycin, probably by increasing the cement porosity (Penner et al, 1996).

Antibiotic carriers currently used include collagen sheets (Humphrey et al, 1998; Martins et al, 1998) (Collatamp), chains of PMMA cement beads on a metal cable and antibiotic PMMA cement prepared in theatre either as a static spacer or as part of a prosthesis that allows movement. Collagen sheets impregnated with gentamicin have the advantage of being broken down and absorbed by the body leaving no residue. A high initial local concentration of antibiotic is achieved via normal diffusion mechanism, levels rapidly decline from a peak at 4–5 hours. Breakdown of the collagen carrier releases further antibiotic (Gristina et al, 1988) with local levels remaining above minimum inhibitory concentration values for 28 days in animal studies (Gristina et al, 1976).

ANTIBIOTIC AND CEMENT MIXTURES

PMMA cement beads on a metal cable have proved a successful method of delivering antibiotics. These beads have a large surface area to volume ratio, and therefore release more antibiotic per mass of cement than solid PMMA spacers. A fixed formulation and dose of antibiotic in the pre-manufactured beads, as well as difficulty removing ingrown beads at subsequent surgery, has recently made them a less popular choice for the revision of infected joint replacements. The release of antibiotic from the cement is directly related to the concentration of antibiotic, the surface area for diffusion, the solubility of the antibiotic and the characteristics of the cement carrier.

Antibiotic-loaded cement prepared in theatre is a versatile option. The antibiotic choice and concentration can be modified according to the clinical situation and infecting organism if known. Where there is extensive bone loss precluding a mobile spacer, excellent stability can be achieved using an antibiotic cement spacer supported by Rush nails or other metallic implants in the medullary canals. This allows early patient mobilization following first stage knee revision, but soft tissue planes can still scar up rapidly compromising the range of motion following the definitive second stage reconstruction.

Inclusion of antibiotic in the cement allows delivery of therapeutic levels of antibiotic to the cement bone or cement soft tissue interface without causing significant systemic release or side effects. There have been no reports of systemic antibiotic toxicity from the use of antibiotic cement. Adding large quantities of antibiotics to the cement changes the physical characteristics of the cement making it more porous which increases the antibiotic elution rate. Vigorous mixing with the addition of air bubbles increases the cement porosity and affects both the elution characteristics and mechanical strength of the cement.

The formulation of the PMMA including the addition of antibiotic powder, along with the addition of barium, colouring agents and the technique for mixing the cement, all affect the

physical properties of the cement. Palacos (Smith and Nephew, Memphis, TN, USA) is the bone cement with the best elution characteristics in in-vitro studies (Marks et al, 1976). The addition of antibiotic powder up to 5% of the total cement mass has been shown to produce minimal affects on the mechanical properties of PMMA but when adding 12.5% antibiotic, the compressive strength is significantly affected (Lee et al, 1977). The recommended maximum amount of antibiotic is 2 g per 40 g packet of bone cement (5%) for permanently implanted prostheses, however, for temporary spacers, the long-term mechanical properties of the cement are less important allowing the addition of much higher concentration of antibiotics.

ANTIBIOTIC RESISTANCE

Resistance is a potential problem when using antibiotic-loaded cement. Antibiotic-resistant organisms are found in 88% of infected total hip implants where gentamicin-loaded cement is used in the primary procedure and in only 16% of patients where gentamicin is not added (Hope et al, 1989).

Bacterial biofilm glycocalyx increases resistance of bacteria to the host immune system and provides a niche for the development of antibiotic resistance. Bacteria that secrete a glycocalyx that enables them to adhere to implants are therefore more likely to develop antibiotic resistance (Donlan and Costorton, 2002). The problem bacteria include *Staphylococcus aureus*, coagulase negative staphylococci, particularly *Staph. epidermidis*, and *Pseudomonas* spp.

Bacteria involved in the race to contaminate the implant surface may be initially antibiotic sensitive, antibiotic resistant or antibiotic tolerant but inhibited. Tolerant inhibited bacteria can remain in the biofilm until they develop antibiotic resistance and cause a late infection.

REDUCING REVISION RATES

Antibiotic prophylaxis has, however, been shown to be effective in reducing revisions for infection following primary hip replacement. The Norwegian registry data compared four groups. Systemic antibiotics with antibiotic laden cement gave the lowest risk of revision for infection (0.14%). The relative risk increased by 4.3 times for systemic antibiotics alone, by 6.3 times for antibiotic cement alone, and by 11.5 times for no prophylaxis (Espehaug et al, 1997).

