Original article
https://doi.org/10.18019/1028-4427-2024-30-6-822-830

Clinical results of using a silver-containing preparation as part of an antimicrobial spacer in the treatment of periprosthetic hip joint infection

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Abstract

Introduction Periprosthetic infection (PPI) is one of the most serious complications of primary arthroplasty. Its rates range between 1.1 and 2 %. This study presents a comparative analysis of the results of the sanitizing stage of two-stage treatment of patients with chronic PPI of the hip joint (HJ) using an antimicrobial spacer impregnated with highly dispersed silver and without its impregnation.

Purpose To conduct a comparative analysis of the clinical efficacy of using HD-Ag for impregnation of an antimicrobial spacer in patients with chronic PPI HJ during the sanitizing stage.

Materials and methods A retrospective study is based on the analysis of the treatment outcomes of 223 patients with PPI HJ with antimicrobial spacers implanted during the sanitizing stage. Two groups of patients were formed based on the impregnation of bone cement with only an antibiotic or its combination with HD-Ag, group 1 (n = 112) and group 2 (n = 111), respectively. The evaluation of the treatment outcomes at a follow-up period of at least 2 years was carried out in accordance with the modified Delphi criteria. The reliability of differences in quantitative parameters between the groups was analyzed using nonparametric Mann – Whitney test, whereas Fisher test was used to analyze relative indicators. The differences were considered significant at $p < 0.05$.

Results The spectrum of pathogens was comparable in both groups. The recurrence rate in groups 1 and 2 was 23.2 % and 17.1 %, respectively ($p > 0.05$), while for monobacterial infection caused by gram-positive bacteria it was significantly lower in group 2 ($p = 0.012$).

Discussion As reported, the recurrence rate of periprosthetic infection varies from 8 to 40 %, depending on the nature of the infectious process and the type of pathogen. In the group with the use of HD-Ag as part of an antimicrobial spacer, the effectiveness of the sanitizing stage was 82.9 % and in the comparison group it was 76.8 %. However, a subanalysis of the effect of the etiology of PPIs on treatment results showed that the use of AM-spacer with a combination of silver and vancomycin led to a statistically significant reduction in the risk of recurrence in patients with monobacterial infection caused by gram-positive pathogens and provided arrest of infection in 89.7 % of cases.

Conclusion In the sanitizing stage of two-stage treatment of chronic peri-implant hip infection caused by gram-positive bacteria, the antimicrobial cement spacer impregnated with highly dispersed silver showed high efficiency. However, further development of new combinations for bone cement impregnation is required to expand the spectrum of antimicrobial activity of the spacers.

Keywords: peri-implant infection, periprosthetic infection, antimicrobial spacer, highly dispersed silver, bone cement impregnation

For citation: Bozhkova SA, Gadzhimagomedov MSh, Tikhilov RM, Artyukh VA, Antipov AP, Afanasyev AV, Toropov SS, Muravyeva YuV. Clinical results of using a silver-containing preparation as part of an antimicrobial spacer in the treatment of periprosthetic hip joint infection. *Genij Ortopedii*. 2024;30(6):822-830. doi: 10.18019/1028-4427-2024-30-6-822-830

INTRODUCTION

Currently, joint replacement (JR) is an effective method for treating a number of diseases and injuries of the hip joint, which in some cases has no alternative. Over the years of widespread use of this intervention in practical medicine, implant designs, surgical techniques, and perioperative pharmacological support of patients have been significantly improved, and resulted in excellent anatomical and functional results in the majority of cases. One of the rare but most severe complications of this surgical intervention is periprosthetic infection, the rates of which vary from 1.1 % after primary JR due to osteoarthritis to 2 % after hip replacement (HR) due to a femoral neck fracture [1]. Revision surgeries result in the development of an infectious complication in 7–15 % of cases [2, 3, 4], and currently, according to domestic and foreign authors, infection is one of the main causes of revision joint replacement [5, 6, 7].

Two-stage revision JR is still the operation of choice in most cases of chronic PPI of the hip joint [8]. A recently published meta-analysis analyzed 46 publications with the outcomes of two-stage treatment of 5,009 patients with infections in the hip joint [9]. On average, the recurrence rate of the infectious process was 8.35 %, while in seven studies included in this analysis, the PPI recurrence was diagnosed in more than 15 % of cases: from 16.7 % in the first two years after the second stage [10] to 27 % during a five-year follow-up in the study of Theil et al [11]. The implantation of any type of spacer may result in complications such as recurrence of the infectious process, dislocation, fracture or migration of the spacer, fracture of the femur [12, 13]. Moreover, one of the most significant risk factors for treatment failure was the detection of bacterial growth from the joint during the second stage of treatment [14].

