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Treatment of Periprosthetic Infection with Silver-Doped Implants Based on Two-Dimensionally Ordered Linear Chain Carbon

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Abstract

Relevance. Formation of pan-resistance microorganisms, microbial biofilms on implants and recurrent infection rate stimulate the search for optimal prosthesis materials for treatment of periprosthetic infection (PJI). ***Purpose of the study*** — to compare the efficiency of two stage PJI treatment with simultaneous implantation of a spacer in combination with implants with silver-doped coatings based on two-dimensionally ordered linear chain carbon (TDOLCC+Ag) during the first stage and the conventional revision with a spacer only. ***Materials and methods.*** The study included 72 patients with PJI of the knee (n = 42) and hip (n = 30) joints. Control group (conventional revision) consisted of 35 patients and the main group (TDOLCC+Ag coated implant incorporated in a spacer) — 37 patients. Mean age of the patients was 61 years. Temporary components were replaced by the final components during revision at the second stage. Evaluation methods: clinical, X-ray, laboratory, microbiological and follow up history. ***Results.*** Inflammation markers and synovial fluid cytosis in the groups at the first revision stage featured equal high base values. During the second stage leucocyte count and cytosis reached normal values, ESR decreased twofold in both groups, CRP decreased five times in the main group. Throat and nasal swabs demonstrated growth of Staphylococcus aureus at 24.3-32.4% in both groups. The leading inducer of PJI was staphylococcal flora with MRSA share of 7.1% and MRSE — from 62.5 to 66.7%. End-points of evaluating treatment outcomes were revision spacer implantation at the second stage of sanation and recurrent PJI. Control group featured implantation of more revision spacers (5) as compared to the main group (1) after the treatment. Two recurrent PJIs were reported for the control group in 11 months while no recurrent infection was reported for the main group. ***Conclusion.*** The study demonstrated statistically significant improvement in the outcomes of PJI treatment by spacers with implants coated by TDOLCC+Ag as compared to the conventional treatment option.

Keywords: periprosthetic infection, revision arthroplasty, implants, microbial films, antibiotic resistance, antibacterial coating.

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Introduction

Increasing number of joint arthroplasties leads to the increasing rate of infectious complications [1, 2]. According to M.M. Kheir et al [3] and V.E. Krebs et al [4] the infectious complications constitute up to 2.2% after hip joint arthroplasty (HA) and to 2.3% after knee joint arthroplasty (KA). In Russian Federation the complications rate after HA was 0.4% and 0.2% after KA in 2017 [5].

Treatment of peri-prosthetic joint infection (PJI) is always challenging and cost-consuming. It is related to pan-resistance of microorganisms, microbial bio-films on prosthesis components, bone stock deficit resulting from each subsequent surgery, high costs due to multistage procedures and recurrent infection rate. PJI also has a social aspect to it while such complications result in decline in quality of life, various disabilities and possible lethal outcome for the patients [6, 7].

Staphylococcus aureus in nasopharynx is a significant risk factor for surgical site infection [8, 9, 10, 11]. PJI prophylaxis by decolonization of MRSA may reduce the number of surgical site contamination approximately by 39% [12].

Currently two stage revision is most often used for treatment of PJI. Aim of the first stage is joint sanation and spacer insertion along with mechanical debridement of pathological tissues including ultrasound method to destroy microbial biofilms. Final prosthesis was implanted as the second stage. Biofilm protects the pathogens from antibiotic exposure [13]. It's necessary to create conditions preventing microbial biofilms formation in the area of the temporary (spacer) or final prosthesis [6, 14] to improve treatment outcomes.

Creation of implants with surface bacterial activity is a promising area in the medicine. Some studies were dedicated to examination of the modified properties of implant surface aimed at minimizing bacterial adhesion, inhibiting biofilm formation and providing effective eradication of bacteria to protect implanted biomaterials. One of the studies demonstrated biofilm inhibition on titanium implants on iodine carrier [15]. Another publication reports the results of implants with diamond-like coating in orthopaedic surgery [16].

