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Intraarticular and serum vancomycin concentration added to acrylic cement

Research Article

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Abstract: Background. Vancomycin is the antibiotic of choice in therapy of orthopaedic implant infections caused by methicillin-resistant bacteria but its use poses a risk of toxicity, especially in patients with renal insufficiency. Addition of vancomycin to acrylic cement may cause systemic exposition to this drug eluting from cement to serum, which may require high-flux hemodialysis. Methods. A patient hemodialysed twice a week underwent implantation of a spacer due to methicillin-resistant S. epidermidis infection of knee prosthesis. The spacer was made of acrylic cement loaded with 0,55 g of gentamicin per 40 g of cement and 6 g of vancomycin into totally 120 g of cement. The measurements of vancomycin concentration in serum within 9 days and in intraarticular fluid within 2 days were performed. Results. Maximal intraarticular vancomycin concentration was reached 7 hours after surgery (120 μg/mL) and was over Minimal Inhibitory Concentration for 47 hours. The serum concentration reached maximal value (2,6 μg/mL) 13 hours after implantation of spacer and was 2,3 μg/mL on 9-th postoperative day. Conclusion. This composition of acrylic cement spacer containing gentamicin and vancomycin was found therapeutically effective and not necessitating high-flux hemodialysis in a hemodialysed patient with chronic renal failure.

Keywords: *Antibiotic loaded acrylic cement spacer • End-stage kidney disease • Hemodialysis • High-flux hemodialysis • Infected knee prosthesis • Two-stage revision • Vancomycin*

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1. Introduction

The aim of the study was to determine whether the addition of 5% of vancomycin to 40 g of acrylic cement is effective for local therapy of periprosthetic joint infections and also safe and not necessitating high-flux hemodialysis in an chronically hemodialysed patient, when a total of 120 g of cement with 6 g of vancomycin is used for the intra articular spacer. The prevalence of septic complications after joint arthroplasty in patients with chronic renal failure is significantly higher than in the population of healthy people and can be as high as 19% [1]. This is partially due to an increasing number of people who previously underwent joint arthroplasty and later become dependant on hemodialysis as well as the increasing number of individuals surviving years with renal failure under chronic dialysis, who eventually require arthroplasty. Patients with renal failure pose a special problem due to the need for adjustment of antibiotic doses to glomerular filtration ratio (GFR), which in the case of vancomycinit is especially important to balance the therapeutic effect with potential ototoxicity and nephrotoxicity. Vancomycin is reserved for infections caused by more resistant Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci

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(MRCNS) or penicillin-resistant enterococci. Minimal Inhibitory Concentration (MIC) of vancomycin assumed for most pathogens is 2 mg/L. Vancomycin has a narrow therapeutic index in serum ranging for peak levels 25-50 mg/L and for trough levels 10-20 mg/L. For MRSA trough level may need be higher than 15 mg/L [2].

Despite antibiotic therapy, surgical revision of infected prosthesis should be done, in one-or two-stage manner. When two-stage therapy is preferred, usually antibiotic loaded acrylic cement (ALAC) spacer is inserted after removal of infected prosthesis [3]. The use of antibiotic-impregnated cement allows local concentration exceeding the MIC breakpoint of susceptible organisms while systemic concentrations are usually not detected. Systemic complications are rarely encountered with this type of antibiotic delivery method. Curtis reported one and Jung reported five cases (6% of operated cases) of acute renal failure related to the use of ALAC loaded with tobramycin-cefazolin as spacer [4, 5]. Menge noted the 17% incidence of acute renal injury within 90 days postoperatively, when tobramycin was used in the ALAC spacer [6]. Masri measured the intra articular concentrations of tobramycin and vancomycin at the time of the ALAC spacer removal and during the reimplantation of a definitive joint prosthesis at a mean 118 days after initial implantation [7]. At this time in most patients detectable levels of vancomycin in the knee joint were still present. Also tobramycin concentrations over MIC were noted, when at least 3.6 g of tobramycin and 1 g of vancomycin per 40 g of acrylic cement was used. Addition of potentially toxic antibiotic to cement spacer, which is thought of as temporary implant, seems to be safer than one-stage reimplantation of a new prosthesis using the same antibiotic in the cement. Two-stage technique should minimize the risk of unexpected increase of serum vancomycin concentration above the toxic threshold. For this reason the risk of systemic accumulation of vancomycin is greater after one-stage revision. Also removal of a newly inserted prosthesis with whole cement mantle is more difficult and disabling than removal of a temporary in its spacer.