Apparently, one of the reasons for failure to eradicate pathogens in the area of the infection focus may be an ineffective local depot of antibiotics in an antimicrobial spacer (AMS) at the first stage of revision. Despite the fact that the procedure of bone cement impregnation with various antibacterial drugs is currently routine, according to various authors, the release of antibiotics mainly occurs from the outer layer of cement which is 100 μm thick [15] and continues during the first 24–48 hours after which the elution of drugs slows down and does not achieve effective local concentrations to fight against microbial pathogens [16, 17]. Once the antimicrobial activity of bone cement (BC) ceases, the spacer becomes a foreign body on which bacterial cells can adhere with the subsequent formation of biofilms, which can lead to a relapse of the infectious process [18].

Thus, new approaches are needed to improve the efficiency of local AB-therapy by developing methods to expand the spectrum and increase the duration of the antimicrobial activity of cement spacers. One such method may be additional impregnation of AMS with preparations containing metal ions, in particular, silver ions [RU 2 707 734 C1, RU 2 754 075 C1]. An *in vitro* study found that impregnation of bone cement with vancomycin and highly dispersed silver (HD-Ag) contributes to a significant prolongation of sample's antimicrobial activity (up to 34 days), which effectively prevented the formation of microbial biofilms on their surface during the entire period of AB release [19]. However, the clinical efficacy of this combination of antimicrobial drugs has not been assessed.

Purpose To conduct a comparative analysis of the clinical efficacy of the sanitizing stage using HD-Ag for additional impregnation of an antimicrobial spacer in patients with chronic PPI HJ.

MATERIALS AND METHODS

The study is retrospective and is based on the analysis of the results of 223 patients that underwent treatment for chronic PPI of the hip joint at the Department of Purulent Surgery in the period from 2014 throughout 2018. The study included all patients with PPI of the hip joint who, during the specified period, underwent the first stage of a two-stage treatment of hip joint PPI with the implantation of an antimicrobial spacer (AMS) made of bone cement based on polymethyl

methacrylate (PPMA) and from whom the material was collected for bacteriological examination before surgery (aspirates, tissue biopsies) and/or intra-operatively (tissue biopsies and removed implants).

The patients were divided into two groups. In one of the groups, a highly dispersed silver (HD-Ag) preparation (Poviargol, Technolog LLC, Russia) was used for bone cement impregnation. Group 1 included 112 patients treated in 2014–2016, who, during the two-stage treatment of PPI of the hip joint, had an AMS implanted which was based on gentamicin-containing bone cements made of PMMA, additionally impregnated with vancomycin, during the first (sanitizing) stage. Group 2 included 111 patients treated from 2016 to 2018 with AMS impregnated with ancomycin and a silver preparation.

Steps of the sanitizing phase of the two-stage treatment of hip PPI were skin incision along the lateral surface of the thigh with subsequent anterolateral approach to the hip joint; excision of scars in the joint cavity; removal of the femoral and acetabular components of the endoprosthesis or spacer; treatment of the acetabulum with cutters until blood dew; abundant washing of the wound with antiseptic solutions; installation of a cement spacer and drainage; suturing of the wound.

The study assessed the patient's gender, age, duration of the infectious process at the time of the index surgery, white blood cell count, CRP and ESR levels in the blood upon admission and 5–7 days after surgery, type of pathogen, and correspondence of the microbiological examination results (culture and PCR diagnostics) of pre- and intra-operative samples. Patient treatment outcomes were assessed according to the modified Delphi criteria [20]. A satisfactory outcome was defined as the absence of signs of PPI recurrence after the second stage of treatment (reimplantation) or "life with a spacer" without the development of signs of an infectious and inflammatory process for two years after the sanitizing stage. An unfavorable outcome was a relapse of infection after a sanitizing operation or after reimplantation, as well as a death due to the generalization of the infectious process during the follow-up period.

Records, systematization of primary data and visualization of the obtained results were performed in Microsoft Office Excel spreadsheets. Statistical analysis was performed using the Past 4 software system. To describe quantitative indicators, a test for normal distribution was performed. With a normal distribution, the mean value and standard deviation were used to describe the parameter. For distribution different from the normal, the median (Me), and the lower (Q1) and upper (Q3) quartiles (25–75 % ICI) as measures of dispersion were used. The reliability of differences in quantitative parameters (age, duration of the infectious process, number of sanitizing operations at the time of the index operation) between the groups was analyzed using the nonparametric Mann-Whitney test. Fisher's test was used to analyze relative indicators. Differences between the groups were considered statistically significant at $p < 0.05$.

