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Treating Periprosthetic Joint Infection With Silver-Impregnated Carbon-Coated Spacers: Mid-Term Outcomes

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Abstract

Background. Periprosthetic joint infection (PJI) is a severe complication of arthroplasty. The widely accepted treatment standard for PJI is a two-stage revision arthroplasty involving the articulating spacers. The implant surface provides an ideal environment for bacterial adhesion, facilitating mature biofilm formation. To prevent bacterial adhesion effectively, the surface of the implanted device must be modified with an efficient coating. The ability of a modified coating based on two-dimensional linear carbon chains (2D LCC) with silver (Ag) impregnation to inhibit biofilm formation and provide efficient bacterial eradication has been investigated in several experimental studies. However, there is a lack of publications on clinical studies evaluating the effectiveness of such coatings.

The aim of the study — to assess mid-term outcomes of knee and hip PJI treatment using spacers coated with two-dimensional linear carbon chains impregnated with silver.

Methods. This study is based on the results of the examination and two-stage revision arthroplasty of 144 patients with newly diagnosed knee and hip PJI. Patients were divided into two groups: the first (main) group received articulating spacers coated with 2D LCC+Ag, while the second (control) group received articulating spacers with antibiotics. Anamnestic, clinical, laboratory, microbiological, and statistical methods were used in this study. The evaluation of short-term results was performed using the KSS, Harris, VAS, and EQ-5D-5L scales at 3 months after surgery, and mid-term results were assessed at 2 years.

Results. The study confirmed the high antibiofilm activity and safety of spacers coated with 2D LCC+Ag. Both groups showed a reduction in inflammation markers during treatment. Before the second stage of treatment, both groups experienced a statistically significant decrease in CRP, procalcitonin, and presepsin levels, as well as synovial cytosis and neutrophil content. The frequency of recurrences after two-stage treatment was significantly lower in the first group compared to the second group. In the mid-term period, the first group had higher scores on the KSS and Harris scales by 20.5 and 7.0 points, respectively. Results on the EQ-5D-5L were 10/0.08 points higher, and the intensity of pain according to VAS was three times lower in the first group.

Conclusions. The use of spacers coated with 2D LCC+Ag allows for a faster resolution of the inflammatory process, reduces the incidence of PJI recurrences, and predicts active protection of the implant surface from microbial colonization and biofilm formation. This, combined with antibiotic prophylaxis, provides a favorable therapeutic and preventive effect against PJI recurrence.

Keywords: arthroplasty, periprosthetic infection, implant-associated infection, microbial biofilms, antibacterial coating.

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Среднесрочные результаты лечения перипротезной инфекции с применением спейсеров с углеродным покрытием, импрегнированных серебром

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Реферат

Актуальность. Перипротезная инфекция (ППИ) — тяжелое осложнение эндопротезирования. Общепризнанным стандартом лечения ППИ является двухэтапное ревизионное эндопротезирование с применением артикулирующих спейсеров. Поверхность имплантатов — идеальное место для бактериальной адгезии, способствующей образованию зрелой биопленки. Для создания предотвращающего адгезию бактерий барьера необходимо изменить поверхность имплантированного устройства с помощью эффективного покрытия. Способность модифицированного покрытия на основе двумерно упорядоченного линейно-цепочечного углерода (ДУ ЛЦУ+Ag) ингибировать образование биопленки и обеспечивать эффективное уничтожение бактерий изучалась в нескольких экспериментальных исследованиях. Однако отсутствуют публикации о результатах клинических исследований эффективности таких покрытий.

Цель исследования — оценить среднесрочные результаты использования спейсеров с покрытием на основе двумерно упорядоченного линейно-цепочечного углерода, легированного серебром, при лечении перипротезной инфекции коленного и тазобедренного суставов.

