Review Article

Antibiotic Elution from Hip and Knee Acrylic Bone Cement Spacers: A Systematic Review

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Knowledge about the elution from antibiotic-loaded cement spacers is an indispensable premise for guarantee of clinical success. A systematic literature search was performed through PubMed. Search terms were "antibiotic elution" and "antibiotic release" in combination with "spacer," "hip spacer," and "knee spacer," respectively. A total of 11 studies could be identified. Seven studies reported on the release of antibiotics after spacer implantation, three studies at spacer removal, and one study on both time points. Seven studies reported on hip spacers, one study on knee spacers, and three studies on both. In eight studies, custom-made spacers have been implanted and in three prefabricated ones. In the majority of the studies, the cement has been loaded with an antibiotic combination, mostly consisting of aminoglycoside (either gentamicin or tobramycin) and vancomycin. Measured concentrations exceeded the minimal inhibitory concentration of the particular pathogen organisms in each case. However, large discrepancies were observed with regard to the height of the antibiotic concentration depending on the antibiotic combination and the antibiotic ratio used. Current literature data indicate a sufficient elution of antibiotics after spacer implantation and at spacer removal, respectively. Future studies are required to optimize the local antibiotic therapy at the site of spacer implantation.

1. Introduction

Periprosthetic joint infections pose a great challenge for the orthopaedic surgeon. At the site of late infections, the implantation of antibiotic-loaded cement spacers is the treatment of choice in Europe and North America with success rates exceeding 90% [1, 2].

Cement spacers have several advantages such as high local antibiotic therapy, preservation of joint mobility in case of articulating ones, less formation of scar tissue, and ease of prosthesis reimplantation [1, 2]. The ideal spacer should possess sufficient pharmacokinetic properties over a prolonged time period in order to eradicate the infection and prevent the emergence of new, multiresistant bacteria strains, if any should have survived after spacer implantation.

The release of antibiotics from cement spacers has been well studied in vitro [3–5]. However, these results cannot be directly transferred to clinical practice. Differences in the cement used and its antibiotic impregnation, addition of one or combination of two or more antibiotics, the amount and/or ratio of the incorporated antibiotic(s), length of spacer implantation, spacer geometry and surface, and spacer articulation are only some of the factors that might have a possible influence on the pharmacokinetic properties in vivo.

The aim of the present work is to summarize the current knowledge about the elution of antibiotics from hip and knee spacers in vivo and distinguish between the release kinetics after spacer implantation and at spacer removal, respectively.