RESULTS

The groups of the study were comparable in terms of age and gender. In groups 1 and 2, the average age of patients was 58 years (CI95 % 53–63) and 60 years (CI95 % 55–65), respectively; the proportion of men was 48.2 % and 51.5 %; The proportion of patients with a history of sanitizing operations in group 1 was slightly higher than in group 2: 22.1 % and 14.4 %, respectively ($p = 0.098$); however, the average duration of the infectious process did not differ significantly in the compared groups ($p = 0.560$).

The groups were comparable in terms of the level of blood inflammation markers (CRP, ESR) and the number of leukocytes at the time of admission of patients to the hospital (Table 1). However, in the group of impregnated silver preparation, more pronounced dynamics of ESR normalization were observed in comparison with the preoperative level ($p = 0.003$) and compared with group 1 ($p = 0.005$).

Table 1

Dynamics of laboratory tests in the groups

Inflammation markers	At admission		*P* value	Before discharge		*P* value
	Group1	Group 2		Group 1	Group 2	
leucocytes, 10^9/l, Me (MIC)	7.8 (6.4–9.4)	7.6 (6–9.3)	0.325	7.2 (5.5–8.2)	6.1 (4.9–8.1)	0.623
CRP, mg/ml, Me (MIC)	25.9 (11.2–44.8)	23.8 (9.3–42.8)	0.203	19.2 (12–31.6)	13.8 (7.2–23.4)	0.339
ESR, mg/ml, Me (MIC)	50 (28–75.5)	51 (27–68)	0.533	47 (34–67.7)	*35 (14–50)	**0.005**

Note: * significantly different from the initial level at admission (p = 0.003)

Analysis of the results of bacteriological tests of intra-operative material showed that positive growth of microorganisms was obtained in 96.4 and 98.2 % of cases ($p = 0.415$), respectively, in groups 1 and 2, while the etiology of PPI was polymicrobial in 27.6 % (31 out of 112 cases) and 18.9 % (21 out of 111 cases) ($p = 0.122$).

The species spectrum of pathogens causing PPI of the hip joint was comparable in the groups (Table 2). The leading pathogens were staphylococci (*S. aureus, S. epidermidis* and other coagulase-negative staphylococci) that comprised 63 % and 56.3 % of the total, respectively in groups 1 and 2. The isolation rates of methicillin-resistant strains was 32.1 % (36 of 112) and 31.5 % (35 of 111) of cases ($p = 0{,}922$). Among gram-negative pathogens in both groups, non-fermenting bacteria (*Pseudomonas aeruginosa* and *Acinetobacter spp*.) were more frequent than *Enterobacteriaceae*.

Table 2

Bacterial spectrum in the groups

Возбудители	Group 1 (*n* = 112)		Group 2 (*n* = 111)		*P* value
	N	%	*N*	%	
S. epidermidis	46	32.2	39	29.3	0.610
S. aureus	37	25.9	32	24.0	0.729
Enterococcus spp.	12	8.4	20	15.0	0.073
Non-fermenting bacteria (*P. aeruginosa* and *Acinetobacter spp*.)	8	5.6	10	7.5	0.627
Other CoNS	7	4.9	4	3.0	0.424
Streptococcus spp.	10	7	6	4.5	0.379
fem. Enterobacteriace	7	4.9	4	3.0	0.424
Propionibacterium spp.	5	3.5	3	2.2	0.540
Corynebacterium spp.	3	2.1	2	1.5	0.712
Candida	2	1.1	0		0.172
Other	6	4.2	13	9.8	0.107
Total	143	100	133	100	

Note: other CoNS — coagulase-negative staphylococci except *S. Epidermidis*; N — number of patients in the groups

It was established that the results of microbiological tests of pre- and intra-operative materials completely coincided only in 47.3 % (53 of 112) and 56.7 % (63 of 111) of cases, respectively, in groups 1 and 2 (Fig. 1).