Материал и методы. Исследование основано на результатах обследования и двухэтапного ревизионного эндопротезирования 144 пациентов с впервые выявленной ППИ коленных (КС) и тазобедренных (ТБС) суставов. Пациенты были разделены на две группы: первую группу составили пациенты с артикулирующим спейсером, покрытым ДУ ЛЦУ+Ag, вторую группу — пациенты, которым был установлен артикулирующий спейсер с антибиотиками. В исследовании использовали анамнестический, клинико-лабораторный, микробиологический, статистический методы. Оценка ближайших результатов выполнялась по шкалам KSS, Harris, ВАШ, EQ-5D-5L через 3 мес. после операции, среднесрочных – через 2 года.

Результаты. Исследование подтвердило высокую антибиопленочную активность и безопасность спейсера с покрытием на основе ДУ ЛЦУ+Ag. В динамике произошло снижение уровня маркеров воспаления в обеих группах. Перед вторым этапом лечения в группах произошло статистически значимое снижение СРБ, прокальцитонина и пресепсина, цитоза и содержания нейтрофилов в суставном пунктате. Частота рецидивов после двухэтапного лечения была статистически значимо ниже в первой группе по сравнению со второй. По шкалам KSS и Harris в среднесрочном периоде результат в первой группе был выше на 20,5 и 7,0 баллов соответственно. Результаты по шкале качества жизни EQ-5D-5L были выше на 10/0,08; по ВАШ выраженность болевого синдрома в первой группе была в 3 раза меньше.

Заключение. Использование спейсера с покрытием на основе ДУ ЛЦУ+Ag позволяет быстрее ликвидировать воспалительный процесс, снизить число рецидивов ППИ, прогнозировать активную защиту поверхности имплантата от колонизации микроорганизмами и формирования микробных биопленок, что вкупе с медикаментозной антибиотикопрофилактикой обеспечивает хороший лечебно-профилактический эффект в отношении рецидива ППИ.

Ключевые слова: эндопротезирование суставов, перипротезная инфекция, имплантат-ассоциированная инфекция, микробные биопленки, антибактериальное покрытие.

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BACKGROUND

Joint arthroplasty is currently recognized as the gold standard for the treatment of patients with stage III-IV osteoarthritis. Joint arthroplasty offers several advantages, including rapid relief of pain and full restoration of the patient's mobility within a short rehabilitation period [1, 2].

However, one of the major complications of joint arthroplasty is periprosthetic joint infection (PJI). PJI is a severe complication both for the patient, necessitating repeat surgeries, and for the healthcare system, leading to increased hospitalization duration and high economic costs [3]. The frequency of PJI after primary joint arthroplasty ranges from 0.5% to 3.0% [4], and it can reach up to 30% in revision procedures [5, 6, 7].

A significant complicating factor in the course of PJI is the rapid formation of bacterial biofilms on implanted metal structures [8]. The primary goal in treating implant-associated infections is the prevention of these processes [9].

The widely accepted treatment standard for PJI is a two-stage revision arthroplasty involving the use of articulating spacers, typically impregnated with antibiotics [10]. These spacers can be made of a single material, most commonly polymethylmethacrylate (PMMA), or can be composite (cement-metal, cement-polyethylene, cement-ceramic, etc.) [11]. PMMA is used as a matrix to provide antibiotic depot [10, 11]. Attempts have been made to incorporate antiseptics or particles of halogens and metals with antimicrobial activity (silver, zinc, copper, etc.) into PMMA, but such studies are scarce [12, 13]. Since microorganisms do not develop resistance to substances with broad bactericidal activity, creating new antimicrobial coatings for implant components represents a promising direction in the treatment of infectious complications in joint arthroplasty with spacer use [14, 15].

The implant surface provides an ideal environment for bacterial adhesion, facilitating mature biofilm formation [16]. To prevent bacterial adhesion effectively, the surface of the implanted device or material must be modified, either directly or with the use of an efficient coating [17].