2. Materials and Methods

2.1. Inclusion of Studies. A literature search was performed through PubMed until November 2016 (Figure 1). Search terms were "antibiotic elution" and "antibiotic release" in combination with "spacer", "hip spacer", and "knee spacer", respectively. Only English studies and those solely reporting about the release of antibiotics from acrylic bone cement hip and knee spacers in vivo were included. In vitro studies,
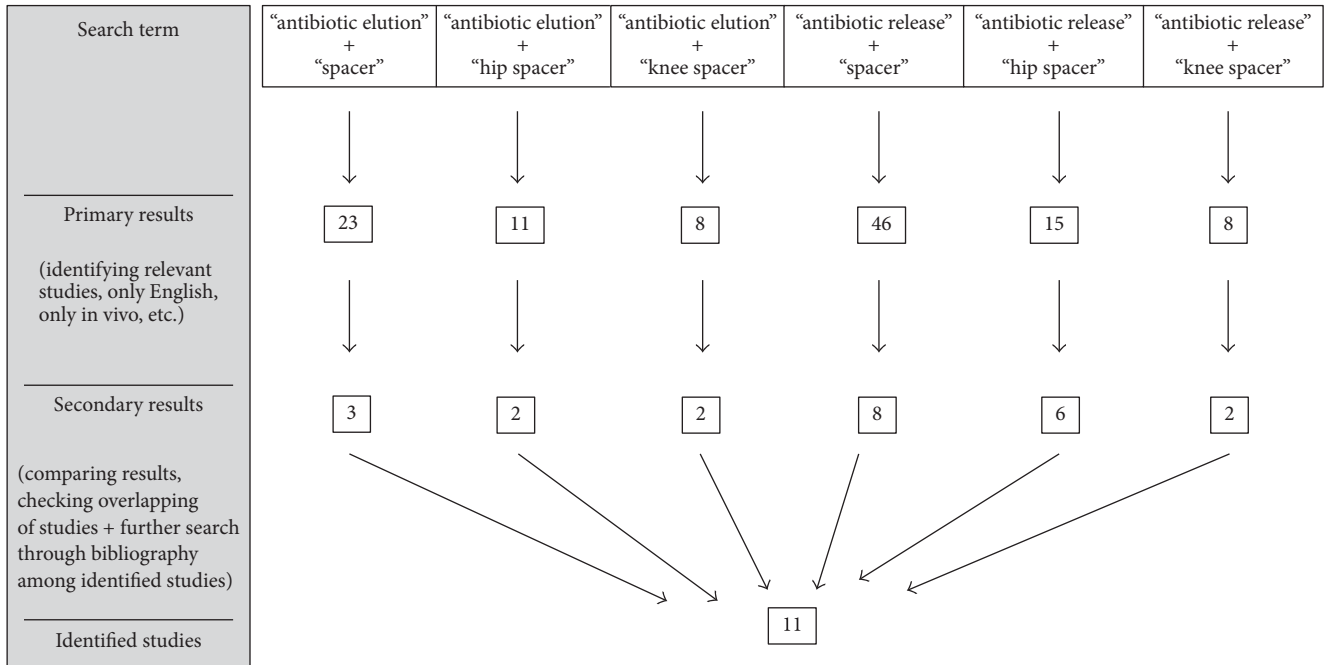
FIGURE 1: Literature search for identification of studies about antibiotic elution from acrylic bone cement hip and knee spacers in vivo.

reviews, and case reports were excluded. Among the primarily identified studies, a search was carried out through the bibliography of each article for further identification of relevant studies. All publications were analyzed with regard to joint localization, number of spacer implantations, cement used, antibiotic impregnation, type of spacer, time of measurement of the antibiotic elution (after spacer implantation versus at spacer removal), and pharmacokinetic findings.

3. Results

A total of 11 studies [6–16] could be identified (Table 1). Seven studies reported on the release of antibiotics after spacer implantation [6–8, 11–13, 16], three studies at spacer removal [9, 14, 15], and one study on both time points [10]. Seven studies reported on hip spacers [6, 9–13, 16], one study on knee spacers [15], and three studies on both [7, 8, 14] (Table 1). In eight studies, custom-made spacers have been implanted and in three prefabricated ones. Only one study investigated the properties of cement spacers impregnated with a single antibiotic [12]. In all other studies, the cement has been loaded with an antibiotic combination, mostly consisting of an aminoglycoside (either gentamicin or tobramycin) and vancomycin. In all studies, the incorporated antibiotics were in powder form except for one [11]. All data about the production and antibiotic impregnation details of hip and knee spacers are summarized in Table 1.

3.1. Antibiotic Elution: After Spacer Implantation. All studies determined the local antibiotic concentrations in the joint fluid collected in the redon drain. The time period of measurement varied between the first 24 postoperative hours and seven postoperative days after spacer implantation. In

the studies with a longer measurement period, the antibiotic elution demonstrated a biphasic profile, consisting of initial high concentrations, which then constantly decreased over time. The highest values determined were observed in a study where vancomycin and aztreonam were incorporated into 40 g bone cement with initial values exceeding 1,000 μg/ml (impregnation dose 3 g vancomycin + 4 g aztreonam/40 g cement; average amount of cement/spacer 86.7 ± 10.3 g) [10]. At the site of a gentamicin-vancomycin combination, some large discrepancies with regard to height of the measured concentrations could be seen among the studies. Anagnostakos et al. determined maximum concentrations of gentamicin and vancomycin at 39 and 72 μg/ml, respectively, when 1 g gentamicin and 4 g vancomycin (both powder) were impregnated into 80 g cement for spacer production. Hsieh et al. reported mean local levels of gentamicin at 58.3 mg/l and of vancomycin at 485.5 mg/l on day 1 when liquid gentamicin was combined with vancomycin powder (impregnation dose 480 mg gentamicin + 3 g vancomycin/40 g cement; average amount of cement/spacer 72.2 ± 11.4 g) [11]. All initially determined concentrations in all studies were beyond the minimal inhibitory concentrations of the causative bacteria. All data about the antibiotic elution after spacer implantation is summarized in Table 2.

