Antibiotic-loaded bone cement in total joint arthroplasty

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Periprosthetic joint infection is a devastating complication after total joint replacement. Prevention is mandatory and systemic antibiotic prophylaxis is nowadays a recognized cornerstone. Further addition of local antibiotics eluting from bone cement is a real possibility but its routine use is controversial. Pros and cons of its routine use in primary and revision total joint arthroplasty will be discussed.
Cement spacers carrying high doses of antibiotic(s) are currently accepted during two-stage treatment of infected prosthetic joints. Several issues such as alternatives to classic antibiotics, optimal dosages and others will also be explored.

Keywords : bone cements ; arthroplasty, replacement ; prosthesis-related infections ; anti-bacterial agents ; administration & dosage.

INTRODUCTION

Total joint arthroplasty (TJA) is one of the most successful procedures in orthopaedics and excellent results are expected in virtually all cases. Periprosthetic joint infection (PJI) is one of the most frequent and challenging complications after TJA *(6,7)*.

Polymethylmethacrylate or simply bone cement has been historically used as a carrier for local antibiotic therapy. Its ability to elute antibiotics has proven its value in the management of several forms of bone and joint infections including PJI. Antibiotic-loaded bone cement (ALBC) may be defined as low dose, containing up to 2 g of antibiotics per 40 g cement, or high dose. The former is usually recommended for prophylaxis while the latter is commonly used for treatment.

This review will focus on several aspects of the use of ALBC. The controversy surrounding the routine use of ALBC for prosthesis fixation in primary and revision TJA will be discussed. Even though cement spacers carrying high doses of antibiotic(s) are currently considered to be the standard of care for patients undergoing two-stage revision surgery, there are still uncertainties regarding several different practical issues that will also be addressed.

Antibiotic-loaded bone cement in primary total joint arthroplasty

Perioperative systemic antibiotic prophylaxis has gained an indisputable role in surgical site infection prevention and is now universally recommended *(1)*. Nevertheless routine local antibiotic prophylaxis using ALBC for prosthesis-bone fixation is still a matter of open debate.

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Effectiveness

There is increasing evidence showing that the use of ALBC delivering high concentrations of antibiotics locally is indeed effective in reducing the infection rate. There are two landmark studies. Both are large retrospective studies concerning total hip replacements : Espehaug *et al* (15) involving 10.905 arthroplasties and Engesaeter *et al* (14) including 22.170 arthroplasties. Both studies conclude that the use of ALBC together with systemic prophylaxis significantly lowers the risk of revision. A third recent (2008) large meta-analysis (38) that included 21.445 total hip arthroplasties from 6 studies, concluded that ALBC alone is similar to systemic antibiotics and suggested that the combination of ALBC and systemic antibiotics is probably the best choice, reducing the rate of infection by approximately 50%.

Unfortunately, information regarding total knee arthroplasty (TKA) is meager and not as compelling. Although *in vitro* studies do reveal the ability of ALBC to exhibit increased antibacterial activity in TKA (47) this may not be the case *in vivo*. The most frequently cited studies to show ALBC efficacy are the ones by Chiu and coworkers (9,10). The first included no more than 78 primary TKA in patients with diabetes mellitus (10) and a year later (9) results were published regarding 340 primary TKA. Both studies found that cefuroxime-impregnated cement was effective in the prevention of early to intermediate deep infection. Nevertheless, more recent papers conducted by Gandhi *et al* (18) and Namba *et al* (34) involving 811 and 2030 total knee replacements performed with ALBC respectively, failed to demonstrate superiority in reducing infection rates. However, these results should be interpreted cautiously because they were retrospective reviews with possible selection bias. In 2013, Hinarejos *et al* (24) published their results of a prospective randomized study with 2948 cemented total knee arthroplasties failing to show a decrease in the rate of infection with erythromycin and colistin-loaded bone cement. Again, these results should also be read carefully because this lack of benefit may be due to the less than optimal choice of antibiotics.

This lack of effectiveness regarding infection as an endpoint is also shown by Bohm *et al* (5) in a larger retrospective study including 20,016 TKA with non-ALBC and 16,665 with ALBC. Notwithstanding, they did find a significant higher proportion of revision for aseptic loosening in the non-ALBC group. Interestingly, Engesaeter *et al* (14) also found that the patients receiving systemic prophylaxis only had a 1.3 times higher risk of revision with aseptic loosening as the endpoint when compared to the systemic and ALBC combined regimen. These data raises the question of whether some "aseptic" loosening are really misdiagnosed subclinical low grade infections that are prevented by the use of ALBC.

Potential drawbacks

Despite the proven benefits just discussed, there are potential drawbacks associated with ALBC. This is why some authors advocate against its routine use and preserve it for revision surgery and high-risk primary cases (21).

A classical concern is that adding antibiotic to bone cement may have a negative impact on its mechanical strength. However it has been proven that the doses required for prophylaxis (< 2 g antibiotic per 40g cement) do not compromise the fixation which is the critical point to achieve a functional and painless joint (27). These results are further reinforced by the aforementioned studies that prove a lower incidence of aseptic loosening using ALBC (5,14).