The intra articular and endosteal use of vancomycin in therapy of periprosthetic joint infection in patient with renal failure poses special challenges due to the risks of overdosage or subtherapeutic concentration. A desired elution of vancomycin in an otherwise healthy patient can evoke concern in a hemodialysed patient because vancomycin couldn't be hemodialysed in standard conditions [8].

2. Material and method

In order to assess the safety of admixture of vancomycin into the ALAC-spacer, vancomycin concentration in serum was tested within 216 hours (9 days) after implantation of acrylic cement spacer loaded with vancomycin and compared with recommended levels of this drug in the course of systemic treatment. Concentrations in intra articular fluid were measured within 47 hours i. e. up to the routine removal of Redon drain. The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. Informed consent has been obtained from the patient for publication. According to the Ethical Committee of Medical University of Warsaw this study is not understood as experiment on humans or animals, but as publication of results of therapy. The patient was a 88-year-old woman with chronic renal failure who was admitted to the hospital with infected prosthesis of right knee. She underwent bilateral total knee arthroplasty (TKA) with cemented IBPS prosthesis 15 years earlier. She suffered from end-stage kidney disease probably due to hypertensive nephropathy and was hemodialysed for two years. Beside the arterial hypertension, she suffered also from stable coronary artery disease. She underwent perforation of duodenal ulcer complicated by peritonitis 2 years earlier, was implanted with central catheters of vena cava superior several times and has arterio-venous shunt for hemodialysis. She had a residual diuresis and was hemodialysed twice a week. On admission she was respiratory and circulatory stable, without edema. The body weight was 55 kg, height 155 cm. The right knee joint was painful, with effusion. Normal active and passive range of motion was maintained. On radiographs no evident periprosthetic osteolysis was visible (Fig. 1a and 1b). Blood parameters were as follows: WBC 11.5 x 10^3/μL, with Neutrophils 95,7%, RBC 4.9 x 10^9/μL, Hgb 115 g/L, HCT 3.62 L/L, PLT 350 x 10^3/μL, sodium concentration 143 mmol/L, potassium concentration 5.1 mmol/L, creatinin concentration 5.0 mg/dL (ref. 0,6-1,3 mg/dL), blood urea concentration 91 mg/dL (ref. 15-38 mg/dL) and C-reactive protein (CRP) 25 mg/L (ref. <10 mg/L). The culture of the joint fluid revealed methicillin-resistant *Staphylococcus*

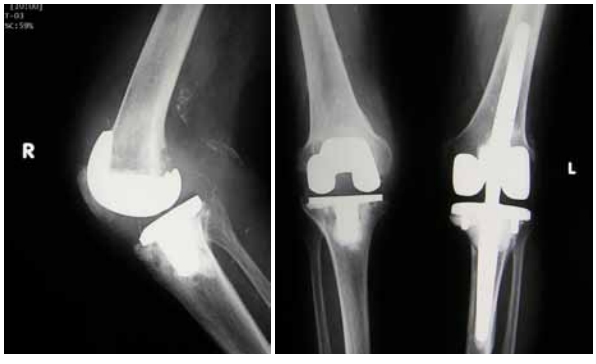

Figure 1a and 1b. Infected right knee prosthesis; left knee without infection.

epidermidis (MRSE), susceptible to gentamicin, vancomycin, teicoplanin, clindamycin, norfloxacin, rifampicin and co-trimoxasole (i.e. trimethoprim-sulfamethoxazole) with the MIC value for vancomycin 2 mg/L. Loosened prosthesis and all infected soft tissue were operatively removed and a hand–made, articulated spacer made of acrylic cement loaded commercially with 0.55 g of gentamicin into 40 g of cement (Palamed G, Heraeus Medical GmbH, Wehrheim, Germany) and additionally loaded with 6 g of vancomycin into a total of 120 g of cement powder was implanted into the joint (Fig. 2). In the intraoperatively taken biopsies of tissues surrounding prosthesis, chronic inflammation with lymphocytes, hemosiderosis, focal haemorrhages and fibrosis was stated. The cultures from the specimens revealed MRSE strain with the same resistance pattern as identified preoperatively. After surgery no systemic antibiotics were administered according to our good experience with only local administration of antibiotics in ALAC and in order to avoid unnecessary load with systemic vancomycin. Patient was hemodialysed on the first postoperative day and then twice a week. Enoxaparine was given during hemodialysis and next subcutaneously 40 mg daily during the whole hospital stay. Postoperative vancomycin concentrations in serum and intra articular fluid were measured using the enzyme immunoassay method Emit (the VIVA-TWIN® System, Siemens). The intra articular drain was removed after 47 hours due to risk of superinfection – according to assumed policy of drain management after prosthesis revision.

