

Animals of the second and third groups were also divided into two subgroups according to the period of withdrawal from the experiment (day 28 of the study and life expectancy monitoring). Treatment of animals began on the 5th day after transplantation of LL cells. Before the start of LL cell inoculation, all mice underwent a Morawitz blood clotting time test. The procedure was carried out on days 14 and 28 of the study, which made it possible to evaluate the effect of LL carcinoma and LL carcinoma+ enoxaparin on the coagulation activity of the experimental mice. On the 28th day of the study, animals of the corresponding groups were euthanized for hematological parameters examination, and the removal of lungs (for metastases counting) and spleen (for further examination). Analysis of the data obtained revealed a significant decrease in the metastatic activity of LL carcinoma with the administration of the direct anticoagulant enoxaparin. The drug studied inhibited the formation of metastases in the lungs by 60.9% and its growth by 96.9%.

According to our results, a disturbance of blood coagulation activity occurs at the background of metastasizing tumor growth. The blood clotting time in animals with grafted LL carcinoma decreased almost 13 times, which indicates a hypercoagulable state at the stage of DIC syndrome. There was a 2.29-fold decrease in the number of platelets in the blood of animals with LL carcinoma, which indicates their enhanced sequestration, characterized by redistribution from the pool of circulating platelets in favor of the splenic pool. At the same time, therapy with enoxaparin at a dose of 10 mg/kg was accompanied by a significant increase in blood clotting time by 6.2 times and an increase in the number of platelets in the blood of experimental mice.

The data obtained provide insight into the involvement of paraneoplastic hypercoagulability syndrome in the pathogenesis of metastasis and can form the basis for experimental justification for the use of direct anticoagulants as accompanying therapy for the treatment of metastatic forms of tumors.

**Key words:** anticoagulants, Lewis lung carcinoma, metastases, C<sub>57</sub>BL/6 mice.

**ORCID and contributionship: / ORCID автора та його внесок до статті:**

Munko M.A.: <https://orcid.org/0000-0001-7784-9625> <sup>ABCDEF</sup>

**Corresponding author / Адреса для кореспонденції**

Munko Maksym Andriiovych / Мунько Максим Андрійович

SI «Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine» / ДУ «Інститут фармакології та токсикології НАМН України»

Ukraine, 03057, Kyiv, 14 Anton Tsedik str. / Адреса: Україна, 03057, м. Київ, вул. Антона Цедіка 14

Tel.: 0685105243 / Тел.: 0685105243

E-mail: [munandmax@gmail.com](mailto:munandmax@gmail.com)

**A** – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article / **A** – концепція роботи та дизайн, **B** – збір та аналіз даних, **C** – відповідальність за статистичний аналіз, **D** – написання статті, **E** – критичний огляд, **F** – остаточне затвердження статті.

*Received 28.09.2023 / Стаття надійшла 28.09.2023 року*

*Accepted 28.02.2024 / Стаття прийнята до друку 28.02.2024 року*

DOI 10.29254/2077-4214-2024-1-172-203-208

UDC 616-74:615.462:678.742.3:57.084

**Nakonechna O. A., Kyslov O. V.**

## THE ROLE OF PRO-INFLAMMATORY CYTOKINES IN RATS AFTER IMPLANTATION OF POLYPROPYLENE SURGICAL MESH WITH A COATING BASED ON TANTALUM AND ITS DERIVATIVES

Kharkiv National Medical University (Kharkiv, Ukraine)

[ov.kyslov@knu.edu.ua](mailto:ov.kyslov@knu.edu.ua)

*Since the early 2000s, polypropylene has become the main material used in hernia repair. However, negative statistics regarding the development of the inflammatory process after implantation of surgical meshes made of different materials still remain disappointing. The development of the inflammatory process after implantation of polypropylene surgical meshes is observed in 30-40% of patients. These data force scientists all over the world to continue the search for the optimal surgical mesh according to the chemical composition, which would suit specialists not only from the side of the physical properties of the surgical mesh, but also from the side of its biocompatible and anti-inflammatory properties. In recent years, tantalum has been successfully used to produce biocompatible medical implants in surgery, orthopedics, and orthodontics.*