The ability to modify the implant surface to minimize bacterial adhesion, inhibit biofilm formation,andensureeffectivebacterialeradication for the protection of implanted biomaterials has been studied in several investigations. Some authors have demonstrated low efficiency in using diamond-like coatings containing a combination of sp2- and sp3-carbon high-energy bonds, limiting their application in traumatology and orthopedics [18, 19]. Results from other studies have revealed the advantages of coatings based on two-dimensional linear carbon chains (2D LCC) due to their structural characteristics, such as good adhesion to the surface of metal implants, strength, and biological compatibility [20]. D.V. Tapalsky and colleagues conducted a multicenter study aimed at assessing the antibacterial activity and biological compatibility of coatings for metal structures based on 2D LCC. The results showed that coatings based on 2D LCC+Ag provide a pronounced surface bactericidal effect and have the ability to prevent the formation of microbial biofilms on metal surfaces. Coatings based on 2D LCC are safe and do not induce cytotoxic effects [21].

However, there is a lack of publications in the literature regarding the results of clinical studies on the effectiveness of coatings based on 2D LCC..

The aim of this study — to assess mid-term outcomes using spacers coated with two-dimensional linear carbon chains impregnated with silver (2D LCC+Ag) in the treatment of periprosthetic joint infection in large joints of the lower extremities

METHODS

Study design

An open prospective cohort randomized study was conducted at the Center from 2017 to 2021. It was based on the results of examination and surgical treatment of patients with newly diagnosed periprosthetic joint infection (PJI) of the knee and hip joints.

The *inclusion criterion* for patients in the study was a confirmed case of PJI according to the criteria of the 2013 International Consensus Meeting on Periprosthetic Joint Infection [22].

Exclusion criteria patients under 18 years of age, pregnancy, and patient refusal to participate at any stage of the study.

After applying the inclusion and exclusion criteria, 144 patients were selected for the study: 82 with PJI of the hip and 62 with PJI of the knee, including 71 females (49.3%) and 73 males (50.7%).

Patients were randomized into two groups using random number generation with Excel software.

In the first (experimental) group, patients were implanted with an articulating spacer coated with two-dimensionally ordered linear-chain carbon with silver (DU LCUC+Ag). In the second (control) group, traditional articulating spacers with antibiotics were used (see Figure 1).

Patients in both groups were comparable in terms of gender and age (Table 1).

During the study, a thorough medical history was collected to identify comorbidities and potential risk factors that could have contributed to the development of PJI. An analysis of the most commonly occurring somatic pathology was performed.

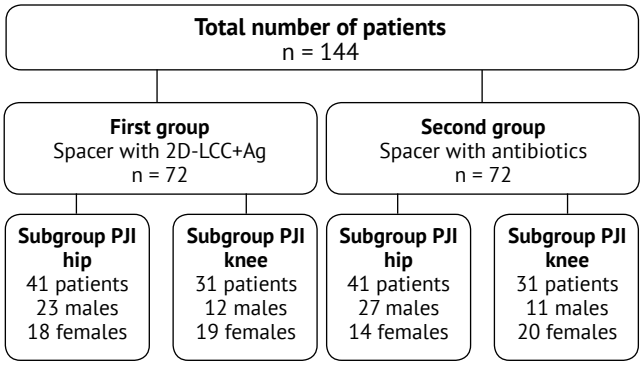

Fig. 1. Study flowchart

The treatment of PJI was performed using a two-stage revision arthroplasty method. The goal of the first stage was joint sanitation using a spacer in combination with mechanical treatment of pathological tissues. In the second stage, after infection control and assessment of clinical and laboratory parameters, a permanent endoprosthesis was implanted. All patients received empirical or etiotropic antibiotic therapy based on the antibiotic susceptibility of the pathogen isolated from the focus.

Outcome assessment

Comparative evaluation of pain syndrome and laboratory parameters (CRP level, ESR, D-dimer) in the first and second groups was conducted before and after treatment. The assessment of joint function based on functional rating scales was performed separately for the hip and knee joints.

The interval between the two stages of re-endoprosthesis was assessed in days and was statistically significantly shorter in the first group of patients than in the second group, with 64.5 (53–103) days in the experimental group and 78 (63.5–111.0) days in the control group, p = 0.010. After treatment, a comparative assessment of the severity of pain syndrome, quality of life, joint function (based on rating scales), and laboratory parameters (CRP level, ESR, procalcitonin, presepsin, cytosis, and neutrophil content in joint punctate before I and II stages of treatment) was conducted. The assessment of midterm functional

Table 1

Distribution of patients by gender and age

Indicator	First group		Second group		p
	n	%	n	%	
Males	35	48.6	38	52.8	0.617
Females	37	51.4	34	47.2	0.617
Mean age, years Me (Q1–Q3)	63.5 (57.5–70.0)		62.0 (54.5–69.0)		0.500

treatment results was performed 2 years after treatment using the KSS, Harris, VAS pain, EQ-5D-5L scales.

