

HK 71: How long do antibiotics elute from PMMA spacers?

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Response/Recommendation: Although many confounding factors influence antibiotic elution levels over time, making it difficult to compare studies regarding antibiotic delivery via PMMA spacers, the available data indicates sufficient release occurs to maintain levels above the minimum inhibitory concentration (MIC) of most bacteria for at least 6 to 12 weeks.

Level of Evidence: Low

Delegate Vote:

Rationale

Many factors influence the antibiotic elution characteristics of PMMA spacers, including the type, concentration, and combinations of antibiotics (with synergistic effects of two or more antibiotics), as well as the type and porosity of the cement itself [10,26], the geometry of the spacer, and the cement mixing technique [1-3] (Table 1). Because there are great differences in these specific details, it is difficult to directly compare studies and different outcomes may result from different preparation methods. For this review, reports were selected that gave results for elution characteristics where antibiotics were used in powdered form, at a cumulative antibiotic proportion of not more than 10%, using one or more antibiotics added to PMMA without any other additives (such as glycine, calcium phosphate, or carbonate).

Antibiotic elution from PMMA spacers has been extensively evaluated in vitro, typically involving measurements of antibiotic levels in fluid using fluorescence polarization immunoassays, or by examining zones of inhibition on culture plates. Most studies investigate devices other than spacers, such as PMMA disks as surrogates [4-7]. Since the release of antibiotics from bone cement is a surface-dependent phenomenon [8], it is valid to question the relevance of these in vitro observations for hip and knee spacers that have a different surface area and geometry. Moreover, the amount and frequency of fluid exchange around bone cement in vitro varies between studies, and although most study protocols changed the eluate daily some only changed weekly [9]. Greater amounts of fluid and more frequent exchanging will influence elution by disturbing the concentration gradient [10]. The concentration gradient between spacer surface and culture medium does not necessarily recreate in vivo conditions that faithfully model antibiotic diffusion to tissue. In addition, antibiotic and physiological differences such as local blood flow and pH may have an influence on the pharmacokinetic behavior of spacers, resulting in different antibiotic elution profiles. Moreover, the spacers are tested in vitro under ideal bacteria growth circumstances. Tryptic soy broth is an ideal growth medium and often a new aliquot of the microorganism was added on a daily basis, whereas the antibiotic amount has not been changed [11]. Therefore, the results of in vitro studies cannot be directly translated into clinical practice under in vivo conditions.

Nearly all in-vitro studies demonstrate very high peaks of antibiotic concentration and elution after 24 hours, followed by a continuous decline [11-29] (Table 2). One of the greatest limitations of several in vitro studies designed to answer the question posed by this review is the duration of the analysis period. Most studies analyzed the elution for a period of several days up to one week [13,15,19,22] (Table 2). For these short periods, sufficient release of antibiotics over the minimum inhibitory concentration (MIC) were observed [13,15,19,22]. Boelch et al [23] reported sufficient release of vancomycin and gentamicin for the whole test

period of 28 days, Slane et al [18] the same for tobramycin and vancomycin, and Galvez-Lopez et al [12] for 7 of 11 different antibiotics across the test duration of 30 days. Oungeun et al. [20] observed sufficient elution for a test period of 6 weeks for vancomycin and erythromycin, Kummer et al [9] for vancomycin, gentamicin, and daptomycin, and Liawrunrueang et al [28] for gentamicin (Table 2). Three independent studies reported substantially shorter elution periods for vancomycin compared to other antibiotics [24] [21] [16].

In an in vitro model, Stevens et al [26] simultaneously demonstrated the three important considerations of PMMA type, antibiotic synergy, and antibiotic dosage. In their study, a Palacos articulating knee spacer containing both vancomycin and tobramycin (3 g vancomycin and 3.6 g tobramycin per 40 g PMMA), eluted in excess of the MIC for most common orthopaedic pathogens for greater than 80 days. However, PMMA spacers may certainly exhibit different activity in vivo. The anatomical location, the vascular supply and perfusion of the infected area, and the protein binding capacity of each antibiotic used are some of the parameters that may actively influence spacer performance in vivo.

Due to the limitations of the in vitro studies, the more important investigations to address the issue of sufficient elution period for PMMA spacers are in vivo studies. Here, methodologically, the different studies can be separated into animal in vivo studies and human in vivo studies. The latter can be further distinguished between studies where antibiotic concentrations were measured in joint fluid drainage a few days after surgery, and those where the spacers removed during the second surgery of the two-stage protocol were analyzed for continued antibiotic elution.

Numerous factors also influence the release kinetics and elution period from PMMA in vivo. Beside the factors mentioned above, the surface roughness and total surface area of the spacer, the duration of spacer implantation, spacer geometry, spacer articulation, and the environmental circumstances are recognized as factors influencing antibiotic release from bone cement in vivo [30-32]. Moreover, articulating spacers generally exhibit abrasion from cement particles [33], potentially leading to new surfaces on the spacer from which antibiotics can elute, which may be associated with increased and prolonged antibiotic release [21,34]. In addition, an increase in the distance between the cement and the surrounding tissues results in decreased concentration of the antibiotic in the tissue [35]. The type of tissues around the spacer also affects antibiotic elution from the spacer and antibiotic diffusion into the inflamed tissues. Cancellous bone absorbs more antibiotic than cortical bone, and any hematoma (dead space) that potentially lies between the spacer and the bone or soft tissues absorbs more antibiotic than cancellous bone [35,36].