*The aim of our study was to determine the content of IL-1 $\beta$  and IL-6 in the blood plasma of experimental animals 28 days after implantation of polypropylene surgical meshes with a coating based on tantalum and its derivatives, in particular tantalum oxide and nitride.*

*The experimental groups included 40 male rats of the WAG population. A 15x15mm polypropylene surgical mesh with different types of coatings was implanted between the abdominal wall and the colon with the help of surgery. 28 days after surgery, blood was collected to determine the content of IL-1 $\beta$  and IL-6.*

*The data obtained after the conducted studies indicate that coatings made of tantalum and tantalum oxide do not contribute to the occurrence of the inflammatory process in comparison with the results of a group of experimental animals that were implanted with a surgical mesh without a coating.*

*Coatings based on tantalum and tantalum oxide demonstrated excellent anti-inflammatory effects and demonstrated excellent biocompatibility, which indicates to us the possibility of further improvement of surgical meshes by applying biocompatible coatings to achieve better results in surgical practice.*

**Key words:** tantalum, tantalum oxide, interleukin-1 $\beta$ , surgical meshes, interleukin-6, tantalum nitride.

### Connection of the publication with planned research works.

The study is a fragment of the National Research Council of the Department of Surgery №1 of KhNMU on the topic: «Development of surgical technologies for the diagnosis and treatment of diseases and injuries of the digestive system using hybrid (open and minimally invasive) operations» (state registration number: 0119U002909).

### Introduction.

Over the past two decades, polypropylene surgical meshes have become an integral part of the treatment of various types of hernias and other soft tissue reconstructions. These materials significantly improved the results of hernioplasty, reducing the frequency of hernia recurrences, promoting tissue healing [1].

However, the development of inflammatory and infectious processes associated with the use of polypropylene surgical meshes pose significant problems for postoperative recovery and prediction of implantation results. This is a multifaceted issue that includes the analysis of the body's innate immune response to foreign materials, the possibility of bacterial contamination during surgery and the subsequent risk of infection associated with the implanted surgical mesh, the state of the patient's immune system [2]. Understanding these complexities is critical to developing strategies to reduce risks and improve the quality of hernioplasty material. When surgical mesh is implanted, our body recognizes it as a foreign body, which causes an innate immune response [3]. This response is initially characterized by an acute inflammatory phase when neutrophils and macrophages are recruited to the site of implantation. These immune cells release cytokines and chemokines, substances that mediate inflammation and recruit additional immune cells [4].

Although this reaction is a natural part of the healing process aimed at facilitating tissue recovery, the very presence of the mesh and the material from which it is made can provoke the further development of the inflammatory process, which leads to chronic inflammatory reactions and the occurrence of an adhesion process [5].

Interleukin-1 beta (IL-1 $\beta$ ) and interleukin-6 (IL-6) are key cytokines in a complex immune signaling network, play a critical role in mediating the inflammatory response, and promote interaction between innate and adaptive immunity [6]. This process goes beyond simple involvement in immune defense mechanisms to influence processes related to cell growth and differentiation, tissue repair, and metabolic regulation. Thus, the determination of IL-1 $\beta$  and IL-6 in the blood of patients has attracted considerable attention from researchers due to their contribution to the pathogenesis of various inflammatory and autoimmune diseases, as well as their potential as therapeutic targets and biomarkers to

assess the course of the disease and response to treatment [7].

The evolution of surgical mesh technology reflects constant efforts to solve the problems of the development of inflammatory and adhesion processes at the site of surgical mesh implantation, which leads to the development and use of new materials and structures aimed at minimizing complications [8]. The latest achievements of scientists led to the development of surgical meshes with experimental coatings aimed at improving the biocompatibility of the implant [9].