Statistical analysis

Statistical data processing involved calculating the mean and standard deviation (M±σ). In the absence of a normal distribution or for rank data, the median (Me), upper and lower quartiles (Q1–Q3) were determined.

Statistical significance of differences between data with a normal distribution was assessed using Student's t-test, and for non-normally distributed or rank data, the Mann-Whitney nonparametric test was used. Differences in dynamics were evaluated using the Wilcoxon criterion. For qualitative data, differences were assessed using the χ^2 criterion. Statistical analysis was performed using Statistica for Windows 10.0, and data were considered statistically significant at a probability of error (p) less than 0.05.

RESULTS

At baseline, there were no significant differences in general blood analysis parameters between the study groups. Baseline levels of inflammation markers were also comparable. However, both groups experienced a decrease in these markers during the course of treatment. The level of CRP was lower in the first group, while levels of procalcitonin and presepsin were comparable. The cellular count and neutrophil count in the joint punctate normalized in both groups, with all values falling within the reference range (Table 2).

The recurrence rate after the first stage of treatment in the first group was 2.8% (2 out of 72) compared to 11.1% (8 out of 72) in the second

Table 2

Results of laboratory examination of patients before stages I and II of treatment

Indicator	Term	First group (n = 72)	Second group (n = 72)	p
White blood cells, $\times10^9$/L	Before stage I	7.9 (7.0–9.8)	8.5 (7.1-10.3)	0.287
	Before stage II	6.5 (5.9–8.0)*	7.2 (5.8–8.6)*	0.275
ESR (Erythrocyte sedimentation rate), mm/h	Before stage I	46.5 (29.5–69.5)	43.0 (25.5–73.5)	0.694
	Before stage II	20.5 (12.0–32.0)*	18.0 (10.0–34.0)*	0.379
Hemoglobin, g/L	Before stage I	121.0 (112.0–132.0)	122.0 (110.0–140.5)	0.361
	Before stage II	121.0 (111.0–130.0)	124.0 (113.5–136.0)	0.145
Red blood cells, $\times10^{12}$/L	Before stage I	4.3 (4.0–4.7)	4.45 (4.1–4.8)	0.210
	Before stage II	4.4 (3.9–4.9)	4.4 (4.2–4.9)	0.225
Platelets, $\times10^9$/L	Before stage I	316.5 (275.5–385.5)	337.5 (283.0–420.5)	0.266
	Before stage II	270.5 (232.0–314.0)	267.0 (222.0–330.5)	0.951
CRP (C-reactive protein), mg/L	Before stage I	17.6 (7.9–73.5)	39.1 (12.7–71.3)	0.082
	Before stage II	5.0 (2.6–8.2)*	5.0 (4.5–11.8)*	0.029
Procalcitonin, pg/mL	Before stage I	0.032 (0.02–0.076)	0.04 (0.02–0.0655)	0.414
	Before stage II	0.02 (0.02–0.032)*	0.023 (0.02–0.04)	0.09
Presepsin, pg/mL	Before stage I	300.0 (204.5–300.0)	300.0 (250.0–448.0)	0.055
	Before stage II	190.0 (150.0–191.0)	200.0 (200.0–200.0)	0.085
Cytosis, cells $\times10^3$/L	Before stage I	17500.0 (4312.5–49250.0)	15000.0 (5370.0–45500.0)	0.881
	Before stage II	382.5 (110.0–1100.0)*	300.0 (150.0–814.0)*	0.921
Neutrophils, %	Before stage I	93.0 (88.5–95.0)	92.0 (88.5–95.0)	0.854
	Before stage II	12.0 (12.0-48.0)*	12.0 (12.0–70.0)*	0.885

*Differences in dynamics according to the Wilcoxon test at $p<0.05$.

group (p = 0.049). There were no recurrences after the second stage in the first group, and the values remained the same at 2.8% (2 out of 72) compared to 20.8% (15 out of 72) in the second group (p < 0.001).