Several in vivo studies on animals, especially those evaluating selected shapes of PMMA-spacers, merit discussion here. In dogs, Adams et al [37] noted detectable concentrations of tobramycin and vancomycin from PMMA beads over a period of 28 days. Chapman and Hadley [38] observed a peak of antibiotic release on the first day, but no elution after 37 days in serum and soft tissue from antibiotic-loaded cement pellets implanted in the intramedullary canal of rabbit femora and quadriceps muscle. On the other hand, Bunetel et al [39] reported sufficient release of gentamicin up to 18 months after femoral implantation of gentamicin (0.6 and 1.2 g per 40 g PMMA) in sheep, and Chohfi et al [40] observed adequate elution for 3 months using high dose vancomycin (3 g in 40 g PMMA) impregnated cement in sheep femora. Gatin et al [41] noted sufficient release of colistin in PMMA for implantation of a silicone elastomer implant in the knee of rabbits for the whole test duration of only 21 days. The differences reported may simply be the result of various methodological differences and inherent weaknesses in the study designs.

The studies of greatest relevance are clinical investigations in humans with spacers. However, in vivo analysis of the drainage fluid concentration is limited by the time for which the drainage tubes could be left in situ, usually a period of only a few days. Anagnostakos et al. [42] confirmed sufficient antibiotic elution in the drainage fluid for 7 days when adding vancomycin to Palacos R+G-cement. As with the in vitro studies and animal in vivo studies, the analysis of the antibiotic concentration in the joint fluid drainage demonstrated a peak after 24 hours, well above the MIC of the microorganism for all tested antibiotics, followed by a much lower concentration for several days [40,42-46], typically still greater than the MIC at the end of the test period (Table 3). However, the antibiotic concentrations collected from drains are not necessarily representative of the full pharmacokinetic properties of the spacers but instead reflect only their intra-articular surfaces. Particularly for hip spacers, this only accounts for the pharmacokinetic properties of either the spacers head alone or the spacer head in combination with a spacer cup. The antibiotic release from the spacer stem in the femoral medullary cavity cannot be determined from the joint fluid, and the measured concentrations represent only a portion of the true antibiotic elution in vivo [3]. Fink et al [34] measured the antibiotic concentration in the membrane around hip spacers 6 weeks after implantation, and noted antibiotic levels above the MIC for gentamicin, clindamycin, and vancomycin. Bertazzoni Minelli et al. [51] analyzed the antibiotic concentration in the periprosthetic tissue in two cases after explantation of hip-spacers and reported concentrations greater than those determined in other elution studies, with values obtained locally exceeding the MICs of most of the common pathogens involved in periprosthetic joint infections.

Generally, because elution for longer periods in vivo could not be measured from drainage fluid, the analysis of spacers after removal during the second-stage of two-stage revision arthroplasty seems to be more appropriate to address the question posed by this review. Joint aspiration at the time of spacer removal and analysis of the antibiotic concentration in the joint fluid revealed a sufficient concentration above the MIC for 3 months and more in most studies [47,48,50] (Table 3).

One additional feature of hip spacers, hemispacer versus articulating two-part spacers, may influence the antibiotic release in clinical use. Hsieh et al [43] reported sufficient antibiotic concentrations above the MIC in the joint fluid of 46 hip spacers with vancomycin and aztreonam after a mean period of 107 days. These spacers were articulating two-part spacers with a cemented stem head articulating on a cement cup. These observations are in concordance with the findings of Fink et al [34], who noted sufficient concentrations of gentamicin, clindamycin, and vancomycin in the tissue around the spacer after 6 weeks. These spacers were also two-part articulating spacers with a metal head articulating on cement cups. These articulations create wear, as confirmed by histological analyses, x-ray fluorescence spectroscopy, and plasma-mass spectrometry [33]. This wear exposes new surfaces, from which additional antibiotic elution can then occur. However, Masri et al [47] reported sufficient antibiotic concentrations 4 months postoperatively when using Prostalac spacers containing tobramycin. Therefore, two-part articulating spacers in the hip (as well as articulating knee spacers) may have additional advantages regarding antibiotic elution, and may also prevent acetabular bone resorption and spacer migration (as sometimes observed with hemi-spacers) [1].

The potential value of long-term antibiotic elution from spacers has been verified by studies evaluating the residual antimicrobial and pharmacokinetic properties following their explantation. Bertazzoni Minelli et al [51] and Kelm et al [49] both demonstrated sufficient elution kinetics and bacterial growth inhibition for all tested spacers, independent of their particular implantation period. Finally, Griffin et al [52] analyzed 6 spacers with different

dosages of vancomycin and tobramycin after removal between 37 and 175 days (average 85 days) and noted no adhering biofilm using scanning electron microscopy, perhaps an indirect sign of sufficient release of antibiotics for these periods.

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