Patient was mobilized with knee joint in orthosis with partial weight bearing and discharged on 14th postoperative day when she was fully ambulatory with crutches, the wound was completely healed and the knee joint free of haematoma or signs of infection. Patient underwent 2nd stage 7 months after the 1st stage. For implantation of a new revision knee prosthesis (AGC- Dual Articular, Biomet) the same composition of acrylic cement containing 5% of vancomycin was used. Only two packages of cement were necessary for prosthesis fixation (i. e. totally 80 g of cement with 4 g of vancomycin). The postoperative course was uneventful. After 3 years the knee was free from any infection. (Fig. 3a and 3b).

3. Results

The vancomycin concentrations in serum were tested within 216 hours and in intra articular fluid during 47 hours after implantation of cement spacer and are shown in Table 1. The local concentration of vancomycin in the intra articular drain (intra articular fluid) was maximal 7 hours after surgery and reached maximally 120 mg/L. After 47 hours it was 85 mg/L and still over clinical breakpoint values. The maximal serum concentration with the value 2.6

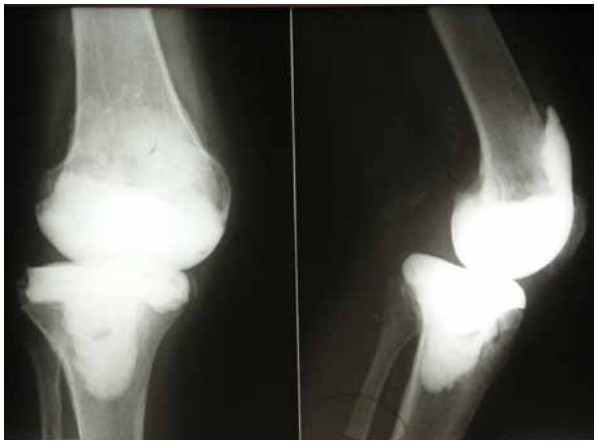

Figure 2. Hand-made spacer containing 5% of vancomycin in 120 g of acrylic cement.

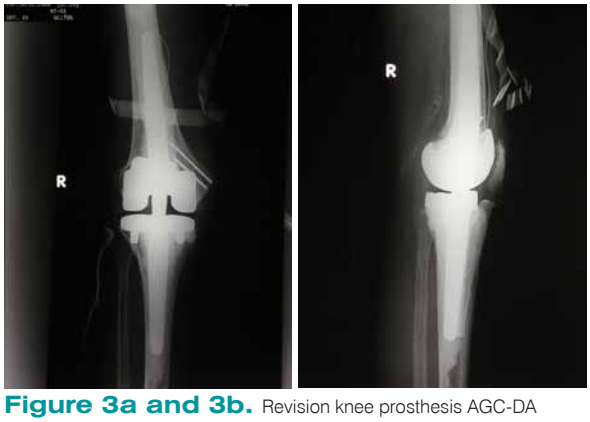

Figure 3a and 3b. Revision knee prosthesis AGC-DA implanted with cement loaded with 5% of vancomycin. Two Kirschner wires stabilising cortical bone of medial femoral condyle are visible.

Table 1. Release of vancomycin from acrylic cement spacer: concentrations in serum and intra articular fluid [mg/L].