3.2. Antibiotic Elution: At Spacer Removal. Three studies determined the antibiotic concentrations in the local joint fluid found at spacer removal, whereas one study measured them in the local tissue. The length of spacer implantation varied from six weeks to several months. All measured concentrations were above the minimal inhibitory concentration of the particular causative organism in each study despite an apparent trend toward decreasing levels over time

TABLE 1: Production and antibiotic impregnation details of hip and knee spacers.

Study	Joint	Number of spacer implantations	Cement used	Spacer type	Antibiotic impregnation and type
Anagnostakos et al. [6]	Hip	17	Palacos	Custom-made	0.5 g G + 2 g V/40 g cement powder
Balato et al. [7]	10x hip 8x knee	18	Palacos	Custom-made	1 g G + 1 g C powder
Bertazzoni Minelli et al. [8]	5x hip 6x knee	11	Cemex®	Prefabricated*	1.9% G, 1.9% G + 1.25% V, 1.9% G + 1.9% V, 1.9% G + 2.5% V, 1.9% G + 5% V powder
Fink et al. [9]	Hip	14	Palacos	Custom-made	7 × 1 g G + 1 g C/40 g cement, 7 x 1 g G + 1 g C + 2 g V/40 g cement powder
Hsieh et al. [10]	Hip	46	Simplex	Custom-made	4 g V + 4 g A/40 g cement powder
Hsieh et al. [11]	Hip	42	Simplex	Custom-made	~300 mg G + 3 g V/40 g cement liquid G + powder V
Isiklar et al. [12]	Hip	10	n.r.	Custom-made	2 g V/40 g cement powder
Kelm et al. [13]	Hip	10	Palacos	Custom-made	0.5 g G + 2 g V/40 g cement
Masri et al. [14]	34x hip 15x knee	49	37x Palacos 12x Simplex	Custom-made	1.2–4.8 g T + 1-2 g V/40 g cement powder
Mutimer et al. [15]	Knee	12	Cemex	Prefabricated	Gentamicin powder
Regis et al. [16]	Hip	7	Cemex	Prefabricated**	2.5% G + 150–170 mg V powder

V: vancomycin; G: gentamicin; C: clindamycin; A: aztreonam; T: tobramycin; *: in 9/11 cases additional impregnation by drilling in the spacer and filling with vancomycin-loaded cement; **: in all cases additional impregnation by drilling in the spacer and filling with vancomycin-loaded cement; n.r.: not reported.

TABLE 2: Findings about the antibiotic elution from hip and knee spacers after spacer implantation in vivo.