A method of processing for titanium plates by silver-doped two-dimensionally ordered linear chain nanostructured carbon (TDOLCC+Ag) (patent of Russian Federation № 2697855) was developed, tested *in vitro* and patented in the framework of a multicenter clinical research under the aegis of The Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy (IACMAC).

Laboratory tests have proven the ability of above coating to completely prevent formation of microbial biofilms by antibiotic resistant *S. aureus* and *P. Aeruginosa* strains with earlier identified high potency for film formation. Coatings were created by ion-stimulated carbon condensation in the vacuum on the surface of titanium plates [17].

Considering the fact that biofilm starts forming in the first hours after arthroplasty it's very important that the implant material was resistant to biofilm formation and non-toxic for the patient [7, 18]. During the study the TDOLCC+Ag coatings were examined in respect of antibacterial activity, surface bactericidal activity, resistence to mechanical effect, anti-biofilm activity and biocompatibility. Observed bactericidal activity towards antibiotics resistant strains of microorganisms as well as ability of coatings to prevent biofilms formation [7] combined with high mechanical resistance and absence of cytotoxic effect [18] served as a basis for a hypothesis on a possible improvement of efficiency of sanation surgeries for PJI treatment by using silver coated implants.

Purpose of the study — to compare efficiency of two stage revision procedure for PJI treatment including implanting in the first stage of a spacer with implants coated by silver-doped two-dimensionally ordered linear

chain carbon (TDOLCC+Ag) and a conventional treatment method using only a spacer for revision.

Materials and Methods

The study included 72 patients with PJI developed after hip and knee arthroplasty who underwent treatment in 2017-2018 at the Federal center of traumatology, orthopaedics and arthroplasty under the Health Ministry of Russia (Cheboksary), hereinafter — the Center. The study was performed in compliance with ethical principles of Declaration of Helsinki of 1975, rev. of 1983.

Inclusion criteria — PJI developed after primary and revision hip and knee arthroplasty.

Exclusion criteria — planned one stage revision, patient's refusal to participate in the study.

All patients in both groups were given etiotropic antibiotics therapy (ABT) in accordance with approved algorithm: 2 weeks — intravenous, next 6 weeks — peroral, break for 2 weeks, afterwards — triple microbiological control testing of synovial fluid from the operated joint [19]. The average interval between two stages of revision was 13 weeks [95% CI 6; 56].

The first stage consisted of surgical debridement of the purulent site, revision with removal of pathological tissues and implants, remnants of the bone cement, thorough rinsing of surgical would with pulse-lavage. Then a preselected or intraoperatively formed spacer (using moulds of individual dimensions) was implanted. Antimicrobial spacer component consisted of bone cement with gentamicin adding vancomycin powder calculated as 5-10% of the cement mass (depending on microorganism isolated during diagnostics stage).

Patients were divided into groups depending on time of surgery: all patients with PJI operated in 2017 were included into the control group, and all patients operated in 2018 — into the main group (after implants with TDOLCC+Ag became available at the Center).

During the first stage of revision spacers with antibiotics (AB) were implanted in group I (control) which included 35 patients (Fig. 1 a). 37 patients of group II (main) received AB spacers and implants with TDOLCC+Ag during the first stage of treatment (Fig. 1 b).

Fig. 1. Implant types:
a — no coating; б — with TDOLCC+Ag coating

TDOLCC+Ag coating was generated in a PVD Coating Machine "URM 3.279.070 Diamond" (Russia) by ion-stimulated carbon and silver condensation. Holes were drilled in a graphite cathode where silver pins were then inserted. TDOLCC+Ag film was synthesized by condensation of silver and carbon ions on titanium implant in the result of thermal evaporation and ion sputtering argon in the argon ions flow (Fig. 2).

The serial implants with silver sprayed coating to prevent colonization of infectious agent without changing geometry of the implant are not custom made. For treatment of knee PJI the coating was applied on tibial components, for hip PIJ — on stem and head of temporary prosthesis. The coating area of implants does not play a role due to no direct curative effect. Preservation or replacement of knee ligaments prior to insertion of a temporary implant was of no importance and was not considered for evaluation of results while there was no aim to decrease joint mobility at the present treatment stage. Fixation of implants coated by TDOLCC+Ag was achieved by cement with AB (gentamicin with vanco-

mycin depending on isolated pathogen). The authors did not evaluate the presence and volume of possible bone defects prior to the second stage of revision due to no relation between purpose of the study and specifics of bone tissue of the patient.

