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REVIEW

Use of antibiotic-loaded cement in total knee arthroplasty

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Abstract

Bone cement has the capacity to release antibiotic molecules if any antibiotic is included in it, and these elution properties are improved as cement porosity is increased. *In vitro* studies have shown high local antibiotic concentration for many hours or few days after its use. Antibiotic loaded bone cement (ALBC) is helpful when treating an infection in total knee arthroplasty (TKA) revision surgery. The purpose of this paper was to review the evidence for the routine use of ALBC in TKA in the literature, its pros and cons. Many authors have recommended the use of ALBC also in primary TKA for infection prophylaxis, but the evidence based on data from National Registries, randomized clinical trials and meta-analysis suggest a protective effect of ALBC against infection when used in hips, but not (or only mild) in knees. A possible explanation to this finding is that the duration and quantity of locally elevated antibiotic levels after surgery are smaller in TKA, due to the smaller amount of cement used for fixation in TKA-only a layer in the bone surface. There are some concerns about the routine use of ALBC in primary TKA as prophylaxis against infection: Firstly, there is a risk of hypersensivity or toxicity even when the chance is highly improbable. Secondly, there is a reduction in the mechanical properties of the cement, but this can be probably neglected if the antibiotic is used in low doses, not more than 1 g per 40 g cement package. Another significant concern is the increased economic cost, which could be overlooked if there were enough savings in treating fewer prosthetic infections. Finally, there is also a risk of selection of antibiotic-resistant strains of bacteria and this could be the main concern. If used, the choice of the antibiotic mixed in ALBC should consider microbiological aspects (broad antimicrobial spectrum and low rate of resistant bacteria), physical and chemical aspects (thermal stability, high water solubility), pharmacological characteristics (low risk to allergic reactions or toxicity) and economic aspects (not too expensive). The most commonly used antibiotics in ALBC are gentamicin, tobramycin and vancomycin. In conclusion, there is a paucity of randomized clinical trials in the use of ALBC in primary TKAs and the actual

evidence of the effect of ALBC in reducing the risk of infection is insufficient. This, in addition to concerns about patient safety, risks of increase in the antibiotic resistance of microorganisms and the increase in costs in the procedure, lead us to recommend a cautious use of ALBC, perhaps only in high-risk patients (immunocompromised, morbidly obese, diabetic and patients with previous history of fracture or infection around the knee) unless the benefits of ALBC use were fully proven. Meanwhile, the rigorous use of peri-operative prophylactic systemic antibiotics and adoption of efficient antiseptic procedures and improved surgical techniques must be considered the gold standard in infection prevention in TKA surgery.

Key words: Antibiotic loaded cement; Antibiotic toxicity; Total knee arthroplasty; Infection; Prophylaxis; Economic cost; Antimicrobial resistance

Core tip: The bone cement capacity to release antibiotic molecules has been helpful in the treatment of prosthetic infections. Many authors have recommended the use of antibiotic loaded bone cement (ALBC) in total knee arthroplasty (TKA) for infection prophylaxis, but the actual evidence suggests a minimal, if any, protective effect against infection in TKA. There are some concerns against its routine use in primary TKA: The risk of toxicity, possible mechanical properties reduction, a significant increase in the cost of the cement, and the risk of selection of antibiotic-resistant bacteria. We recommend a cautious use of ALBC, perhaps only in high-risk patients, unless its benefits were better proven.

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INTRODUCTION

The development of an infection after a total knee arthroplasty (TKA) is a serious complication, which is difficult to cure with antibiotics because the biofilm mode of growth protects the infectious bacteria against the systemic antibiotics effects and the host immune system[1-3].

TKA infection usually requires revision surgery, causes significant limitation and less satisfaction in the patient[4], long hospitalization and very expensive procedures to treat it[5]. The usual rate of infection after TKA is 1%-2%[3,5,6], but the rates tended to decrease in the last decade probably because of an improved patient selection and patient optimization, increased awareness of correct systemic antibiotics and chlorhexidine decolonization protocols[7]. In the last years some authors in large retrospective series have reported deep infection rates lesser than 1%, using antibiotic-loaded bone cement (ALBC)[8,9] or without ALBC use[10].