We turned our attention to tantalum coatings, which are famous for their corrosion resistance and excellent biocompatibility, demonstrating excellent results in surgery, orthodontics and orthopedics [10].

In order to study the body's immune response to the implantation of polypropylene surgical meshes with a coating based on tantalum and its derivatives, we evaluated the content of interleukins IL-1 $\beta$  and IL-6 in the blood plasma of experimental animals.

### The aim of the study.

Determination of the content of pro-inflammatory cytokines, namely IL-1 $\beta$  and IL-6, in the blood plasma of experimental animals 28 days after implantation of polypropylene surgical meshes with a coating based on tantalum and its derivatives, in particular tantalum oxide and nitride.

### Object and research methods.

The experimental groups included 40 male rats of the WAG population weighing 220 $\pm$ 20 g. After acclimatization in the vivarium of the Kharkiv National Medical University, which lasted 21 days, the experimental animals were randomly divided into six groups. The first (intact) group included 6 rats. The second group included 6 rats that underwent surgery, but without implementation of a surgical mesh. The third group included 7 rats with an implanted surgical mesh coated with tantalum. The fourth group included 7 rats with an implanted surgical mesh covered with tantalum oxide. The fifth group includes 7 rats with an implanted surgical mesh covered with tantalum nitride. The sixth group included 7 rats with an implanted surgical mesh without a coating.

Rats were maintained under standard laboratory conditions in accordance with the Standard Rules for the Arrangement, Equipment and Maintenance of Experimental Biological Clinics, following the general principles of bioethics in accordance with the Declaration of Helsinki adopted by the World Medical Assembly in 1964. Animals received the same amount of water, access to food was free in all groups.

With the help of surgical intervention, polypropylene surgical mesh «Omega II standard» (Ukrtechmed, Ukraine) measuring 15x15 mm was implanted between the abdominal wall and various sections of the colon. Anesthesia was performed by intraperitoneal administration of the drug «Relax» (BioTestLab, Ukraine) at a

dose of 8 mg/kg, the active substance of which is 1% propofol. Fixation of the surgical mesh was performed with suture material «Prolene» (ETHICON®, USA) with simple sutures along the top of the mesh, knots towards the aponeurotic plane, minimizing the amount of intraperitoneal foreign body.

After 28 days, experimental animals were decapitated and blood was immediately collected into sterile K2 EDTA VACUTAINER tubes (BD Vacutainer®, China). Blood samples were used to determine IL-1 $\beta$  using the «IL-1 $\beta$  ELISA Kit» (Abcam, USA) and IL-6 using the «IL-6 ELISA Kit» (Abcam, USA) on a «Solar» PV-1251C spectrophotometer. The content of IL-1 $\beta$  and IL-6 in the blood plasma of rats was determined in pg/ml.

Statistical processing of the obtained data was performed using the Graph Pad Prism program (Graph Pad, USA). Indicators were compared using the non-parametric Mann-Whitney U-test. Results by group were presented as the median (Me) range. Differences at  $p < 0.05$  were considered statistically significant.

When handling experimental animals, we strictly followed the guidelines of the EU Directive No. 63 of 2010 on the protection of animals used for scientific purposes and the Council of Europe Convention on the protection of vertebrate animals used for experimental and other scientific purposes, which was adopted at the meeting in Strasbourg in 1986, Law of Ukraine No. 3447-IV, Articles 26, 31 «On the Protection of Animals from Cruelty Treatment», «General Ethical Principles of Animal Experiments», adopted by the Fifth National Congress on Bioethics (Kyiv, 2013). The study was approved by the Bioethics Committee of the Kharkiv National Medical University (protocol No. 3 dated September 21, 2020).

#### Research results and their discussion.

Implantation of surgical mesh during hernioplasty causes a cascade of reactions in the body. Over the past decade, there has been increasing concern about the use of polypropylene surgical mesh due to the complications it can cause. First of all, this is the development of a long-term inflammatory process with the threat of developing purulent-septic complications. During a prolonged inflammatory process, the activity of neutrophils increases, and the release of histamine and interleukins from mast cells plays an important role in the body's immune response. Cases are also known from the scientific literature when surgical intervention with the implantation of a polypropylene mesh can also cause the development of adhesions and purulent-necrotic processes [11].