A relevant concern is that ALBC may promote the emergence of antibiotic-resistant microorganisms. It is well known that ALBC has an optimal surface for colonization and that prolonged exposure to antibiotic in sub-inhibitory levels allows mutational resistance to occur (48). An in vitro study by Thomes *et al* (46) showed a lower overall rate of infection in the gentamicin-loaded cement group, but also a significantly higher rate of gentamicin-resistant germs in this group. Hope *et al* (25) on a study of 91 patients with deep infection of a cemented total hip arthroplasty demonstrated the use of gentamicin-loaded cement was significantly associated with the emergence of gentamicin-resistant coagulase-negative staphylococci. This concern is further reinforced by recent clinical studies that have found an increasing prevalence of gentamicin-

resistant microorganisms, especially coagulase-negative staphylococci, in prosthetic joint infections (35,39,45). A way to obviate this problem could be the use of two or more combined antibiotics. However this may considerably increase the concerns with potential toxicity and allergic reactions.

There are no significant reports of systemic toxicity or allergic reactions with the use of low-dose ALBC and this may be due to the fact that the most frequently used antibiotic worldwide is gentamicin that has an intrinsic low incidence of allergy. This may not be the case if other antibiotics such as vancomycin and cephalosporins become more popular. There are no studies showing advantage of a specific antibiotic, nonetheless there is a consensus that vancomycin should not be used in the context of prophylaxis and should be reserved for treatment purposes (22,27).

To this date, data on the use of ABLC in primary uncomplicated arthroplasty is mostly retrospective. It is not entirely clear whether the advantage of routinely using ABLC outweighs the potential disadvantage of promoting resistant microorganisms. Therefore a clear recommendation for or against its use in the general population cannot be made and we need to evaluate its cost-effectiveness as well as additional indirect costs.

Antibiotic loaded bone cement in spacers

Although numerous studies report favourable outcomes after one-stage revision surgery, two-stage has traditionally been considered as the gold standard for management of chronic infections (36). Two-stage exchange consists of debridement, resection of infected implants and placement of a temporary antibiotic-impregnated cement spacer and finally, delayed reimplantation of a new prosthesis after infection is deemed to be eradicated.

Rationale

There are two main goals behind antibiotic loaded cement spacers. The first is to provide direct local delivery of high doses of antibiotics. This allows for more effective treatment of infected poorly vascularized bone while avoiding systemic toxicity that can result from high dose intravenous therapy alone (28). The second is to decrease soft tissue contractures, maintaining joint stability and even mobility thus facilitating reimplantation surgery (33,40). Several different studies have confirmed infection eradication rates over 90% with the use of high dose antibiotic loaded cement spacers (12).

Choice of antibiotic(s)

Choosing the correct drug(s) is of paramount importance. They must possess certain characteristics in order to be effective after cement mixing. Thermal stability is one of them, as the polymerization of polymethylmethacrylate is an exothermic reaction. Other important characteristic is water-solubility, to permit elution into surrounding tissues, while allowing a gradual release over time for a sustained bactericidal effect (28). A last but relevant practical issue is that it must be available as powder since adding a liquid antibiotic to the cement mixture significantly decreases its mechanical strength (3,23).

Several antibiotics have been shown to be effective after cement mixing (Table I) (23,28). On the other hand, some potentially interesting antibiotics such as tetracyclines and rifampin lack antibacterial activity when mixed with cement (28).

It is feasible to manufacture a spacer choosing which antibiotics to use according to the causative microorganism. Nevertheless it is not uncommon to face an unknown pathogen. That is why commercial spacers and many surgeons aim for a broad antimicrobial coverage effective against most frequently isolated microorganisms such as Staphylococcus aureus and coagulase-negative staphylococci including methicilin- resistant and also gram negative microorganisms (43,49). By far the most frequently used and studied antibiotics in this circumstance are vancomycin and aminoglycosides such as tobramycin or gentamicin.

With methicilin and even vancomycin-resistance on the rise there has been increasing attention in the study of alternatives to vancomycin. One of them is daptomycin and it has been shown by Kaplan *et al* (30) that it is possible to load 2 g of daptomycin and 3.6 g of tobramycin into a 40 g packet of bone cement without any impact on its mechanical properties. Another antibiotic that has been studied *in vitro* is teicoplanin. Chang *et al* (8) studied the

Table I. — Antimicrobials frequently used in bone and joint infections that may be added into bone cement

Anphotericin B	Ciprofloxacin	Levofloxacin
Amikacin	Clindamycin	Linezolid
Amoxicillin	Colistin	Meropenem
Ampicillin	Daptomycin	Piperacillin/Tazobactam
Cefazolin	Erythromycin	Teicoplanin
Cefotaxime	Fluconazol	Tobramycin
Cefuroxime	Gentamicin	Vancomycin

antibacterial effects of daptomycin, vancomycin and teicoplanin loaded bone cement against methicilin-susceptible, methicilin-resistant and even vancomycin-intermediate Staphylococcus aureus strains. Interestingly, their results showed that all antibiotics maintain their antibacterial activities after cement mixing. They also revealed that teicoplanin-loaded cement presented better elution efficacy and provided longer inhibitory periods against all Staphylococcus aureus strains.