Functional status and pain levels, despite similar baseline values, were more favorable in the first group after the second stage of PJI treatment and in the midterm postoperative period. Pain levels among individuals without PJI recurrence were also better in the first group. Quality of life was assessed using the EQ-5D-5L questionnaire, and the results after treatment were better in the first group than in the second group based on the EQ-VAS general well-being score and EQ-5D-5L score (Table 3).

The positive dynamics of laboratory parameters were accompanied by improved joint function. Two years after the completion of treatment, joint function was better in the first group, as assessed by the Harris score for hip joint and the KSS score for knee joint (Table 4, 5).

Table 3

Midterm results on the EQ-5D-5L questionnaire for patients without PJI recurrence

Indicator	First group (n = 70)	Second group (n = 57)
EQ-5D-5L, proportion	0.88 (0.84–1.00)	0.80 (0.64–0.88)
EQ-VAS, points	90.00 (90.00–95.00)	80.00 (70.00–90.00)

p<0.001.

Table 4

Functional status of the hip joint according to the Harris scale in patients with PJI

Follow-up period	First group	Second group	p
Before stage I	28.0 (23.0–37.0)	28.0 (20.0–42.0)	0.286
Before stage II	38.0 (31.5–41.0)	37.0 (31.3–40.0)	0.818
2 years after stage II	91.0 (87.0–93.3)	84.0 (77.5–87.0)	<0.001

Table 5

Functional status of the knee joint according to the KSS scale in patients with PJI

Assessment scale	Follow-up period	First group	Second group	p
KSS Knee Score, points	Before stage I	32 (32–35)	32 (32–35)	0.946
	Before stage II	50 (37–50)	45 (31–45)	0.046
	2 years after stage II	90 (74–95)	70 (30–84)	0.002
KSS Functional Score, points	Before stage I	30 (30–30)	30 (30–30)	0.966
	Before stage II	35 (35–45)	35 (35–35)	0.047
	2 years after stage II	75 (71–95)	65 (47–83)	0.005

Pain levels before the first and second stages of treatment in the first and second groups were comparable (Table 6). However, midterm results were significantly better in the main group.

Microbiological analysis of biological material samples did not identify the pathogen in 21 patients (14.6%), and multiple microorganisms were isolated in 6 patients (4.2%). *Staphylococci*, including *S. aureus* (27.6%), and coagulase-negative *staphylococci* (38.3%) were the most common isolates, while *streptococci* were cultured in 13% of cases (Table 7).

Table 6

Pain score according to the VAS

Follow-up period	Main group	Control group	p
Before stage I	8.0 (7.0–8.5)	8.0 (7.0–9.0)	0.532
Before stage II	5.0 (4.0–6.0)	5.0 (5.0–6.0)	0.137
2 years after stage II	1.0 (1.0–2.0)	3.0 (1.0–4.0)	<0.001

Table 7

Results of microbiological examination of synovial fluid, tissue biopsies, and swabs from removed components

Microorganism	Positive results	
	n	%
Anaerobes	2	1.6
Gram-negative microorganisms	10	8.0
Coagulase-negative staphylococci	41	33.3
Staphylococcus aureus	34	27.6
Staphylococcus epidermidis	13	10.6
Staphylococcus hemolyticus	1	0.8
Staphylococcus lugdunensis	3	2.4
Staphylococcus warneri	1	0.8
Streptococcus sp.	16	13.0
Corynebacterium striatum	2	1.6
Total	123	100.0

DISCUSSION

The study showed a statistically significant reduction in the recurrence rate of infection after using the 2D LCC+Ag coating compared to the results in the second group. It is worth noting that in most studies, an absolute reduction in the recurrence rate of 1.5–2.0 times was observed, but without statistical significance. This fact may be explained by the small number of observations, which is supported by the results of a meta-analysis conducted by M. Fiore and colleagues. The analysis of studies showed that the infection rate after revisions was 13.7% in the group of patients with silver-containing coating implants and 29.2% in the group using implants without coating, indicating the effectiveness of silver-containing coatings in preventing infections (p = 0.019) [23].