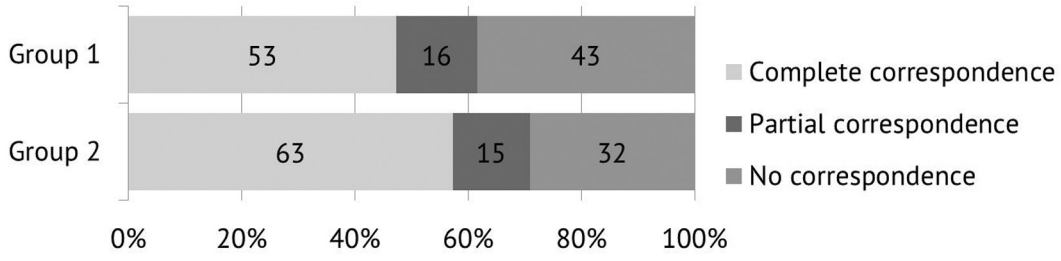

Fig. 1 Correspondence of the results of microbiological examination of pre- and intraoperative biomaterial samples

The analysis of treatment outcomes showed that the recurrence rate in Group 1 was 1.7 times higher than in group 2, 23.2 % (26 of 112) and 17.1 % (19 of 111) of cases, respectively ($p = 0.257$). At the same time, in patients with monobacterial PPI caused by gram-positive bacteria when AMS was impregnated with the silver preparation, relapses of the infectious process were diagnosed almost two times less frequently ($p = 0.012$) than in the comparison group (Table 3).

Таблица 3

Frequency of recurrent infection depending on the etiology of PPI at the time of index surgery

Infection etiology	Group 1			Group 2			*P* value
	Total	Recurrence		Total	Recurrence		
		N	%		*N*	%	
Монобактериальная Гр+	69	18	26.1	78	8	10.3	**0.012**
Монобактериальная Гр–	8	1	12.5	10	4	40	0.196
Полибактериальная	31	7	22.6	21	7	33.3	0.345

Re-implatation arthroplasty was performed in 73.2 % (82 of 112) and 73.0 % (81 of 111) of patients in groups 1 and 2, respectively. The average period between stages was 8.4 months. At the time of the survey, no information was found on the development of recurrent infection after the second stage. The rest of the patients preferred "life with a spacer" or are in the waiting list for hospitalization to undergo the second stage of treatment.

DISCUSSION

The installation of an antimicrobial spacer at the sanitizing stage of a two-stage revision has two main goals: to increase the effectiveness of systemic antibacterial therapy by creating a local depot of antibiotics in the bone cement and to maintain the anatomical relationship in the joint by filling in tissue defects after the removal of the endoprosthesis components [21]. An ideal spacer should ensure long-term elution of the antimicrobial drug in an effective concentration to stop the infection and prevent the selection and spread of multiresistant bacterial strains [22].

There are many known factors that influence the pharmacokinetic properties of antimicrobial spacers *in vivo*, including differences in the brand of bone cement used, the method of mixing it, the addition of one or a combination of two or more antibiotics, their dose and/or ratio, the duration of spacer implantation, etc. [22]. Despite the fact that the duration of the antimicrobial activity of bone cement has been well studied *in vitro* [16, 23] one cannot directly extrapolate the findings to the clinical situation. At the same time, the number of publications reporting on the elution of antibiotics *in vivo* is limited, and they are characterized by significant discrepancies in the results of determining the maximum concentration of the drug and the duration of its release from the cement [22]. Therefore, in our study, we took the proportion of patients with no signs of infection within two years after the debridement operation as the clinical efficacy of PPI treatment.

The overall effectiveness of treating chronic PPI of the hip joint in the analyzed sample of patients within a two-year follow-up was 79.3 %. It should be noted that the data on the effectiveness of chronic peri-implant infection arrest in the hip joint area in the scientific literature vary greatly. Thus, Petis et al report that the proportion of patients with hip joint PPI arrest was 90 % at 1-year follow-up after revision surgery and 86 % after 5 years [24]. In another study, the authors observed the absence of signs of an infection for two years in 83.3 % of patients [10]. However, it is known that the risk of relapse after sanitizing surgery for PPI of the hip and knee joints significantly depends on the pathogen and is 25–67 % [21, 25, 26]. One of the most significant predictors of treatment failure is considered to be the involvement of gram-negative bacteria and microbial associations in the etiology of PPI, that result in poor outcomes in almost half of the cases [27, 28, 29].

In our study, gram-negative bacteria were isolated in 15.4 % of patients, and in 21.8 % of cases, PPI was caused by microbial associations, which generally corresponds to the reported data of scientific publications. The rates of gram-negative bacteria in the spectrum of PPI pathogens vary from 11.3 to 60.0 % as found by different authors [30, 31, 32]; the incidence of polymicrobial infection ranges from 25 to 45 % of cases [20, 33]. In our cohort of patients, relapses with the participation of gram-negative pathogens in the etiology of the infectious process in the first two years after the sanitizing operation developed 1.5 times more frequently than with PPI caused by gram-positive bacteria, and 1.4 times more frequently in the case of microbial associations than with monobacterial infection. One of the reasons for this may be the low efficiency of antimicrobial spacers impregnated with vancomycin, a drug active only against gram-positive bacteria. The discrepancy (partial or complete) between the results of microbiological examination of pre- and intraoperatively collected materials that we identified indicates the impossibility of impregnating bone cement with an antibiotic with etiotropic action in 47.5 % of cases.

