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Prophylactic use of antibiotic-loaded bone cement in primary total knee replacement

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Abstract Despite significant advances in intraoperative antimicrobial procedures, deep infection remains the most devastating complication following total joint arthroplasty. Clinical studies' results and safety profile of antibiotic-loaded bone cement are discussed in this review. Antibiotic bone cement prophylaxis is a safe and effective strategy in reducing the risk of deep infection following primary total joint arthroplasty.

Keywords Infection · Total knee arthroplasty · Antibiotic-loaded cement

Introduction

Deep infection is one of the most devastating complications following total knee arthroplasty [14, 21]. The risk of infection is greater following total knee arthroplasty than in those of hip arthroplasty [8, 29]. The incidence of deep infection after total knee arthroplasty shows a variable trend, with a range that varies between 1.7 and 12.4% [3, 10, 35]; these values increase considerably in revision of total joint arthroplasty. An infected total knee arthroplasty leads to an unhappy patient, a surgeon with a tarnished reputation and an event that is extremely costly to treat. In an attempt to reduce the risk of infection, many orthopaedic surgeons have introduced antibiotic-loaded bone cement in their clinical practice, using it strategically both for primary and for revision joint arthroplasty. Use of antibiotic-loaded bone cement is becoming standard practice in northern European countries [4, 27, 42], but in several other European countries its use is still a matter of debate (Figs. 1, 2). Since 2003, the Food and Drug Administration (FDA) in the United States has approved its use, fixing precise doses [4].

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Safety profile of antibiotic-loaded bone cement

Antibiotic-loaded bone cement is an effective delivery method for local antibiotics, both for prophylaxis and treatment of deep infections following total joint arthroplasty [5]. The bactericidal activity of the antibiotic-impregnated bone cements proves to be highly effective for at least 7–10 days after the implant and in some studies for more than 10 years [4, 5, 9, 29, 38]. The various antibiotic-loaded bone cements differ not only by type and concentration of antibiotic present, but also by their elution kinetics of local diffusion. The antibiotics that can be used in bone cement preparation are various, in accordance with the particular sensitivity sought, and include penicillin, gentamycin, erythromycin, cephalosporines, tobramycin, vancomycin, cefuroxime, oxacillin, colistin, etc. However, the antibiotic present in the bone cement must be thermo-stable, in such a way as not to undergo structural, and therefore functional, modifications following the

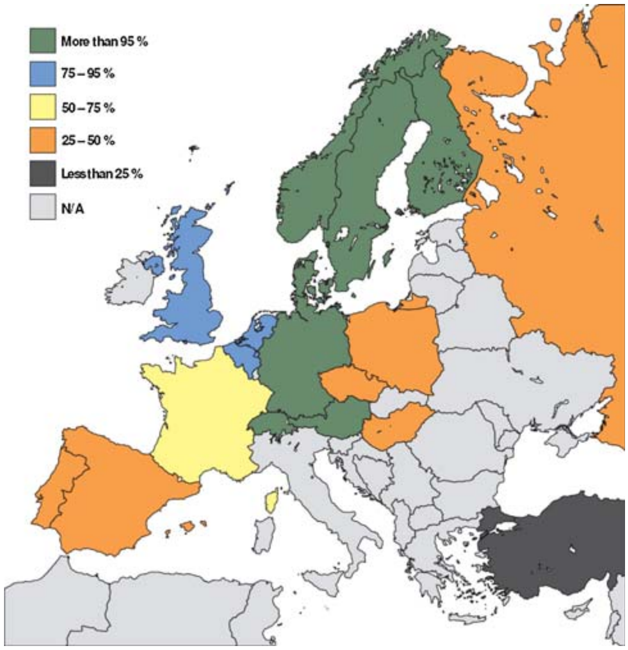


Fig. 1 Percentage of TKR implants in Europe (Data on File, Biomet Cements, Sweden)

exothermic reaction of polymerization of the same acrylic cement (Table 1).

Antibiotic-loaded bone cements are commonly classified as "high dose" cements if they contain more than 2 g of antibiotic per 40 g of cement and "low dose" if they contain less than 2 g per 40 g of cement. Some authors suggest that a dose of at least 3.6 g of antibiotic is desirable for effective elution kinetics and a better therapeutic effect [15, 33]. Among all the antibiotic-loaded cements present on the market, Palacos (Biomet Deutschland, Darmstadt, Germany) has shown more favourable elution kinetics [11,