A	0	3	5	7	13	17	23	47	53	72	96	115	120	168	216
B				120			90	85							
C	0.0	1.8	2.4	2.5	2.6	2.4	2.2	1.9	2.1	2.2	2.4	2.2	2.2	2.1	2.3

Legend to the table:
A: Time laps from implantation of spacer [hours]
B: Concentration in intra articular fluid [mg/L]
C: Serum concentration [mg/L]

mg/L was reached 13 hours after implantation of spacer. On the ninth postoperative day with the value of 2.3 mg/L it was below the therapeutic concentration assumed for systemic administration, obviously not posing the threat of toxic complications.

4. Discussion

Periprosthetic joint infection is regarded as a rare complication of joint replacement among healthy people with the frequency 0.4-0.5%, but it is emerging as a more common problem in individuals with chronic renal failure or immunocompromised patients, who have undergone joint replacement. In these patients the risk of infection of joint prosthesis related to general status is significantly greater than in healthy people after arthroplasty and is assessed to be as high as 19% [1]. The arthroplasty procedures in patients with end-stage kidney disease who are receiving hemodialysis, are associated with a high rate of complications and death, which can reach up to 29% during postoperative hospital stays [9]. Infection with methicillin-resistant organisms can occur in 10% to 50% of all periprosthetic infections, depending on local prevalence of MRSA and MRSE in surgical site infections [10].

Vancomycin is the antibiotic of choice in therapy of periprosthetic joint infections caused by MRSA, MRCNS, or penicillin-resistant enterococci. Therapeutic effectiveness of vancomycin depends on concentration. Published reference ranges for vancomycin vary from 5-10 to 10-20 mg/L for trough levels (for MRSA recommended 15 mg/L) and 25-50 mg/L for peak levels [2, 11]. Serum concentrations of 5.0–10 mg/L usually ensure that the concentration is above the MIC of most vancomycin-sensitive pathogens and that the drug elimination is adequate [2]. Serum concentrations above 80 mg/L increase the risk of ototoxicity and nephrotoxicity.

ALAC has been widely used both for prevention and therapy of periprosthetic joint infections**.** ALAC has a potential of accumulation of antibiotic, which maintain their antimicrobial activity after exothermic polymerisation process and can elute to surrounding bone and soft tissue. In vitro and in vivo studies has revealed that antibiotics can differ as regards their potential to elute from ALAC depending on cement manufacturer, viscosity and porosity after cure process of the cement, the structure of antibiotics itself, their concentration in cement and thermostability [12]. Some antibiotics like aminoglycosides, vancomycin, teicoplanin, cefalosporines, clindamycin, colistyn, ciprofloxacin and meropenem are recommended for mixing with acrylic cement [12, 13]. Addition of selected antibiotic should depend on the susceptibility of infecting organism, potential of the acrylic cement itself to incorporate and liberate the antibiotic and safety reasons after systemic exposition to the drug. Routine use of vancomycin-loaded acrylic cement should be considered when epidemiologic data show an incidence over 50% of methicillin-resistant strains [14]. It was experimentally established in animal models that gentamicin may diffuse from ALAC to adjacent bone in concentrations 4 folds higher than MIC for more than 6 months and elute to periprosthetic haematoma in concentration 20 folds over MIC [13]. In other studies it was stated that an average 20% of all admixed antibiotic is liberated after implantation of spacer and that 15% of antibiotic is eluted from ALAC during first two weeks after implantation [13]. But based on these data, it is difficult to calculate expected exposition of an individual patient to antibiotics. The optimal concentration for antimicrobial effectiveness of antibiotic into acrylic cement spacer has been experimentally proven to be about 10% [12]. It has been also proven that addition of less than 10% of pulverized antibiotic to the acrylic cement doesn't critically impair mechanical properties of the bone cement for construction of spacer [12]. The addition of more than 4.5 g of gentamicin powder into 40 g pulverized cement polymer or the addition of liquid antibiotics causes a decrease in compressive strength [12]. It has been shown that gentamicin in concentrations from 0.5 g to 2.0 g per 40 g of Palacos acrylic bone cement substantially reduces the shear strength of the cement [12]. For the acrylic cement spacer, which is a temporary implant inserted for a limited time, the mechanical properties are less important than the antimicrobial potential of spacer itself. Commercially available ALAC are usually loaded with low-dose antibiotics (up to 1,0 g into 40 g cement), which is regarded as not therapeutic for invasive infection. For example Spacer G (Tecres, Sommacampagna, Italy) contains 1.9 g of gentamicin powder per 100 g of PMMA polymer powder [15].