Since the use of ALBC was introduced by Buchholz and Engelbrecht[11] in 1970 by adding gentamicin to the Palacos bone cement, demonstrating the helpfulness of polymethylmethacrylate (PMMA) as a carrier for topical delivery of antibiotics, the use of antibiotics in the cement has been widely used in the revision surgery of infected arthroplasties because its use seems to be helpful in the treatment of infection, and in non-infected revisions, where a higher risk of infection is well-known[12-14].

There is a consensus in using systemic antibiotics perioperatively to prevent TKA infection. An experimental study suggested that the use of ALBC with vancomycin might lengthen the duration of antibacterial activity in the joint from 28 to 40 h[15].

The use of ALBC in primary TKA to prevent infection varies in different countries. The percentage of orthopaedic surgeons routinely using ALBC in primary TKA is higher than 90% in countries such as the United Kingdom[16], Norway[17,18] or Sweden[4], although the scientific background for its use is uncertain[13,14], while its use is much lesser in other countries like the United States[19-22] and other European countries such as Spain, Poland or Russia[23]. Moreover, in many countries, such as Australia, the use of ALBC is increasing year after year even when the yearly report of the Australian National Joint Replacement Registry reports that the risk of revision for infection or the risk of revision for any cause are the same if an ALBC or a plain cement is used[24].

The use of ALBC to reduce the incidence of infection in primary TKA has been encouraged based on the Nordic National Registries of Arthroplasties results that showed a reduction in the rate of infection using ALBC, mainly in total hip arthroplasties (THA)[17,18,25]. Nevertheless, the evidence in TKA is lower than in THA: there is a small number of prospective studies that have evaluated the rate of infection in groups with plain cement or ALBC, and the results of them seem to be controversial[21,26].

The objectives of this article are: (1) To review the antibiotic elution properties of PMMA; (2) To update the available evidence supporting the routine use of ALBC in TKA based on its effect in reduction of deep infection and on risk of revision surgery for infection or for any cause; and (3) To highlight the main concerns about the routine use of ALBC in primary TKA: A possible reduction in the mechanical properties of the cement, risks of allergic reactions or toxicity because of the antibiotics, the risk of development of antimicrobial resistances, and the economic cost.

ANTIBIOTIC ELUTION PROPERTIES OF PMMA

During the polymerization reaction of bone cement

Table 1 Ideal properties of antibiotics to be used in antibiotic loaded bone cement

Broad antibacterial spectrum
Low percentage of resistant bacteria
Low protein binding
Low risk for allergic reactions
Low toxicity risk
High water solubility
Thermal stability
Chemical stability

there is an increase in temperature that causes the formation of air bubbles. Some of these bubbles escape from cement, but some other do not escape, causing some porosity in it. The final porosity of bone cement depends not only on the composition and method of manipulation, but also on the viscosity of the cement[2]. An increased cement porosity causes a decrease in the mechanical properties, but an increase in the capacity of the cement to release antibiotic molecules if any antibiotic is included in it.

The composition of different bone cements differs and so the potential for release antibiotics is not the same: Palacos cement seems to release higher gentamicin concentrations than other cements because of its high viscosity[27]. But the elution can be different with different antibiotics: CMW1 was better than Palacos and Simplex in the release of vancomycin[28].

The initial release after exposure of ALBC to a fluid is mainly a surface phenomenon, while sustained release over the next days is a bulk diffusion phenomenon[2]. The elution of antibiotics from ALBC has been advocated to be effective for many days[29], but some other authors sustain that the process is sufficient for only few hours[30,31]. Nevertheless, the hydrophobicity of the cement limits the antibiotic release at less than 10%, and most of this antibiotic is released during the first hours after surgery[2,32,33]. Three days after its use there is no effect of antibiotic in the ALBC in *in vitro* studies[33].