Table 1 List of thermo-stable antibiotics used in antibiotic-loaded bone cements

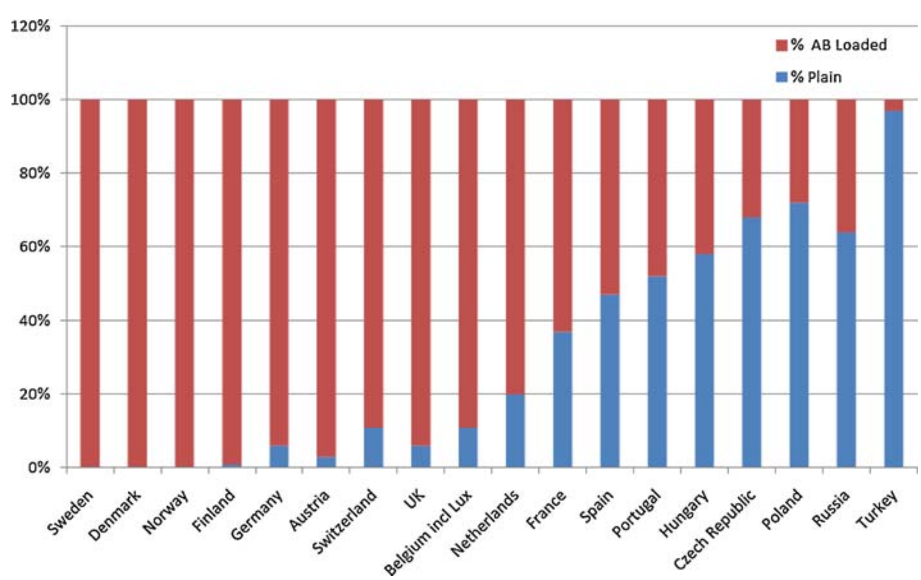
Gentamycin	Colistin
Clindamycin	Methicillin
Cefalotin	Tetracycline
Tobramycin	Lincomycin
Erythromycin	Dicloxacillin
Oxacillin	Vancomycin
Cefuroxime	Trimetoprim

15, 33]. Concentrations of antibiotics released from Palacos's Cement Depot are sufficient to penetrate dead cortical bone [11]. High dose bone cements are used to prepare antibiotic-loaded beads or spacers in the presence of active infection. Low dose bone cements are used as prophylaxis or treatment for the fixation of prosthetic implants [16, 17].

Despite antibiotic-loaded bone cement having the advantage of reducing the risk of deep periprosthetic infection, routine use of this material might mean certain, potential disadvantages from a clinical point of view. The main disadvantages are the development of an allergic reaction, local and systemic toxicity, changes to the mechanical properties of the bone cement, emergence of phenomena of antibiotic resistance and cost.

In regards to the concerns that antibiotic-loaded bone cement, by virtue of its progressive and continuous release of antibiotics, may be harmful for the organism; currently there are no significant studies that confirm this hypothesis. In an in vivo study carried out by Wahlig et al. [41], in which Palacos R (Biomet Deutschland, Darmstadt, Germany) antibiotic-loaded bone cement was used to fix orthopaedic prostheses, the gentamycin concentration detectable from the superficial and deep drains was,

Fig. 2 Use of antibiotic loaded vs. plain cement in Europe in the year 2007 (Data on File, Biomet Cements, Sweden)



respectively, 50 and 10 μg/ml on the first day after surgery. On the second day, this concentration had dropped to a quarter of the value, initially. Concurrent serum concentrations plummeted to below 1.5 μg/ml, but on the second day they were no longer detectable, suggesting that soft tissues constitute a barrier to gentamycin diffusion. From this study, it is evident that the risk of toxicity is negligible when a low dose of antibiotic-loaded bone cement is used.

The effects of the antibiotic on the mechanical properties of the cement have been the subject of study for a number of different authors. The use of antibiotic-loaded bone cements containing more than 2 g of antibiotic is highly detrimental to the mechanical properties of the cement itself [2, 21]. The antibiotic-loaded bone cement used in clinical practices is low in dosage. This type of cement not only has a negligible and inconsistent reduction of the static and fatigue strengths compared to the conventional type [8, 25, 29], but also has a normal prosthetic fixation, the latter being evaluated by means of radiostereometric analysis [1]. Lewis et al. [25] have demonstrated that the addition of gentamicin sulphate powder (4.22 wt/wt%) does not degrade the mechanical, physical and thermal properties of commercially available cement brands widely used in total joint replacements.