Local application of vancomycin in acrylic cement in therapy for periprosthetic joint infections caused by MRSA is still under research. It has been proven in animal studies on 30 sheep that vancomycin can be liberated from a spacer containing 3 g of the antibiotic in 60 g of cement and reaches mean concentration in sheep cortical bone 4 folds (range 3-5) over breakpoint MIC during 3 months [16]. In the same study performed in 10 patients undergoing primary joint replacement using the same vancomycin-containing acrylic cement, the levels in drainage fluids were 5 times over breakpoint MIC after 24 hours and equal to breakpoint MIC after four days. Vancomycin was undetectable in urine after 10 days. In the study by Kelm, 10 hip spacers, containing 1 g of gentamicin and 4 g of vancomycin into 80 g of acrylic

cement (Refobacin-Palacos, Merck, Germany) were studied [17]. The antibiotics' release was determined by measurements in secretion fluid from the intraarticular drainage in 10 patients, every 24 hours. The vancomycin elution was higher than that of gentamicin in all patients. The antibiotic concentrations reached their peak values of 2 to 5 mg/L within the first 2-3 days, and fell constantly over the following 10 to 12 days, eventually under the therapeutic serum concentration values. When adding vancomycin to acrylic cement, it is difficult to precisely estimate the expected dose of antibiotic which will be finally liberated from acrylic cement and get into systemic circulation. For the acrylic cement containing 1 g of gentamicin and 1 g of vancomycin into 40 g of cement (Vancogenx, Tecres, Sommacampagna, Italy), elution tests *in vitro* have shown, that cumulative doses of gentamicin and vancomycin liberated during 24 hours did not exceed recommended daily doses for adults in systemic therapy. Those are 3-5 mg/kg per day for gentamicin and 30 mg/kg per day for vancomycin. It is regarded as unlikely that gentamicin and vancomycin liberated from cement and absorbed from the joint space could reach toxic serum concentrations in healthy people.

In patients with chronic renal failure the ototoxic effect of vancomycin must be considered. When given intravenously in hemodialysed patients, vancomycin dosing is mainly influenced by the timing of administration, the type of filter used, and the duration of dialysis [8]. Transgression of toxic concentration requires high-flux hemodialysis due to high molecular weight of vancomycin. Standard membrane dialysis is largely ineffective and much slower in clearing such molecules [18]. High-flux hemodialysis is characterized by increased clearance of middle-weight molecules (defined by beta-2 microglobulin clearance over 20 mL/min). The high-flux membranes – as compared to conventional hemodialysis – typically have a higher ultrafiltration coefficient and allow for enhanced elimination of larger molecules previously not amenable to hemodialysis.

In presented case measurements of vancomycin concentration in serum and postoperative haematoma in the knee joint with ALAC spacer revealed that intra articular concentrations (85 mg/L) during 47 hours were well over breakpoint MIC of vancomycin for managed MRSE strain. Serum concentrations during nine days were largely below toxic level and thus not requiring high-flux hemodialysis. Despite greater technical problems and time consumption related to intraoperative performance of the spacer and addition of accessory antibiotic, the admixture of 6 g of vancomycin to 120 g of acrylic cement has been proven to be therapeutically effective and safe for presented patient hemodialysed due to chronic renal insufficiency. Besides the antimicrobial effect, the use of acrylic cement spacer with vancomycin allowed for maintenance of the knee mobility and supportive function of the lower extremity in the two stage revision due to TKA infection. Despite of the safety proven in the presented case–when vancomycin is added to acrylic cement in patients with end-stage kidney disease, antibiotic concentration in intra articular fluid and in serum should be monitored. The presented above results should be interpreted with caution and may not be generalised.

5. Conclusion

Addition of 6 g of vancomycin to 120 g of acrylic cement fabrically loaded with 0.55 g of gentamicin per 40 g of cement (Palamed G, Haereus) was found therapeutically effective and not necessitating high-flux dialysis in hemodialysed patient with chronic renal failure. Two-stage revision with the use of acrylic cement spacer loaded with 5% of vancomycin has been proven a suitable method in MRSE periprosthetic joint infection for a patient hemodialysed twice a week due to chronic renal insufficiency.

Conflict of interests

Authors disclose any conflict of interests

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