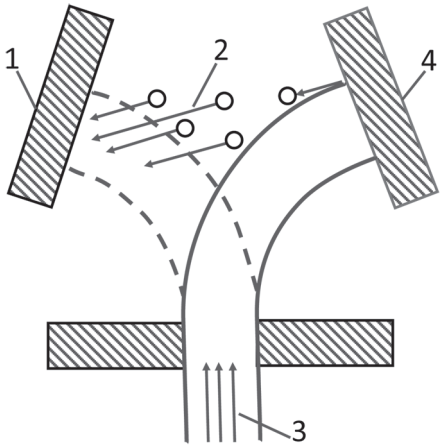

Fig. 2. Drawing of obtaining carbon films:
1 – base (titanium plate);
2 — carbon stream;
3 — stream of argon ions;
4 — graphite target

PJI diagnostics was based on clinical data: pain, fever or local hyperthermia, edema, fistula (basing on US test and fistulography) and positive blood culture, all being separate symptoms or a combination of those. Diagnosis was supplemented by X-ray examination and laboratory tests (increased leucocyte count and ESR in the general blood test, CRP, cytosis manifestation in synovial fluid with bacteriological culture). According to requirements of the authors the patients should have presented the results of three punctures prior to the first stage of revision, one of such punctures was mandatary performed in the Center. In case of a highly virulent organism (*Staphylococcus aureus*, gram-negative and anaerobic flora) it was sufficient to receive result of one puncture [19]. Considering presented aspirate tests the cytosis examination of synovial fluid prior to the first stage of treatment was performed once or up to three times. Joint punctures with evaluation of cytosis level were made with the same frequency prior to second stage of sanation to control its efficiency. Interval between punctures was 1-7 days. Cytosis values in the groups were calculated as arithmetic mean separately for single, double and triple punctures.

Pharynx and nasal swabs for presence of *Staphylococcus aureus*, MSSA and MRSA were taken in patients at PJI diagnostics stage. Intraoperatively during first and second stage of revision procedure the authors harvested tissues (from 3 to 6 specimen) for microbiological examination as well as removed components (including temporary implants coated with TDOLCC+Ag). To isolate microorganisms from microbial films the removed components were treated in ultrasound cleaner BRANSON 8510 (USA) for 5 minutes at frequency of 40±2 kHz and capacity of 0.22±0.04 W/cm^2 followed by culturing of obtained lavages.

During catamnesis stage the authors verified and evaluated the outcomes of revision arthroplasty (PJI recurrence). Follow up periods were calculated as arithmetic mean of months from the second stage sanation to control examination of the patient, and averaged 11 months [95% CI 24; 30].

Study design is presented on Figure 3.