The elution can be improved by using liquid antibiotics instead of powder ones in the cement, but this choice creates a reduction in the compressive strength of the cement[34]. The use of vacuum-mixing of the cement causes a reduction in the cement porosity[2] and different effects on the elution properties of antibiotics in different commercially available cements[35]. However, the vacuum-mixing technique has been related to lesser quantity and size of bubbles in the cement, and the lesser porosity has been related to a worse elution of the antibiotic in the surrounding tissues[36].

The ideal properties of antibiotics to be used in ALBC are related in Table 1. The most commonly used antibiotics for its use in ALBC are aminoglycosides (mainly gentamicin and tobramycin)[36]. These antibiotics maintained their antibacterial properties after being mixed with PMMA, keeping a greater duration of the activity against most of the pathogen bacteria when *in vitro* analysed[37,38]. Another frequently used antibiotic in ALBC is vancomycin because of its activity against Gram-positive pathogens (the most frequent causes of TKA infection), but it lacks of any effect on Gram-negative[38].

The association of two or more antibiotics in the cement has been used for the treatment of prosthetic infection. The systemic use of more than one antibiotic is justified because of possible synergistic combination of antibiotics. Vancomycin and aminoglycosides (gentamicin or tobramycin) is a usual combination of antibiotics used in bone cement, and combining tobramycin and vancomycin in bone cement improves elution of both antibiotics *in vitro* and may translate into enhanced elution *in vivo*[39]. Nevertheless, there is no sufficient clinical experience in the use of more than one antibiotic in cement in the prevention of infection of TKA.

EFFECTS OF ALBC ON INFECTION PROPHYLAXIS IN TKA

Data from studies based on National Registries

In THA there are some studies from the Norwegian Arthroplasty Registry that have proven that the rate of revision because of infection and the rate of revision for any cause was lower if an ALBC was used, but all these data refer to hip surgery[18,25,40]. As far as we know, there is only one randomized study that has proved that gentamicin loaded cement was more effective in reducing the infection rate in THA than systemic antibiotics[41]. However, this reduction showed no statistical significance in a later revision of the same group with a longer follow-up[42].

In TKA, there is some evidence from the Finnish Registry[14] of a lower infection incidence if an ALBC was used in primary TKA, but the relative risk (RR) (1.35, 95%CI: 1.01-1.81) is much lower than the previously reported in THA. Moreover, data from other Registries do not support the Finnish data: in the Australian Registry in the short, mid or long-term follow-ups, when data from more than 100000 TKA were analysed there was no difference between ALBC and plain cement in the rate of revision because of infection (0.4%-0.5% at 1 year, 1.0% at 5 years, 1.3% at 13 years) or in the rate of revision for any cause (5.4% *vs* 5.3%, RR 1.07)[24]. In another recent analysis of two-year revision rates in the Canadian Joint Replacement Registry analysing more than 20000 TKA inserted with ALBC and more than 16000 with plain cement there were no significant differences between groups in total revision rates, even when age, sex, comorbidities and diabetes were standardized (1.40% *vs* 1.51%). The revision rates for infection were also similar in both types of cement[43].

Data from randomized trials and large comparative series

There is even more confusion when we analyse the

results of prospective studies. A randomized controlled trial (RCT) that compared cefuroxime loaded cement with plain cement in 340 TKA found a decrease in the deep infection incidence in the antibiotic group, but the deep infection incidence was higher in this study[26]. Two more papers from the same researchers recommended the use of ALBC in patients with a higher risk of infection: diabetic patients[44] and rheumatic patients[45].

