

ОБЗОРЫ И РЕЦЕНЗИИ

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Antibiotic-loaded bone cement and its widespread use: is it justified?**Giovanni Calonego**

Tecres SpA — Sommacampagna (VR), Italy

Along with a steady rise in the volume of joint prostheses implanted every year worldwide, there has been a rise in revision after total hip arthroplasty (THA) and total knee arthroplasty. Among the main reason for THA revision, infection accounts for 12.0–25.2 %. Nowadays the use of antibiotic-loaded bone cement (ALC) with the aim to reduce periprosthetic joint infection (PJI) has greatly increased. The use of ALC in primary prosthesis fixation is still debated. So in order to be able to provide a reasonable and scientific answer to this question one should first analyze data from scientific literature. In terms of prophylaxis, it was demonstrated in many investigations that the combined use of systemic antibiotic and ALC in THA was producing the lowest risk of revision due to infection. The release of antibiotic from ALC has a well known kinetics, with a peak release during the first days followed by a long tail of lower release. The choice of adding an Aminoglycoside (Gentamicin) was based on release studies which demonstrated that among antibiotics Gentamicin was showing the best elution performances from the bone cement, the most extended spectrum of activity and no negative effects on mechanical performances. As regards possible problems associated with the presence of antibiotic in bone cement the following should be considered: systemic toxicity, hypersensitivity reaction, mechanical hazards, bacterial resistance hazards and cost rising. In conclusion, the use of ALC must be considered as a support strategy in prevention and not the solution of infections; in primary implants, ALC is justified only in high risk patients; it is recommended for revisions; the perfect antibiotic in ALC does not exist; avoid using Vancomycin as first step; ALC is successful only if associated with systemic antibiotics. Key words: total hip arthroplasty, total knee arthroplasty, antibiotic-loaded bone cement, periprosthetic joint infection.

Наряду с ростом количества эндопротезов, имплантируемых в мире каждый год, наблюдается увеличение ревизионных вмешательств после тотального эндопротезирования тазобедренного (ТЭТБС) и коленного суставов. Среди основных причин таких операций на долю инфекционных осложнений приходится 12,0–25,2 %. Сегодня значительно увеличилась частота применения насыщенного антибиотиками костного цемента (НАКЦ) для профилактики и борьбы с перипротезной инфекцией. Целесообразность его использования при первичном эндопротезировании дискутируется. Чтобы получить обоснованный ответ на этот вопрос, проанализированы данные научной литературы. Показано, что комбинированное применение антибиотика системного действия и НАКЦ при ТЭТБС обеспечивает самый низкий риск ревизионных операций вследствие инфекции. Кинетика высвобождения антибиотика из НАКЦ хорошо известна: пик приходится на первые дни после операции с последующим длительным менее активным выбросом. Выбор для насыщения антибиотика из группы аминогликозидов (гентамицина) основан на результатах исследований, выявивших у него наилучшую способность высвобождения из костного цемента, широкий спектр действия и отсутствие негативного влияния на механические свойства. Среди возможных проблем, связанных с применением НАКЦ, следует отметить системную токсичность, реакции гиперчувствительности, опасность механического повреждения и бактериальной резистентности, повышение стоимости. Вывод: использование НАКЦ следует рассматривать как стратегию профилактики развития и распространения инфекции при ревизионных операциях. При первичном эндопротезировании применение НАКЦ оправдано только у больных группы риска. Нет идеального антибиотика для НАКЦ, а его использование успешно только в комбинации с антибиотиками системного действия. Необходимо исключить Ванкомицин в качестве первого назначения. Ключевые слова: тотальное эндопротезирование, тазобедренный сустав, коленный сустав, насыщенный антибиотиками костный цемент, перипротезная инфекция.

Key words: total hip arthroplasty, total knee arthroplasty, antibiotic-loaded bone cement, periprosthetic joint infection**Introduction**

Total hip and total knee arthroplasty (THA, TKA) are clinically efficacious and cost-effective interven-

tions with numerous investigators reporting excellent long-term results in terms of reducing pain and improving function and quality of life in patients with

debilitating hip and knee disease [20, 21]. Along with a steady rise in the volume of joint prostheses implanted every year worldwide, there has been a rise in revision THA and TKA [10]. Among the main reason for THA revision, infection accounts for 12–14.8 % [20], while for the TKA the percentage is much higher, 22–25.2 % [21]. Periprosthetic joint infection (PJI) is therefore among the main reason for revision.

Improved surgical techniques, the adoption of stringent and efficient antiseptic pre-operative and intra-operative procedures and the optimization of peri-operative systemic antibiotic prophylaxis has led to a significant reduction of deep infection and subsequent revision from 5–10 % to 1–2 % during the last 20 years [1]. ALC was introduced in the early 70s by Buchholz [15] with the aim to reduce PJI.

Nowadays the use of antibiotic-loaded bone cement has greatly increased: it has become standard practice in northern European countries, while in several other European countries its use is still a matter of debate [19]. In US, ALC has only been approved in 2003 and, despite the approved intended use would only cover the second stage following a septic revision, ALC use has currently exceeded 25 % of the total bone cement market.

Antibiotic in bone cement prevents bacterial adhesion: bacterial adhesion is the first step towards bacterial colonization, multiplication and formation of a biofilm. Bacterial growth on implants depends on biofilm production: the higher the roughness of the material, the higher the bacterial adhesion. PMMA is characterized by a rough surface. Bacteria resistance to antibiotic effect and immune host system is 1000 times higher in biofilm [11]. The aim is therefore to avoid to get to this point when biofilm forms, leading to a chronic infection where the implant will have to be removed.