In our study, the recurrence rate in the second group was 20.8%, which is consistent with the literature. For example, V.V. Pavlov and colleagues reported a recurrence rate of 19.5% in patients treated for hip and knee PJI [24]. V.A. Ivantsov and colleagues reported a 14.4% unsatisfactory outcome rate in knee joint PJI treatment [25]. The recurrence rate of hip joint

PJI in F. Schwolow's study was 14.4% with an average follow-up of 8 years [26]. According to A.S. Steinicke and colleagues, the infection-free survival of knee and hip endoprostheses was 77% (95% CI 64–89) after 1 year and 38% (95% CI 18–57) after 5 years [27]. The variation in recurrence rates among studies may be due to differences in the duration of follow-up.

The use of the new coating in our study resulted in lower leukocyte and neutrophil counts and a lower recurrence rate in the first group of patients. This indicates effective control of the infection process. T. Shirai and colleagues observed a less severe inflammatory response in patients using iodine-coated spacers [28].

The use of the new coating can also impact joint function and pain levels. Better joint function results (reference values of cell count and neutrophil content in the punctate, reduction in blood inflammatory markers) after the second stage of debridement were observed in the first group. This suggests faster infection control with the use of silver-doped carbon coating, better biocompatibility compared to uncoated spacers, which ultimately may positively affect joint function. The joint function assessed by Harris score for hip joint and KSS score for knee joint was better in the first group, and pain levels were less pronounced than in the second group [29, 30].

The effectiveness of PJI treatment is further confirmed by improved quality of life for patients. For example, J.L. Cahill and colleagues reported that patients whose PJI resolved had higher scores on quality of life and VAS compared to patients with PJI recurrence after two-stage revision [31]. A decrease in quality of life with the development of PJI is supported by the results of a study by N.R. Poulsen and colleagues, in which patients with PJI recurrence had worse quality of life than patients with resolution after two-stage revision [32]. Our study showed similar results.

CONCLUSIONS

The use of a spacer with a coating based on 2D LCC+Ag allows for faster resolution of the inflammatory process, achieving lower neutrophil and CRP levels in the blood, as well as reduced cytosis and neutrophil content in joint punctate. It also leads to a decrease in the recurrence rate of PJI in both knee and hip joints.

The faster and more effective resolution of PJI in the main group contributes to improved prosthesis function. Patients in the main group achieved better knee and hip joints function results, higher quality of life according to the EQ-5D-5L and lower pain levels on the VAS scale.

The assessment of midterm results of PJI treatment provides grounds to predict active protection of the implant surface from microbial colonization and biofilm formation. This, combined with antibiotic prophylaxis, ensures a good therapeutic and preventive effect against PJI recurrence. To study the long-term results of using spacers coated with 2D LCC+Ag, further research is planned.

The results obtained confirm the justification for the wider use of spacers coated with 2D LCC+Ag for the treatment of periprosthetic infection, considering the need for revision surgery.

DISCLAIMERS

Author contribution

Malyuchenko L.I. — study concept and design, literature search and analysis, writing the article.

Nikolaev N.S. — study concept, drafting the article.

Yakovlev V.V. — data collection and processing, drafting the article.

Preobrazhenskaya E.V. — study concept and design, data analysis and interpretation, drafting the article.

All authors have read and approved the final version of the manuscript of the article. All authors agree to bear responsibility for all aspects of the study to ensure proper consideration and resolution of all possible issues related to the correctness and reliability of any part of the work.

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Ethics approval. The study was conducted in accordance with the principles of the Helsinki Declaration (World Medical Association Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013) and the «Rules of Clinical Practice in the Russian Federation» (Order of the Ministry of Health of the Russian Federation dated June 19, 2003, No. 266). The conduct of the study was approved by the local ethics committee of the federal center of traumatology, orthopedics and arthroplasty of the Ministry of Health of Russia,

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