On the other hand, some other studies have not found a decreased infection incidence if ALBC was used: in a large retrospective study including more than 22000 TKA Namba *et al*[46] did not find that the use of tobramycin or gentamicin loaded cement prevented infection after TKA in the general population (in fact the infection rate was higher in the group of patients treated with ALBC, even after a multivariate stepwise logistic regression analysis was done), or in the subgroup of diabetic patients[46]. In another prospective non-randomized study including 1625 TKA, Gandhi *et al*[21] was not able to find that the use of cement with tobramycin was associated with a decrease in the infection rate[21]. More recently, Hinarejos *et al*[47] in the larger randomized clinical trial about ALBC in TKA, analysing almost 3000 patients, found that ALBC with erythromycin and colistin does not decrease the incidence of global infection or deep infection, which is 1.4%, considered to be in the standards of infection incidence, not as the high incidence reported in the randomized study by Chiu *et al*[26].

Data from meta-analysis

A meta-analysis studied the efficacy of ALBC in THA and considered that the rate of deep infection could be reduced from 2.3% to 1.2% with its use. The RR of revision was also significantly reduced (0.72) when using ALBC in THA[48]. However, this effect has not been found in the knee in none meta-analysis.

Recently, a meta-analysis has studied the protective effect of ALBC in TKA and THA[49]. They found that the superficial infection rate was similar with ALBC and with plain cement. A reduced rate of deep infection could be found when analysing only the trials on THA, but there was no effect in the trials on TKA or in those including both hips and knees. The possible effect of antibiotics in the cement in hips is not necessarily the same as in knees. A second recent meta-analysis about the use of ALBC only in TKA has also failed to find differences in the deep infection rate including only RCTs or including also comparative trials with enough quality[50].

In summary, the evidence based on data from some Registries, RCTs and meta-analysis suggests a protective effect of ALBC against infection when used in hips, but not in knees. A possible explanation to this finding is that the duration and quantity of locally elevated antibiotic levels after surgery are smaller in TKA, due to the smaller amount of cement used for fixation in TKA (usually only a thin layer on the surface)[43].

MECHANICAL PROPERTIES OF ALBC

In vitro studies suggest that the addition of antibiotic to PMMA causes a decrease in the compressive and tensile strengths of bone cement by small quantities of antibiotic powder, and continues to decrease as doses of antibiotic increase[51]. It is widely accepted that high-dose ALBC (more than 2 g per 40 g of cement) should only be used in cement spacers or beads, which are used temporarily (usually some weeks) in the treatment of prosthetic infections because of the worsening of mechanical properties of the cement. For the prophylactic use of ALBC the antibiotic should be used at low doses, less than 2 g per 40 g of cement, because the main objective of the cement is the implant fixation[31,52]. Other authors are more restrictive and based on *in vitro* studies suggest not to add more than 1 g of antibiotic per 40 g of cement because of the decrease in the mechanical properties, which can be perceived with only 1 g of antibiotic[33].

The negative effect of antibiotics on the mechanical properties of the cement could appear even in the low-dose antibiotics when using some antibiotics such as imipenem[38], or if liquid antibiotic instead of powder is used[34,53].

The use of vacuum-mixing of the cement causes less porosity[35] and less reduction of the tensile fatigue strength of ALBC than hand-mixing[22,54]. Nevertheless, as it has been said before, the reduction in the cement porosity is desirable in terms of mechanical strength of the cement, but not in the antibiotic elution properties.

When the aseptic loosening has been analysed comparing ALBC and plain cement, trying to refuse a negative effect of adding low doses of antibiotics on the mechanical properties of PMMA, there was not a significant difference in the incidence of aseptic loosening when using one or the other type of cement[26]. In radiostereometric analysis studies there were no significant differences in prosthetic subsidence between both types of cement in hips[55] or between different ALBC in TKA[56]. Finally, the results from the Norwegian Arthroplasty Register found that the use of ALBC does not decrease the survival rate of hip replacements compared to plain cement[18], suggesting a good mechanical performance in a wide clinical setting.

RISK OF TOXICITY OF ALBC

Bone cellular toxicity of ALBC

Some experimental studies have evaluated the negative effects of some antibiotics on the osteoblasts derived from trabecular bone and have found decreased levels of alkaline phosphates suggesting cellular toxicity, mainly by gentamicin[57,58]. Nevertheless, probably the concentrations necessary for this cellular toxicity are not achieved when ALBC is used *in vivo* in low doses with prophylactic purposes[52].