Antibiotic-loaded bone cement maintains its mechanical properties if it is correctly prepared with suitable vacuum systems [23, 24]. The use of vacuum mixing systems, compared to manual procedures, lowers the presence of air in the cement, and therefore its porosity, thus reducing the risk of aseptic loosening of prosthetic knee implants [28]. Mau et al. [30] carried out a study of six different mixing systems present on the market, four common and two of recent introduction, with as many antibiotic-loaded bone cements, to assess the ease of handling and reliability of the systems, and the degree of porosity and torsion strength of each cement. This author states that the best performance was obtained with the Cemvac and Optivac systems, which show both a reduced formation of micro (<1 mm) and macro (>1 mm) pores and, therefore, a reduced lack of structural homogeneity. They also demonstrated a high torsion strength (>63 MPa) of the antibiotic-loaded bone cements, if compared with manual mixing systems without a vacuum. Mau [30] closely correlates the formation of pores, both with the design of the mixing system and with the duration and quantity of vacuum applied, in the presence of a minimum application of 0.5 bar. Furthermore, according to this author, all the antibiotic-loaded bone cements used pass the minimum strength level, fixed at 50 MPa as envisaged by the ISO 5833 standard, necessary to obtain an optimal strength.

In regards to the possible development of allergic reactions, in the literature there are no episodes associated with use for prophylaxis purposes of antibiotic-loaded bone cement containing gentamycin or tobramycin [4, 15, 34, 40]. Bourne [4] states that in more than 100,000 prosthetic implants, in which antibiotic-loaded bone cement was used, no allergic phenomenon occurred. Instead, the presence of allergic phenomena was pointed out following medication by systemic means with cefuroxime but not in association with antibiotic-loaded bone cement [7]. The continual growth in the use of antibiotics in cements might lead to the emergence of allergic reactions by the organism, following which removal of the cement and the entire prosthetic implant would be determined [15].

Another potential disadvantage is represented by the onset of the phenomena of drug resistance. This attention is mostly focused on methicillin-resistant staphylococci and vancomycin-resistant enterococci. Cement is an ideal surface for adhesion, colonization, and bacterial growth, in that it allows the formation of a biofilm which isolates the micro-organism from the surrounding environment; the formation of the biofilm transforms the bacterium from a "planktonic" phase to an "adhesion" one [19, 26, 31]. Antibiotic-loaded bone cement, and in particular that containing gentamycin, has shown greater effectiveness in reducing these biofilms on the surface, and according to certain authors, this mechanism is not correlated to the kinetics of diffusion [15, 19, 22, 39]. Furthermore, the use of antibiotic-loaded bone cement, due to its slow, long-term release, would lead to a prolonged exposure to the antibiotic with insufficient inhibitor levels, so much so as to generate genetic modifications in the micro-organism itself, thereby starting off the mechanism of drug resistance [2, 15, 19, 36]; this mechanism is still in the study phase, in that it has not been confirmed by completely satisfactory results. Hendriks et al. [19], who maintains the effectiveness of antibiotic-loaded bone cement in prosthetic implants, states that drug resistance may occur, only in a haematogenous way, years after the implant, and at the time of infections by coagulase-negative staphylococci of the CN5115 strain. The same author states that in case of revision of prosthetic implants in which antibiotic-loaded bone cement containing gentamycin was used, it would be preferable to use a cement with a different antibiotic. Gallo et al. [13], following an in vitro study, states that the association of vancomycin with the gentamycin present in low-dose cement is an excellent protection against prosthetic infections, especially in the presence of resistant staphylococci.

Compared with the cost of plain bone-cement products, the cost of equivalent antibiotic-loaded bone-cement products has become increasingly volatile in recent years [20]. The overall health-care costs for the routine use of antibiotic-loaded bone-cement would be $60,000 for every 100 patients (at a $300 increased cost per packet) if two packets of cement were used for each joint replacement. At about $50,000 for the treatment of an infection at the site of a total joint replacement [20], the 1.2% rate of decrease for infections is sufficient to recover all costs for the routine use of antibiotic-loaded bone cement. The additional indirect costs of lost productivity and long-term disability, the potential costs of legal actions and the cost of plain bone-cement more than justify the cost of antibiotic bone cement prophylaxis.

Profile of effectiveness and choice of antibiotic-loaded bone cement

Antibiotic-loaded bone cement has been used for more than 30 years for the fixation of prosthetic implants. The antibiotic present in the cement has a direct action on the micro-organism, diminishing the probability of an infection and increasing the effectiveness of systemic treatment. The mechanism with which the antibiotic is released by the cement is not understood very well; however, one supposes that at the base there is a mechanism of diffusion on the surface, and that the quantity released locally is correlated to the composition of the cement, its porosity, concentration, the preparation technique, the section of the surface in contact with biological fluids and to the intrinsic characteristics of the antibiotic present [32, 37]. Release of the antibiotic is strictly time-dependent and biphasic, with a peak in the first hours, followed by a slow and progressive decrease that can be measured in months or years [18]. The release of antibiotic is incomplete and is mostly confined to the surface of the cement; this aspect may be traced back to the absence of communications between the internal part of the cement and biological fluids.