Unfortunately, unlike vancomycin that was shown effective in numerous studies, clinical trials on these antibiotics are scarce or even absent. Cortes et al (11) recently published a case report demonstrating the successful use of daptomycin-impregnated spacer in the treatment of recurrent prosthetic joint infection in a patient with multiple antibiotic allergies and past colonization with multiply antibiotic-resistant organisms. We ourselves have a similar successful case using daptomycin loaded hip spacer (unpublished results). Clinical studies or clinical reports on teicoplanin-impregnated spacers are to the best of our knowledge absent. There are, however, experimental animal model studies suggesting in vivo effectiveness (26).

Alternatives to aminoglycosides are also of great interest. Not only is gentamicin resistance on the rise (not only among staphylococci but also among gram negatives) but also powder gentamicin or tobramycin are increasingly difficult to find in some European countries for those who want to manufacture their own spacers.

Cephalosporins, piperacillin/tazobactam or carbapenems such as meropenem are potential alternatives but clinical evidence with these agents is still scarce. Koo et al (31) did use 2g of cefotaxime per 40g of cement along with vancomycin and gentamicin to impregnate spacers in a study of twenty-two patients with infected total hip arthroplasty, obtaining a 95% infection free rate at final average follow-up of 41 months. Park et al (37) used 4,5 g piperacillin/tazobactam and 2 g vancomycin in their spacers and achieved infection eradication in 32 of the 36 treated patients.

An in vitro study by Samuel et al (41) concluded that meropenem elutes in pharmacologically measurable concentrations from ALBC for a period of 3-27 days depending on the quantity of antibiotic added and remains active against Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli and Klebsiella pneumonia for a period of up to three weeks. There is also interesting evidence that combining meropenem and vancomycin broadens the antibacterial spectrum and enhances the elution of vancomycin in a mechanism described as "passive opportunism" (2,4). To the best of our knowledge there is only a case report on the use of meropenem-loaded cement in a one stage exchange prosthetic hip infection with good clinical outcome (42).

Dosage

One of the most important issues when manufacturing a spacer is to choose the ideal dose of antibiotic(s) that should be added to the cement. Ideally, it should allow for eradication of infection while limiting the emergence of resistant strains and minimizing toxicity. Although there is insufficient data to make a definitive recommendation about the ideal dosage of antibiotic loading, most authors and expert opinions agree it should range somewhere between 10 to 15% of total weight (4-6 g per 40 g of cement) (12,23,33,40). This much has been shown to

be necessary in order to keep antibiotic concentrations in the spacer membrane above minimum inhibitory concentration for several isolates after six weeks (*17*). The rule of thumb is, the more antibiotic(s) you add the less mechanical strength the spacer will have and vice-versa.

Safety profile

There are some reported cases of renal failure with the use of spacers containing high doses of vancomycin and aminoglycosides (*13,29*). Nevertheless, they are uncommon and the overall safety profile of such spacers has been well documented. A study by Evans *et al* (*16*) with 4 g of vancomycin and 4.6 g of tobramycin powder per 40 g of cement showed no toxicity or allergic reactions. Another study by Springer *et al* (*44*) showed no systemic toxicity or allergic reactions with the use of doses as high as 10.5 g of vancomycin and 12.5 g of gentamicin. In fact, it seems that levels of antibiotics in the joint may be as much as ten times the known toxic serum levels without toxic effects and thus be effective even in cases of more resistant organisms.

Antibiotic loaded bone cement in revision surgery

For a multitude of reasons, revision surgery is typically associated with increased risk of infection. In our opinion, this is enough to recommend ALBC use in every cemented revision surgery even in aseptic failures.

When the cause of revision is an infection, this statement becomes indisputable (*19,32*). A landmark review paper by Garvin and Hanssen (*19*) compared the outcome of more than 1,700 one or two-stage exchange hip arthroplasties performed using ALBC with more than 200 cases performed without ALBC. They found a significantly better success rate with the use of ALBC not only in one-stage but also in two-stage procedures. The same benefit of using ALBC during reimplantation was found in a later review paper concerning total knee arthroplasties (*32*). According to Gehrke (*20*) of the renowned ENDO-Klinik group, cemented implant fixation using topical antibiotics is the treatment of choice for single-staged procedures. Although there are several technical requirements for this strategy, it depends largely on preoperatively knowing the bacteria and it's susceptibly pattern as well as the availability of appropriate antibiotics for cement mixing. When these conditions are met, the one stage procedure offers about 85% success rate according to the ENDO-Klinik experience (*20*).

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