Renal toxicity of ALBC

A study found that almost half of the studied patients after using ALBC had detectable aminoglycoside serum concentrations, mostly in high-doses antibiotics cement spacers, but also in some primary surgery cases after low-doses antibiotics ALBC. Many of these patients had an elevation in serum creatinine, so the authors recommended measuring aminoglycoside serum concentrations in the early postoperative period and further monitoring of some patients[59]. On the other hand, Springer *et al*[60] studied the risk of using high doses of antibiotics (gentamicin and vancomycin) in cement spacers for treatment of infected TKA and they concluded that both antibiotics seem to be clinically safe when used locally in ALBC spacers[60].

Patrick *et al*[61] described two cases of acute renal failure after the use of ALBC incorporated in THA. Both patients received antibiotic-laden spacers and subsequently developed acute renal failure in conjunction with elevated serum tobramycin concentrations, suggesting antibiotic toxicity. Several other case reports of acute renal failure associated with the use of ALBC have been reported[62-64]. As ALBC with vancomycin and/or aminoglycosides has the potential for systemic toxicity, it should be used according to guidelines and with monitoring in patients at increased risk for nephrotoxicity[61].

In any case, the risk of nephrotoxicity related to local delivery of antibiotics in the bone cement is much lower than with systemic antibiotics[65] and has been neglected when used in low doses[66,67]. All the reported confirmed cases of acute renal failure happened in cases of infected arthroplasties when an ALBC spacer was used. The risk is much lower in prophylactic use of ALBC for primary fixation of TKA, because the dose of antibiotic in the cement and the amount of cement used are usually lower.

RISK OF ALLERGIC REACTIONS

Antibiotics contained in ALBC, though at low levels, are systemically absorbed and can potentially cause allergic reactions. Particular attention should be paid to an individual's antibiotic allergy history prior to implantation of any ALBC.

The most frequently used antibiotics in ALBC are aminoglycosides (gentamicin and tobramycin), which very rarely cause allergic reactions. The possibility of an allergic reaction may become greater if other antibiotics such as cephalosporins are used[68].

Recently, a case of systemic hypersensitivity reaction to vancomycin-loaded bone cement causing a diffuse painful desquamating rash has been reported in a patient with a prior history of Stevens-Johnson reaction to vancomycin[69]. Antibiotics to which a patient has had a potentially life-threatening reaction should not be used in ALBC.

DEVELOPMENT OF ANTIMICROBIAL RESISTANCE

There is an increasing concern in the emergence of drug-resistant organisms. No direct evidence links the development of bacterial resistance to the routine use of ALBC in primary arthroplasties and some authors do not believe that this risk is increased[67].

On the other hand, there is some evidence supporting the concern about antimicrobial resistance and the risk of selecting resistant mutans bacteria*: in vitro* studies show up to 8% of the antibiotic in ALBC is quickly released after surgery, and thereafter there is a low-dose release, that may not be effective at fighting infection, but can cause antibiotic microbial resistance. Some experimental studies have shown the capacity of many usual TKA pathogens to grow on different ALBC. Prolonged exposure to antibiotic at a dose concentration below the inhibitory one allows the development of mutational resistance in bacteria[2,30]. The use of cement with gentamicin for first implants was associated with the development of coagulase-negative staphylococci resistant to gentamicin[70]. Josefsson *et al*[42] found that 88% of the infected patients who had received gentamicin-loaded cement in primary arthroplasty harboured at least one gentamicin-resistant isolate. Aminoglycoside (gentamicin and tobramycin) resistance rate is higher if an antibiotic spacer is used in 2-stages revision arthroplasty[71], suggesting that the risk of selecting resistant mutans when using ALBC is real.

In a large series of patients Hansen *et al*[7] found that the introduction of routine ALBC in TKA in a hospital did not cause any significant change in the infecting pathogen profile or any alarming increase in antibiotic resistance, but they recognized that the sample size of the infected cohort might not be big enough[7].