The antibiotic used most is gentamycin, by virtue of its broad-spectrum bactericidal effect, its stability at high temperatures and the low incidence of allergic responses [34, 40]. In an in vivo study carried out by Hendriks et al. [18] on the release of gentamycin from the Palacos Cement (Biomet Deutschland, Darmstadt, Germany), one assumes that the concentration of this antibiotic in proximity of the prosthetic implant is 1000 times greater than the minimum inhibiting concentration (MIC) for staphylococci, which is 4 μg/ml.

Discussion

Several prospective and retrospective clinical studies have been carried out to assess the effectiveness of antibiotic-loaded bone cement as prevention for infections following surgery for primary arthroplasty.

In a retrospective study, Buchholz et al. [6] observed that the infection rate of 6% in a historical control group of primary total joint replacements without antibiotic-loaded cement was reduced to 1.6% in a group with prophylactic usage of Palacos gentamicin-laded bone cement.

Through a prospective and randomized study, Chiu et al. [7] assessed 340 primary total knee arthroplasties fixed with cement containing Cefuroxime as an antibiotic and conventional cement. The patients, undergoing surgery in an operating theatre without laminar flows or ultraviolet light, were divided into two groups: the first of 178 patients, where antibiotic-loaded bone cement was used; the second of 162 patients, where fixing took place using simple cement. Despite the small sample, the author points out a significant reduction of infections in the sample with antibiotic-loaded bone cement, where no case of infection was found; a different situation was found in the second sample, where five cases of infection developed. In another article, the same author reports a study on 78 high-risk patients, in that they were affected by diabetic pathology, in which antibiotic-loaded bone cement was used for the prosthetic fixation. Also in this case, the use of antibiotic-loaded bone cement had prevented the development of infections.

In a retrospective study, Espehaug et al. [12] reports the results of the Norwegian Registry on 10,905 cemented primary total knee arthroplasties. The patients were divided into four groups on the basis of the type of prophylaxis: the first group was treated with systemic antibiotic and antibiotic-loaded bone cement, the second with only systemic antibiotic, the third only with antibiotic-loaded bone cement and the fourth underwent no prophylaxis whatsoever. The author states that at a 5-year follow-up, only the association of antibiotic-loaded bone cement with a systemic therapy is an efficient strategy to reduce the risk of infections, especially if gentamycin is used in the cement.

Another retrospective study was carried out by Malchau et al. [27, 28], which analyses the results of the Swedish Registry on 92,675 primary hip arthroplasties carried out between 1978 and 1990. The author states that the laminar flows of operating theatres and the use of antibiotic-loaded bone cement with gentamycin were the only significant factors that reduce the incidence of deep infections. What is more, according to Malchau, the use of Palacos G (Biomet Deutschland, Darmstadt, Germany) as antibiotic-loaded bone cement showed itself to be the most effective in reducing the rate of revision, and that the use of antibiotic-loaded bone cement in prosthetics has an advantageous cost/benefit ratio; it enormously reduces the costs due to revisions.

Through a retrospective study, Bourne [4] assesses the percentage of infections in 1,161 patients undergoing surgery for knee replacement. Bourne divides the sample into two groups: the first group made up of 493 patients, underwent surgery in an operating theatre without laminar flows, using Simplex cement (Striker Howmedica Orthopaedics, Mahawah, New Jersey, USA) associated with erythromycin and colistin; the second group underwent surgery in an operating theatre equipped with laminar flows, using cement without an antibiotic. In both groups, the rate of infection was of 0.6%; this value brings the author to the conclusion that the use of antibiotic-loaded bone cement is as effective in the prevention of infections as the use of laminar flows.

Conclusion

The randomized, prospective and retrospective clinical studies present in the literature have confirmed the effectiveness of the use of antibiotic-loaded bone cement in the prevention of deep infections in the first implant, without affecting the prosthetic outcome. This use becomes even more necessary and proper in the presence of operating theatres lacking systems of clean air, such as laminar flows or ultraviolet light, and in high-risk patients such as those with a compromised immune system (rheumatoid arthritis, LES, immunodepression, psoriasis, tumours), those having undergone antibiotic therapy within the year, diabetics, those over 75 years old and those undergoing revision surgery. The cost of the antibiotic-loaded bone cement is a problem that still requires greater attention in the future. The potential risks associated with the use of antibiotic-loaded bone cement have not materialised, but need a careful and continuous surveillance activity, especially in terms of drug-resistance.

In our opinion, the use of antibiotic-loaded bone cement, in association with a systemic therapy, is a valid strategy to prevent and "fight" an issue that continues to afflict the orthopaedic surgeon, such as post-surgical infection. Anyway we believe that this "weapon" certainly must not lead to failure to comply with the absolute principles of surgical sterility.

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