Study	Place of measurement	Time period of measurement	Pharmacokinetic findings	Infection control
Anagnostakos et al. [6]	Joint fluid	First 7 postop. days	$[G]_{MAX}$ 39 μg/ml, $[V]_{MAX}$ 72 μg/ml on day 1 $[G]_{MIN}$ 1.9 μg/ml, $[V]_{MIN}$ 6.6 μg/ml on day 7 Between days 5 and 7 intermittent increase in the elution of both antibiotics	n.r.
Balato et al. [7]	Joint fluid	First 48 postop. hours	$[G]_{MAX}$ 53.9 μg/ml in the hip group, $[G]_{MAX}$ 44.1 μg/ml in the knee group Mean [G] significantly higher in the hip than in the knee group (30.61 ± 19.47 μg/ml versus 17.43 ± 13.63 μg/ml) one hour after implantation	100%
Bertazzoni Minelli et al. [8]	Joint fluid	First 24 postop. hours	$[G]_{MAX}$ 88 μg/ml in the hip group, $[G]_{MAX}$ 110 μg/ml in the knee group $[V]_{MAX}$ 28.8 μg/ml in the hip group, $[V]_{MAX}$ 158.9 μg/ml in the knee group	100%
Hsieh et al. [10]	Joint fluid	First 7 postop. days	Mean $[V]_{MAX}$ 1,538 μg/ml, mean $[A]_{MAX}$ 1,003.5 μg/ml on day 1 Mean $[V]_{MIN}$ 571.9 μg/ml, mean $[A]_{MIN}$ 313.6 μg/ml on day 7	97.8%
Hsieh et al. [11]	Joint fluid	First 7 postop. days	Mean $[G]_{MAX}$ 58.3 μg/ml, mean $[V]_{MAX}$ 485.5 μg/ml on day 1 Mean $[G]_{MIN}$ 14.6 μg/ml, mean $[V]_{MIN}$ 76.1 μg/ml on day 7	95.2%
Isiklar et al. [12]	Joint fluid	First 24 postop. hours	Mean [V] 57 [32–81] μg/ml	100%
Kelm et al. [13]	Joint fluid	First 7 postop. days	Vancomycin quantitatively higher than gentamicin extrapolated concentration-time curves showed power functions, so that subtherapeutic antibiotic levels can be expected for vancomycin on the 17th postop. day and for gentamicin on the 14th postop. day	n.r.
Regis et al. [16]	Joint fluid	First 24 postop. hours	[G] ranged between 15 and 90 μg/ml; [V] ranged between 13.8 and 40 μg/ml	n.r.

G: gentamicin; V: vancomycin; A: aztreonam; MAX: maximum; MIN: minimum; n.r.: not reported.

TABLE 3: Findings about the antibiotic elution from hip and knee spacers at spacer removal.

Study	Place of measurement	Length of spacer implantation	Pharmacokinetic findings	Infection control
Fink et al. [9]	Local tissue	Six weeks	$[G]_{MAX}$ 50.93 μg/g, $[V]_{MAX}$ 177.24 μg/g, $[C]_{MAX}$ 322.29 μg/g No differences in [G] and [C] regardless of whether V has been added to cement No differences between levels associated with acetabular cup and those with spacer stem	n.r.
Hsieh et al. [10]	Joint fluid	Mean 107 [32–156] days	All [V] and [A] above the MIC despite an apparent trend toward decreasing levels over time	97.8%
Masri et al. [14]	Joint fluid	Mean 118 [42–340] days	No significant differences between hip and knee spacers Highest [T] and [V] when at least 3.6 g T was impregnated Significant increase when the dose of T was increased from at most 2.4 g to at least 3.6 g per cement package V has no significant influence on [T] Increase of the V dose from 1 to 1.5–2 g V per cement package with no significant influence on [T] or [V] Apparent trend toward decreasing levels over time	n.r.
Mutimer et al. [15]	Joint fluid	Median 99 [63–274] days	Median [G] 0.46 [0.24–2.36] μg/ml	100%

G: gentamicin; V: vancomycin; C: clindamycin; A: aztreonam; T: tobramycin; MAX: maximum; MIN: minimum; MIC: minimal inhibitory concentration; n.r.: not reported.

seen in two studies [11, 14]. At the site of hip spacers, no significant differences could be found between the levels associated with acetabular cup and those with spacer stem implantation [9]. In another study, no significant differences were observed between hip and knee spacers [14]. When tobramycin was combined with vancomycin, tobramycin itself and the increase of its incorporated dose had an influence on the elution kinetics of both antibiotics but not vice versa [14]. All data about the antibiotic elution at spacer removal is summarized in Table 3.

4. Discussion

Knowledge about the antibiotic elution from cement spacers is an indispensable premise for guarantee of infection eradication in the management of periprosthetic hip and knee infections. The present work tried to systematically review the current literature about this topic and differ between the pharmacokinetic properties after spacer implantation and at spacer removal.