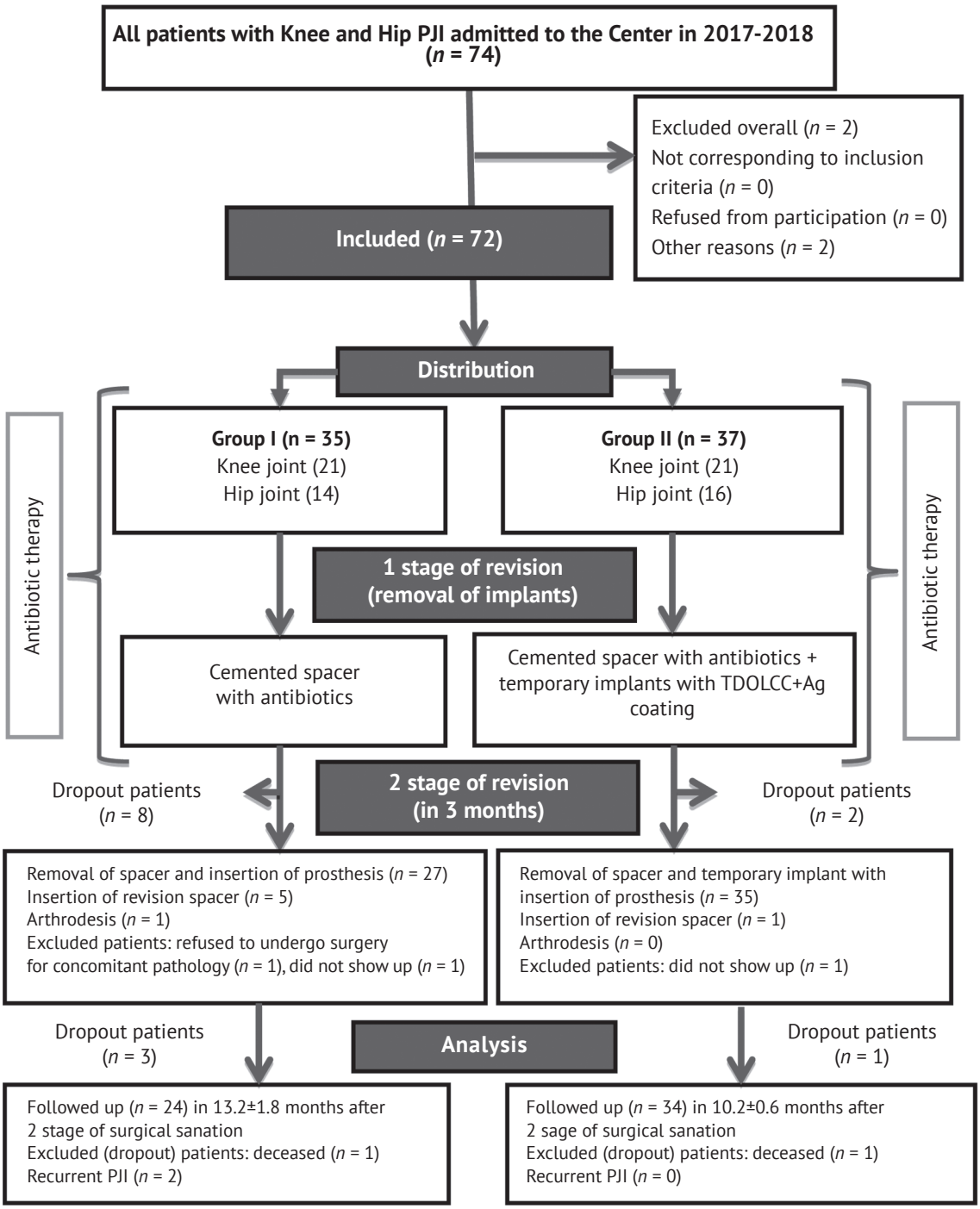

Fig. 3. Study design flow diagram

Statistical analysis

Primary processing of the data included development and filling of an individual electronic medical history of patients in the medical information system "Medialog" for each observation unit, recording in fixed time periods (prior to surgery, intraoperatively and at catamnesis), establishing study protocol on control time points. Data sampling from MIS "Medialog" was performed in accordance with specified parameters.

Statistical processing of obtained data was made by Microsoft Excel 2007. Matching of the selection values to the normal distribu-

tion in MS Excel was verified by a graphic method which allowed to reflect the results as arithmetic mean (M) and standard error (m). Student t-test, Fisher's test, χ^2 were used to evaluate statistical significance of differences of average values in the groups. With 95% confidence interval the difference was considered significant at $p<0.05$.

Results

Initially 74 patients with PJI were included into the study. Two patients were excluded from control group due to single stage revision performed in a period up to 4 weeks after primary hip arthroplasty. To select the surgical tactics of PJI treatment (number of stages in revision procedure) the authors considered the history of its first manifestation at the moment of patient referral to the Center.

10 patients dropped out at the second stage of treatment. 8 patients dropped out from control group: revision spacer — 5, arthrodesis — 1, refusal from surgery due to concomitant pathology and "life with spacer" — 1, and one patient did not show up for unknown reason. 2 patients dropped out from the main group: revision spacer — 1 and one patient did not show up due to referral to another medical facilities.