Infection in total joint replacements can be eradicated in over 90% of cases using a two-stage revision (Whiteside, 1994). However, historically the functional results following such revision have been poor (Cordero et al, 1996). Prolonged immobility leads to joint stiffness and muscle weakness that compromises the result even if the infection is eradicated. The use of mobile antibiotic-loaded cement spacers allows early joint motion and muscle activity that maintains function between surgical stages without increasing the risk of new or relapsing infection.

USE OF PROSTHESES

The PROSThesis of Antibiotic-Loaded Acrylic Cement (PROSTALAC) (Depuy/Johnson & Johnson, Needham, MA, USA) is a prosthesis made of antibiotic-laden acrylic bone cement that minimizes the amount of metal and plastic in the joint and maximizes the amount of antibiotic-laden cement. The system was first introduced in 1987 for knee revision, and various versions and techniques have evolved over the following decade based on the PROSTALAC design (Scott et al, 1993). The initial design involved the surgeon making a cement prosthesis with cement as the articulating surface. High friction and motion only to 75° flexion in knee spacers led to the introduction of metal on polyethylene articulation with a cement post to replace the posterior cruciate ligament function.

PROSTALACs are also used in the hip joint. Antibiotic-loaded cement can be used as a mobile spacer that maintains femoral length and provides a stable hip joint that allows improved mobility between staged hip revision for infection (Haddad et al, 1999).

SURGICAL TECHNIQUE

The surgical technique for the two-stage revision knee replacement requires removal of the infected prosthesis with all the acrylic bone cement, debridement of the infected soft tissue membrane, and thorough lavage. Five or more previously labelled samples are taken for microbiological examination from the infected interfaces, the capsule and the medullary canals before systemic antibiotics are started. The flexion and extension gaps, the prosthesis size and position can all be determined using most revision instruments and jigs. The articulated cement spacer is then manufactured in theatre. This restores the joint line and more normal joint mechanics allowing better function in the interval between stages.

Samples are cultured for aerobic and anaerobic bacteria and fungi, with the use of enrichment broth. Low grade chronic infections are often caused by organisms that are difficult to isolate. A positive late culture result may be difficult to distinguish between contamination, skin

commensal organisms and infection. A positive culture of the same organism from two or more specimens significantly increases the specificity of a positive result (Atkins and Bowler, 1998). An extended sensitivity profile of any positive result is required to confirm that the correct antibiotic was chosen for the cement spacer and for systemic use. This profile will also guide antibiotic prophylaxis at the stage 2 procedure.

Rand and Bryan (1983) reported an overall success rate of only 35% for the early reimplantation of a prosthesis 2 weeks following removal of the infected components. In a series of 44 patients treated between 1987 and 1994, Haddad et al (2000) demonstrated a recurrent infection rate of 5.4% and a reinfection rate of 5.4% giving a total infection failure rate of 10.8%. This is comparable to the infection failures in other series of non-mobile two stage revision total knee replacements. The range of movement averaged 5–91°, a mean increase of 21°, with the majority having complete pain relief following surgery.

FUTURE DEVELOPMENTS

A number of future developments are likely to have an impact on the management of the difficult problem of infected joint replacements. Exciting work in the field of gene therapy has the potential to modulate the production of the glycocalyx or slime by infecting bacteria. This has the potential to reduce the ability of bacteria to adhere and develop, thus allowing the host body to win the race for the surface, but it is not clear how this can be developed into a therapy (Donlan and Costorton, 2002). Development of an acrylic or other carrier that is less exothermic in its polymerization than PMMA may permit the use of thermally sensitive antibiotics or provide optimal carrier elution characteristics for different clinical situations. HM

KEY POINTS

- Infection remains a significant problem affecting between 1 and 2% of joint replacements.
- Polymethylmethacrylate bone cement can be used as a slow release carrier for antibiotics, for structural support, or for both, with antibiotics added as prophylaxis against the common infecting organisms and for treatment of established infections.
- The evidence supports the use of antibiotics in cement as prophylaxis and for treatment of established infections despite the risks of antibiotic resistance.
- The results of revision arthroplasty for infection using antibiotic cement in the form of cement beads, static spacers or mobile spacers such as PROSTALAC are now associated with infection eradication rates of over 90%.
- The mobile antibiotic spacers or PROSTALACs have been shown to eradicate infection as effectively as static spacers with better medium-term functional results.

Conflict of interest: none.

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