The evaluation of the efficacy of spacers with different antibacterial loads based on published reports is difficult [17]. As aforementioned, it is apparent that numerous factors might theoretically have an influence on the release kinetics from bone cement in vivo. Generally, the type and ratio of antibiotics, the quantity of antibiotic(s), the type and porosity of cement, the surface characteristics, the way the cement is prepared, and the environmental circumstances are accepted to be factors with a possible affection on the antibiotic release from bone cement [18]. Therefore, the interpretation of in vivo studies about the elution of antibiotics from cement spacers has some great differences compared with in vitro studies. The majority of the knowledge about elution kinetics

from antibiotic-loaded bone cement origins from studies that investigated cement device other than spacers such as disks [19–22]. Since the release of antibiotics from bone cement is a surface-dependent phenomenon [23], it is questionable to what effect these in vitro observations also account for hip and knee spacers that have a different geometry and surface. Moreover, the amount and frequency of fluid exchange around bone cement in vitro do not fully represent the vascular supply nor the resulting antibiotic diffusion to tissue and hence the in vivo circumstances which certainly cause a different wash-out phenomenon of antibiotics from the cement.

Based on these considerations, it is essential to study and understand the pharmacokinetic properties of cement spacers in vivo. Here, specific factors such as place and length of measurement should be critically evaluated. In the majority of the cases among the identified studies, the elution of hip spacers was studied. After spacer implantation, the determination of antibiotic concentrations occurred in joint fluids collected from the drains during the first postoperative days. However, these concentrations are not fully representative for the whole pharmacokinetic properties from the spacers but mostly for the intra-articular spacer part. Especially at the site of hip spacers, this accounts only for the pharmacokinetic properties of either the spacer head alone or the spacer head in combination with a spacer cup. The antibiotic release from the spacer stem in the femoral cavity cannot be determined in the joint fluid. Therefore, the measured concentrations represent only a part of the true antibiotic elution in vivo, and this has to be born in mind.

Moreover, the elution properties might depend on the fluid amount that washes the antibiotics out from the bone cement. It could be possible that the initially high antibiotic

elution causes a quick saturation of the surrounding tissue. The diffusion gradient that supports the antibiotic release at the beginning is decreased while the tissue saturation is increasing. This could lead to a severe time-dependent reduction of the antibiotic release from spacers [13]. In contrast to that finding, the diffusion gradient in vitro is permanently high. Since in most studies the culture medium is changed daily, the permanently existing differences between spacer surface and culture medium are causing a new, high, and longer lasting antibiotic elution. Unfortunately, the fluid amount in the drains was not always stated in the identified studies.

By a constant decrease of the fluid amount during the early postoperative period, the antibiotic release shows then a normal decrease. If the spacers would be again exposed to "fresh" fluids, the elution of antibiotics could be restarted. This phenomenon could be observed in the studies of Bertazzoni Minelli et al. [24] and Kelm et al. [13]. Both studies investigated the residual pharmacokinetic and associated antimicrobial properties of spacers after their explantation in vitro. 0.05–0.4% gentamicin and 0.8–3.3% vancomycin of the initial amount present were released over a time period of 10 days in the first study [24], indicating that sufficient antibiotic release can persist over several months. Kelm et al. reported similar elution values of gentamicin and vancomycin, and their spacers demonstrated sufficient antimicrobial properties for at least 14 days in vitro independent of their implantation period [13].

The type of antibiotics themselves used for cement impregnation plays also an important role with regard to release kinetics. In the present evaluation, all studies except for one solely used antibiotics in powder form. Antibiotics in powder form have a lower impact on the mechanical properties of bone cement at a ratio of up to 10% [25], whereas antibiotics in liquid form enhance the pharmacokinetic properties while having a negative impact on the mechanical stability [26]. Adding liquid antibiotics reduces the compressive strength of bone cement by 49% and the tensile strength by 46% [27]. Cement spacers are thought to be only interim prostheses so that in the majority of the cases mechanical complications such as spacer fractures might be avoided when liquid antibiotics are used and if the patient is able to put non-weight-bearing on the operated leg until the prosthesis reimplantation. However, in some cases, a prosthesis reimplantation cannot be performed for various reasons, and the patients are left with their spacer in situ [28–30]. Therefore, it is questionable whether the impregnation of bone cement with liquid antibiotics might be advisable and safe, even if the antibiotic elution is hereby enhanced.