Patient groups were equal in gender: ratio of men and women was 20 and 15 in group I, and 19 and 18 in group II, respectively. Mean age in groups was 61 years [95% CI 30; 80]. There were no differences in respect of infection site: knee joint — 21 case in each group, hip joint — 14 in group I and 16 in group II. Analysis of complications after knee and hip arthroplasty for 2017-2018 demonstrated development of PJI after primary procedure in the period up to 4 weeks (early) in 10 patients in group I and in 13 patients in group II; after 4 weeks (late) — in 27 and 24 patients respectively. Groups were comparable in respect of PJI development time ($p>0.05$).

8 out of 10 patients from group I (control) with early PJI referred to the Center in the period up to 4 weeks after primary arthroplasty which was an indication to performed two stage revision.

PJI clinical picture in both groups manifested by pain syndrome in 100% of cases. Edema and hyperemia in group I was reported in 67,2% and 32,4% of patients, in group II — in 62,8% and 37,2% of cases, respectively. Fistula was observed in group I in 27% of cases, and in group II — in 23,3% of cases. Sepsis diagnosis was confirmed clinically and by laboratory tests in each of study groups (one case per each group).

Testing of pharynx and nasal swabs for presence of *Staphylococcus aureus* provided positive results in 12 cases (32.4%) in group I and in 9 cases (24.3%) in group II which indicates significance of opportunistic infection carriage for PJI etiology.

Examination of inflammation markers at the PJI diagnostics stage demonstrated excessive values in both groups without significant differences in leucocyte counts as well as ESR and CRP levels. During treatment of PJI the leucocyte count in both groups reached normal values ($4–9\times10^9$/l) ($p<0.05$). The authors observed statistically significant decrease of ESR — twofold as compared to baseline (<20 mm/h in both groups); significant five times reduction of CRP in the main group (<5 mg/ml). CRP in dynamics was not evaluated in control group (Table 1).

Triple examination of cytosis of the synovial fluid during PJI diagnostics stage demonstrated excess leucocyte counts in both groups (Table 2).

During treatment the authors observed significant decrease in leucocyte count in synovial fluid up to target values (with knee or hip prosthesis) in both groups.

The microbiological landscape of examined aspirates, tissues specimens and lavages from removed implants (after ultrasound cleaning) in both groups in half of all the cases (group I — 52.6%, group II — 48.6%) was represented by staphylococcal microflo-

ra where share of coagulase-negative staphylococci was 36.8% and 21.6% respectively. In the structure of staphylococcal microflora the MRSA share took 7.1% in each of the groups, MRSE specific weight in group I was 66.7%, in group II — 62.5% (Table 3).

Table 1

General blood analysis at stages of revision arthroplasty

Parameters	Group	Prior to first stage of revision arthroplasty		Prior to second stage of revision arthroplasty		*p* prior to 1 stage vs prior to 2 stage
		M±m	*p**	M±m	*p**	
Leucocyte count, 10^9/l	I	9.4±0.5	>0.05	6.7±0.3	>0.05	<0.05
	II	9.2±0.5		7.0±0.3		<0.05
ESR, mm/hour	I	56.4±4.2	>0.05	21.4±3.2	>0.05	<0.05
	II	60.2±5.4		25.2±3.4		<0.05
CRP, mg/ml	I	73.3±12.2	>0.05	–	–	–
	II	71.2±10.6		13.2±2.2		<0.05

* Group I in contrast to group II.

Table 2

Results of triple examination of synovial fluid punctures in study groups at the PJI diagnosis stage and after sanation

Group	Puncture											
	Prior to first stage of sanation						Prior to second stage of sanation					
	first	*p*	second	*p*	third	*p*	first	*p*	second	*p*	third	*p*
I *n* = 35	22694± 5739.2 (*n* = 20)	<0.05	14813± 8506.4 (*n* = 8)	<0.05	24045± 14547.2 (*n* = 7)	>0.05	369.3± 144.9 (*n* = 19)	<0.05	480.3± 176.2 (*n* = 4)	>0.05	308± 107.8 (*n* = 12)	>0.05
II *n* = 37*	52919± 10199,8 (*n* = 6)		41090,2± 8978,4 (*n* = 15)		23608± 10219,3 (*n* = 14)		1475,6± 523,1 (*n* = 16)		1331,9± 768,6 (*n* = 11)		527,4± 243,5 (*n* = 10)	

* Punctures prior to first stage of sanation were not performed in 2 patients of group II due to fistula.