As previously said, the use of ALC in primary prosthesis fixation is still debated, so in order to be able to provide a reasonable and scientific answer to the question «is the widespread use of ALC justified?» we should first answer to a number of other questions: 1) what's the aim about using ALC; 2) what about ALC success rate on infection eradication; 3) what about the best and safest ALC to use; 4), when should ALC be used; 5) is there any potential detrimental effect?

Aim of use of ALC

The release of antibiotic is the main aim of ALC: in literature high dose (> 2 g AB per 40 g PMMA) and low dose (< 2 g per 40 g PMMA) ALC is described [12], it is known that vacuum mixing is better than hand mixing in improving the mechanical performances of the bone cement, however antibiotic release may be greatly

Antibiotics for mixture to bone cement

Table

Ampicillin sulphate	Ceftiozone sodium
Gentamicin sulphate	Clindamycin phosphate
Streptomycin sulphate	Colistin sulphate
Tobramycin sulphate	Meropenem
Teicoplanin	Rifampicin*
Vancomycin hydrochloride	Tigecycline

Note. * — bone cement does not polymerize.

influenced: if we refer to commercially available ALC different cement will be differently affected by vacuum mixing [22]. In principle the reduction of cement porosity will reduce also the antibiotic release potential.

ALC use and infection rate

In terms of prophylaxis, it was demonstrated that the combined use of systemic antibiotic and ALC in THA was producing the lowest risk of revision due to infection [3]. This information was confirmed in a review paper where it was shown that the use of ALC is associated with a significant reduction (50 % less) in the risk of deep infection following THA [8]. However in TKA some recent paper was not able to confirm the same positive results [2, 16].

The release of antibiotic from ALC has a well known kinetics, with a peak release during the first days followed by a long tail of lower release. Therefore it is likely that optimal antibiotic accumulation in the wound hematoma would occur if wound drains were avoided or their duration of use minimized. With the presence of drains significant amount of antibiotic are lost [18].

Which ALC to use

A number of antibiotics (Table) may be admixed to bone cement [6], however commercially available single antibiotic ALC are loaded with an Aminoglycoside (Gentamicin or Tobramycin). Different cements shows different release, even though the same antibiotic is used: results depends on the properties of each cement [18]. The choice of adding an Aminoglycoside (Gentamicin) was based on release studies which demonstrated that among antibiotics Gentamicin was showing the best elution performances [23] from PMMA, the most extended spectrum of activity and no negative effect on mechanical performances.

When to use ALC

Nowadays some concern have arisen for the increase in gentamicin resistance, however the use of gentamicin bone cement for prophylaxis appears justified. Most published papers have shown a positive effect in the use of ALC in terms of infection rate reduction, even though some authors do not agree with the use in primary arthroplasty, unless we are speaking of high risk patients or joint arthroplasty revision [4].

Any potential detrimental effect

As regards possible problems associated with the presence of antibiotic in bone cement the following should be considered: systemic toxicity, hypersensitivity reaction, mechanical hazards, bacterial resistance hazards and cost rising. The discussion will be limited to commercially available ALC. The risk of systemic toxicity is not likely. Toxicity can be dosage or antibiotic dependent. If we refer to gentamicin, diffusion in the bloodstream is minimal (although high concentration may be achieved locally), the risk of hearing loss and renal failure, which is cumulative, cannot be associated to the low serum concentration determined by ALC, while it can be associated to previous doses received within the last few months or years. Eventually acute or chronic kidney injury (AKI, CKI) occur in patients with previous kidney or liver dysfunction. The evidence for hapten mediated hypersensitivity to the interaction of antibiotics and bone cement is very limited [17]; gentamicin sensitization may result from occupational exposure to gentamicin containing bone cements or from systemic medication with aminoglycosides [14].

All ALC on the market fulfill the basic mechanical requirements (ISO Standard 5833), although there are significant difference in mechanical performance [13] among cements. It shall be underlined that no clinical study has proved that a mechanically stronger cement will produce better clinical outcomes.

As concerns bacterial resistance, apparently there is no direct relationship between the use of gentamicin-loaded cement and bacterial resistance increase. In Northern Europe the use of gentamicin-loaded cement in primary prostheses has reached 100 %, however according to the European Antimicrobial Surveillance Network [7] the rate of resistance in these countries is the lowest in Europe.

In any case the use of Vancomycin cement as a primary agent in prophylaxis should be avoided because of the emergence of resistant bacteria and the need to reserve this antibiotic for those patients which require vancomycin for treatment purposes [9].

Eventually, the increasing use of ALC has lead to the increase of costs. This is more relevant in US, where ALC is 3 times more expensive compared to plain bone cement. It was shown that while in primary arthroplasty it increases the overall costs, in revision due to infection the use of ALC was found to have an incremental cost-effectiveness ratio of \$37,355 per QALY, with a cost decreasing of \$650 per patient [5].

Conclusion

In conclusion, the use of ALC must be considered as a support strategy in prevention and not the solution

of infections; in primary implants, ALC is justified only in high risk patients; it is recommended for revisions; the perfect antibiotic in ALC does not exist; avoid using Vancomycin as first step; ALC is successful only if associated with systemic antibiotics; use of ALC significantly rises cost-effectiveness in implant revision.

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НАСЫЩЕННЫЙ АНТИБИОТИКАМИ КОСТНЫЙ ЦЕМЕНТ И ЕГО ШИРОКОЕ ПРИМЕНЕНИЕ: ОПРАВДАНО ЛИ ЭТО?

Джованни Калонего

Текрес СПА – Соммакампанья (Верона), Италия

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