The choices of bone cement and incorporated antibiotics are probably the two most important factors at the site of cement spacers. Palacos® has been regarded to be the cement type with the best pharmacokinetic properties for many years [31, 32]. However, in the past years, several studies have indicated that other bone cements have at least equally good or even superior elution properties as Palacos has [3, 19, 33, 34]. Bitsch et al. investigated in vitro the release of several antibiotics from a new cement, especially designed for spacer production, and could determine a significantly

higher and prolonged antibiotic elution for a period of up to 50 days [3]. Neut et al. demonstrated for Palamed the best elution kinetics among six tested gentamicin-loaded bone cements [33]. Similar in vitro observations were also made by van de Belt and colleagues [34]. Cerretani et al. demonstrated that when vancomycin was incorporated alone into PMMA, the highest elution rates occur from CMW 1 compared to Simplex® and Palacos; however, when combined with imipenem-cilastatin Palacos and Simplex have superior pharmacokinetic properties [19]. These discrepancies among the elution kinetics of different bone cement types might pose a possible explanation for the very high elution of antibiotics observed in one identified study, where Simplex cement was used compared to the other studies (Tables 1 and 2).

Although it is known that commercially available antibiotic-impregnated bone cements have superior elution properties than those with a manual impregnation of an antibiotic due to the more homogenous distribution of the incorporated antibiotics in the cement powder, orthopaedic surgeons frequently need to add other antimicrobial agents to the bone cement of spacers due to the sensitivity profile of the causative pathogen organism. Therefore, knowledge about the synergism between the incorporated antibiotics is important for the clinical performance. Despite the fact that the precise synergism mechanism is not completely understood, it seems that this mechanism can be attributed to the so-called passive opportunism [22]. The second antibiotic appears to act as a soluble additive increasing porosity and thereby enhancing the elution of the first antibiotic or both. When an aminoglycoside (gentamicin or tobramycin) has been combined with vancomycin, in vitro studies have demonstrated a synergistic effect for one [35] or both agents [22] which is maintained in cement when both drugs are released in active form at site of infection. Apparently the amount of synergism might also depend on the ratio of the antibiotics which might also explain the partly large discrepancies with regard to height of antibiotic concentrations released from cement spacers as shown in the present work (Tables 2 and 3).

Due to the decrease of the antibiotic elution from spacers over time, some concerns have been expressed in the past years about the possible growth of bacteria on spacers, hence leading to clinical infection persistence. The present literature shows some partly contradictory results about this topic. Some studies determined the bacteria growth on spacers after their explantation by sonication and could show a bacteria growth on spacers to different percentages, respectively [36–38]. In some cases, the spacers were not loaded with antibiotics which could explain the bacteria growth [38]. However, not every case was associated with a clinical infection persistence [36–38]. Another study investigated this phenomenon by scanning electron microscopy and confocal scanning light microscopy and could not detect any biofilm formation on the spacers [39]. Hence, the theoretical possibility of bacteria growth on spacers is present but cannot be surely supported by hard scientific data.

Despite numerous studies about hip and knee spacers, several topics still remain unclear with regard to the antibiotic impregnation. None of the identified studies investigated whether custom-made or prefabricated spacers release more

antibiotic amounts or higher concentrations, over a prolonged period. Moreover, the properties of antibiotic combinations other than the combination of an aminoglycoside and a glycopeptide are not known. At present, some antibiotic combinations are potential because the choice is limited by safety issue (fluoroquinolones and bone, beta-lactam drugs, and sensitivity/allergy), stability, and compatibility with cement. Last but not least, the ideal ratio for impregnation of bone cement in vivo is also unclear.

5. Conclusion

The management of late periprosthetic infections by means of a spacer implantation is an established method. Current literature data indicate a sufficient elution of antibiotics after spacer implantation and at spacer removal, respectively. However, some large discrepancies with regard to height and length of the sufficient antibiotic release are evident among the identified studies. Future studies are required to optimize the local antibiotic therapy at the site of spacer implantation.

Conflicts of Interest

The authors state that there exist no conflicts of interest.

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