Table 3

Microbiological data in groups I and II basing on microbiological culture of aspirates from intraoperative tissues and lavages from removed implants

Pathogen	Group I	Group II
Culture negative	6 (15,8%)	9 (24,3%)
Staphylococcus aureus	14 (36,8%)	10 (27%)
Coagulase-negative *Staphylococci* (CoNS)	6 (15,8%)	8 (21,6%)
Gram-negative *bacilli*	2 (5.3%)	1 (2.7%)
Streptococci, Enterococci	6 (15.8%)	6 (16.24%)
Mixed infection	4 (10.5%)	3 (8.2%)

In recent years the epidermal staphylococcus (opportunistic human microflora) holds second place after *Staphylococcus aureus* in the etiology of implant-associated infection after orthopaedic surgeries [25, 26] which is also confirmed by our data. Culture negative infections were observed in group I in 15,8% of cases, in group II — in 24.3% of cases. Literature demonstrates similar results in 8-45% of cases and often related to preceding antibacterial therapy [27, 28, 29]. Gram-negative infection was present in a small share of cases.

Mixed infection was observed in 4 cases in group I in combination of: 1) *Staphylococcus aureus, Streptococcus oralis/mitis*, *Acinetobacter baumanii;* 2) *Streptococcus oralis/mitis, Streptococcus salivarius*; 3) MRSE, *Corynebacterium striatum*; 4) *Streptococcus agalactae, Corynebacterium minutissimum*. Group II featured three combinations: 1) *Staphylococcus aureus* MRSA, *Corynebacterium striatum*; 2) *Burkholderia cepacia complex, Staphylococcus aureus;* 3) *Enterobacter cloacae*; *Corynebacterium striatum, Enterococcus faecalis*.

Lavages from implant surfaces after ultrasound cleaning had the most sensitivity for obtaining positive cultures from examined biological materials in both groups. Less sensitivity was characteristic for aspirates (group I — 67.7%, group II — 92.8%) and tissue biopsy specimens (96.7% and 71.4% respectively).

Positive culture of the aspirate (*Staphylococcus aureus*) after first stage of sanation were more often observed in group I ($n = 3$) in contrast to group II ($n = 1$). However, the differences were not statistically significant ($p>0.05$). Besides, group I had patients ($n = 2$) with negative results of culturing but with a set of signs of continued PJI (clinical picture of infection, high parameters of cytosis of aspirates and preserving leukocytosis with increased ESR). Due to failed first stage of sanation 5 patients (14.3%) in group I and 1 patients (2.7%) in group II underwent secondary sanation. Despite no statistical differences there is a clear tendency to a higher efficiency of experimental spacers ($p = 0.0891$). One case in control group resulted in joint arthrodesis. Catamnesis revealed 2 cases of recurrent PJI in control group and one lethal outcome per each group (Table 4).

F-test and χ^2 value verified statistical significance of reported variances in failure rate in both groups ($p<0.05$).

Table 4

Outcomes of PJI treatment

Follow up period	Outcome	Group I $n = 35$	Group II $n = 37$
Interim, 13 weeks after the first stage [95%CI 6;56]	Positive aspirate culture	3	1
	Negative culture + clinical PJI manifestation	2	0
	Re-revisions	5	1
Final, 11 months after the second stage, [95% CI 2;30]	«Life with spacer»	1	0
	Lethal outcome (unknown cause)	1	1
	Patients not examined, reasons for no show up	1 (unknown)	1 (patient addressed another medical facility)
	Recurrent PJI	2	0
	Arthrodesis	1	0

Discussion

While PJI is a problem both for patient and for surgeon, there are various tactical approaches to its treatment. Recently more and more authors incline to a single stage tactics [30, 31, 32]. In the present study the authors had two cases of single stage revisions in patients with early PJI who referred to the Center within 4 weeks from its onset.