In the group using the HD-Ag preparation as part of the antimicrobial spacer in our study, the efficiency of the sanitizing stage was 82.9 %, and 76.8 % in the comparison group. However, a subanalysis of the effect of the PPI etiology on the treatment results showed that the use of an AM spacer with a combination of a silver preparation and vancomycin led to a statistically significant decrease in the risk of relapse in patients with monobacterial infection caused by gram-positive pathogens (OR 0.840; CI 95 % 0.735–0.960), and provided the arrest of infection in 89.7 % of cases. However, this combination did not have a positive effect in the subgroups with PPI caused by gram-negative bacteria and microbial associations.

Silver nanoparticles are known to have an antibacterial effect, but the mechanism of their action on bacteria is not specific, and therefore they act almost equally on gram-positive and gram-negative bacteria [34]. It is reported that silver nanoparticles penetrate into the cell and bind to cell structures [35], act on DNA, preventing the proliferation of bacterial cells, and also destroy the cytoplasmic membrane and lead to the death of bacteria [36]. To date, a number of studies have shown that combinations of nanosilver with antibiotics increase the activity of the latter against strains with multiple drug resistance [37, 38]. Previously, we showed that poviargol contributed to the preservation of the antimicrobial activity of bone cement samples for up to 34 days and prevented the formation of microbial biofilms on them. Apparently, this is what is associated with the greater effectiveness of the complex treatment of patients with chronic PPI of the hip joint caused by gram-positive bacteria. In our opinion, this result may be a consequence of both a longer release of the antimicrobial drug from the bone cement due to an increase in its porosity, and the presence of a synergistic effect of vancomycin and the drug HD-Ag in relation to the inhibition of biofilm formation, proven in a study by other authors [39]. It is possible that the effect of poviargol on microorganisms at the cellular level is also due to the more pronounced dynamics of ESR normalization ($p = 0.005$) and the tendency to a greater decrease in CRP ($p > 0.05$) in the group with bone cement spacers impregnated with the silver drug.

It is important to remember that impregnation of bone cement with additional preparations affects the mechanical and physical properties of the antimicrobial spacer. We previously showed that adding vancomycin or its combination with 2.5 wt. % silver to bone cement did not lead to any deterioration in the mechanical properties of bone cement under bending and compression. A further increase in the silver content to 10 wt. % worsened the strength and elasticity under bending, but did not significantly affect the mechanical properties under compression and significantly increased the antimicrobial activity of the samples [40]. In our opinion, at the sanitizing stage, a decrease in the strength of the spacer is a largely positive factor, since it allows the spacer to be removed without any particular technical difficulties at the stage of reimplantation. However, this limits the use of the combination for permanent fixation.

It is also worth noting that in our study, no cases of reaction of the silver preparation with surrounding tissues, cases of argyria or other adverse events were detected.

CONCLUSION

Impregnation of bone cement based on polymethyl methacrylate with a combination of vancomycin and a highly dispersed silver preparation demonstrated significant clinical efficacy in arrest of periprosthetic hip joint infection caused by gram-positive bacteria (*Staphylococcus spp., Streptococcus spp., Enterococcus spp., etc*.). However, the absence of a significant clinical effect in a subgroup of patients with infection caused by gram-negative pathogens and microbial associations, as well as a significant proportion of cases where the final microbiological diagnosis is established only based on the results of a study of intra-operatively collected materials, indicate the need to develop new combinations for impregnation of bone cement in order to expand the spectrum of antimicrobial activity of spacers.

Conflict of interests *The authors read and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work to ensure that any potential questions related to the accuracy or reliability of any part of the work are appropriately reviewed and resolved.*

Funding source *The work was carried out within the framework of the state assignment for the Federal State Budgetary Institution Vreden National Medical Research Center of Traumatology and Orthopaedics of the Ministry of Health of the Russian Federation (registration number 056-00055-23-00).*

Ethical statement *All manipulations involving human participants in the study were in accordance with the ethical standards of the institutional and/or national scientific ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.*

Informed consent *Not required for this type of study.*

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The article was submitted 01.04.2024; approved after reviewing 20.09.2024; accepted for publication 21.10.2024.

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