CLINICAL DECISION MAKING

Another problem with the use of ALBC relates to clinical decision making. It has been proved that the antibiotic contained in old cement mantles may influence the reliability of cultures taken from the joint fluid[72] as well as from tissues during revision surgery[32]. It is important to consider the presence of antibiotics in the cement mantle of patients with TKA when evaluating aspirate and tissue cultures to decide if a TKA failure is aseptic or septic.

ECONOMIC COST OF ALBC

The additional cost of using commercially available ALBC with tobramycin has been considered 210 USD if one 40-g packet of PMMA is used and 420 USD in case of using two packs[73]. The increase in the cost per package was even greater than 300 USD in another study[21], so the resulting extra-cost of using 2 packages

is considered to be 600 USD[68]. The economic cost of routinely using ALBC in all primaries TKA could be reduced in a very significant way by hand-mixing the antibiotic with the PMMA[9,73], but the elution characteristics and mechanical properties of this hand-made ALBC could be affected.

The additional cost in the cement used for prophylaxis of infection could be compensated if it was really useful in decreasing the risk of infected TKA[67], as the costs for revision of a TKA for infection has been considered to be about 50000 USD[22], and even higher than 100000 USD in some countries[74].

A cost-effectiveness analysis considering revisions due to infection in THA according to the Norwegian Arthroplasty Register data[75] concluded that using ALBC in all primary hips is not cost-effective unless the RR for infection using plain bone cement was > 2.4 than using ALBC, but this is not the case[68]. Another cost-effectiveness analysis stated that a decrease of 1.2% in the rate of TKA infection is necessary to recover the extra costs of the routine use of ALBC[23]. Considering that the protective effect of ALBC in TKA is, according to the available prospective studies and Register studies much less (if any), the routine use of ALBC in economic terms is not justified.

From a merely economic point of view, the use of ALBC might only be justified in high risk groups of patients such as those having rheumatoid arthritis[45], immunodepression, morbid obesity[76-78], and diabetes[78-80], or patients with previous history of infection or fracture in the knee, and those having long surgeries[6,14,81,82], groups where a much higher infection rate than the average could be expected. Moreover, a recent study stated that the use of ALBC in primary TKA might not be justified even in the group of patients considered as high risk[10].

CONCLUSION

Bone cement has the capacity to release antibiotic molecules if any antibiotic is included in it. *In vitro* studies have shown high antibiotic concentrations for many hours or few days after its use. The use of ALBC is helpful in the treatment of infection in revision TKA. If used for infection prophylaxis, the choice of the antibiotic should consider microbiological, physical, pharmacological and economical aspects. The most commonly used antibiotics for prophylaxis in ALBC are gentamicin and tobramycin.

Many authors have recommended the use of ALBC in TKA for infection prophylaxis, but the evidence based on data from National Registries, randomized clinical trials and meta-analysis suggests a protective effect of ALBC against infection when used in hips, but not (or only mild) in knees. A possible explanation is that the quantity of locally delivered antibiotics after TKA is small.

There are some concerns about the routine use of ALBC in primary TKA: the risk of toxicity or hypersensivity, the possible reduction in the mechanical properties (that can be neglected if used in low doses), a significant increase in the cost of the cement, and the risk of selection of antibiotic-resistant bacteria.

There is a paucity of randomized clinical trials in the use of ALBC in primary TKAs and the actual evidence of the effect of ALBC in reducing the risk of infection is insufficient. This, in addition to concerns about patient safety, risks of increase in the antibiotic resistance of microorganisms and the increase in costs in the procedure lead us to recommend a cautious use of ALBC, perhaps only in high-risk patients (immunocompromised, morbidly obese, diabetic and patients with previous history of fracture or infection around the knee) unless the benefits of ALBC were better proven. Meanwhile, the rigorous use of peri-operative prophylactic systemic antibiotics and the adoption of efficient antiseptic procedures and improved surgical techniques must be considered the gold standard in infection prevention in TKA surgery.

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