However, the real practice demonstrates that despite manifestation of infection within 4 weeks from primary surgery the patient is admitted to the hospital at a later period of time, so surgeons have to do the two-stage procedure [20, 33]. At the same time in outpatient facilities the patients receive medical care mainly based on recommendations for antibiotics administration which allows microorganisms to mutate and develop resistance mechanism (selection of resistant strains) and cause latent character of inflammation. 4 weeks timeline is often missed and at a later stage biofilm becomes mature [20], thus two-stage sanation remains the main tactics for PJI treatment in the majority of cases, what was attempted in the present study. To perform a more efficient sanation on the first stage the authors searched for such implant surfaces that would feature a set of properties helping to prevent biofilm formation, possessing bactericidal effect and biocompatibility. Titanium surfaces with TDOLCC+Ag coating possessed such properties. The present study confirmed that patients with PJI often have aggravated history of chronic infection (*Staphylococcus aureus* carriage in nasal passage and pharynx). Some authors consider that carriage of *Staphylococcus aureus* increases risk of infection complications in patients at 85% [21].

Microbial flora of PJI is mainly represented by gram-positive bacteria. Data of the authors correspond to world statistics: first place is held by *Staphylococcus aureus*, second — by *Staphylococcus epidermidis* [34]. *Staphylococcus aureus* is the reason for failed sanation (confirmed by positive cultures at control stage of treatment in both groups) while this pathogen is characteristic for ability to form microbial biofilms [35].

It's worth noting that excellent outcomes were obtained for examination of lavages from implant surfaces after ultrasound cleaning in contrast to aspirate and tissue biopsy specimen tests. The authors consider lavages examination as the most sensitive for identification of pathogens protected by microbial biofilm [20, 21, 22]. Positive microbiological culturing for PJI diagnosis after joint puncture reaches only 93% [30], sensitivity of culturing for tissue biopsy specimens varies from 65 to 94% [24].

In the authors' opinion the examination of cytosis in synovial fluid both at diagnostics stage and at treatment controls is of a great importance. It supports surgeon in selection of operative treatment tactics: in the present study this examination determined the choice of secondary sanation despite negative culture results (probably stipulated by ABT). Synovial fluid examination according to many authors has a high specificity (97-98%) and diagnostic value [23, 24]. Decreased level of cytosis at each subsequent puncture can probably be explained by mechanical evacuation of leukocytes in synovial fluid. Tendency to higher cytosis in the main group as compared to control group in the authors' opinion can be explained by non-specific reaction to an implant with TDOLCC+Ag coating.

While there is no universal surgical treatment of PJI we need an individual approach to each patient considering timelines of PJI, clinical picture, somatic status and isolated pathogen. Two-stage treatment tactics selected for patients in the present study demonstrated a high efficiency of using spacer along with implants coated by TDOLCC+Ag.

The study demonstrated statistically significantly better outcomes of PJI treatment after use of spacers with TDOLCC+Ag coated implants. Laboratory verification was obtained by decreased cytosis level in synovial

fluid, inflammation markers (to normal values) prior to second stage of revision procedure. Clinically in the main group of patients the authors observed a higher efficiency of sanation as compared to control group in respect of microflora culturing and spacer insertion. Catamnesis revealed advantages in use of spacers with TDOLCC+Ag coated implants such as no recurrence of PJI in the short term.

To perform a further analysis of efficiency of "silver" spacers the late follow up evaluation is needed as well as research in larger groups which can provide more precise results.

Publication ethics

All patients gave voluntary informed consent to publication of clinical cases.

Local ethical committee approved the present study.

Competing interests: The authors declare that there are no competing interests.

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Authors' contribution

Nikolaev N.S. — concept and design of the study, literature review.

Lyubimova L.V. — preparing text of publication.

Pchelova N.N. — collection of clinical material.

Preobrazhenskaya E.V. — data processing, editing of text.

Alekseeva A.V. — study design.

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