According to modern scientific research, it is known that mesh implantation during hernioplasty is accompanied by leukocytosis, an increase in the content of IL-6, IL-1 $\beta$ , IL-10 and fibrinogen during the first 7 days after the operation. However, later, 8-10 days after surgery, the levels of markers of the inflammatory process return to normal. The fact that the level of cytokines in the blood plasma remains high always indicates the presence of a long-term inflammatory process at the site of surgical mesh implantation, and as a result, the possible development of an adhesion process [12].

It is known that interleukin-1 beta (IL-1 $\beta$ ) is a powerful pro-inflammatory cytokine that plays a central role in the innate immune response, acting as a key mediator of inflammation. Produced primarily by activated

macrophages, but also by various other cells, including dendritic cells, B cells, and epithelial cells, IL-1 $\beta$  affects a wide range of biological processes, including inflammation, cell proliferation and differentiation, and apoptosis. It is involved in the pathogenesis of numerous inflammatory and infectious diseases, autoimmune disorders, which makes it a critical target for therapeutic intervention and a marker of the course of diseases [13]. IL-1 $\beta$  is synthesized as an inactive precursor, pro-IL-1 $\beta$ , which lacks a signal peptide for classical secretion and requires processing to become active. The conversion of pro-IL-1 $\beta$  into its active form is mediated by caspase-1 in the cytosolic multiprotein oligomeric complex. Activation of the inflammasome is triggered by a variety of stimuli, including microbial pathogens, toxins, and endogenous danger signals, leading to cleavage of pro-IL-1 $\beta$  and release of active IL-1 $\beta$ . This activation mechanism emphasizes the strict regulation of IL-1 $\beta$  activity, and ensures that its powerful pro-inflammatory effects are mobilized only in response to real threats to the body [14].

Interleukin 6 (IL-6) is a multifaceted cytokine that plays a central role in immune regulation, inflammation, and metabolism. The effectiveness of IL-6's action ranges from promoting the acute phase response to facilitating communication between cells of the immune system and influencing metabolic processes. The complexity of the biological functions of IL-6 reflects its involvement in pro-inflammatory pathways, which makes it a key molecule in the pathogenesis of various diseases, as well as a target for therapeutic interventions. It is synthesized by various types of cells: lymphocytes, monocytes, fibroblasts and endothelial cells in response to infectious and inflammatory processes, tissue damage. Unlike many cytokines, which have a more limited source, the wide range of cells capable of synthesizing IL-6 underscores its broad effects on physiological and pathological processes. IL-6 synthesis is regulated at both the transcriptional and post-transcriptional levels, ensuring that its expression is appropriately matched to the physiological context [15]. IL-6 is important for initiating the synthesis of acute-phase proteins during surgery, including C-reactive protein (CRP), ceruloplasmin, and haptoglobin, which perform various immunomodulatory and protective functions. IL-6 also affects the differentiation and activation of T cells, promoting the development of Th17 cells while inhibiting the differentiation of regulatory T cells (Treg), thus shaping the adaptive immune response [16].

As a result of the research conducted on the 28th day, it was determined that in the group of experimental animals that underwent surgery without surgical mesh implantation, the content of IL-1 $\beta$  and IL-6 in the blood plasma was statistically higher by 20% and 30% compared to the values of the intact groups of animals (**fig. 1, 2**).

In the group of experimental animals, after implantation of a tantalum-based surgical mesh, the content of IL-1 $\beta$  and IL-6 was significantly higher by 14.6% and 21.6%, respectively, compared to the results in the group of intact animals. Compared to a control group that underwent surgery without implantation, tantalum-based coatings showed a better outcome. Thus, the content of IL-1 $\beta$  and IL-6 in the tantalum-coated group was lower

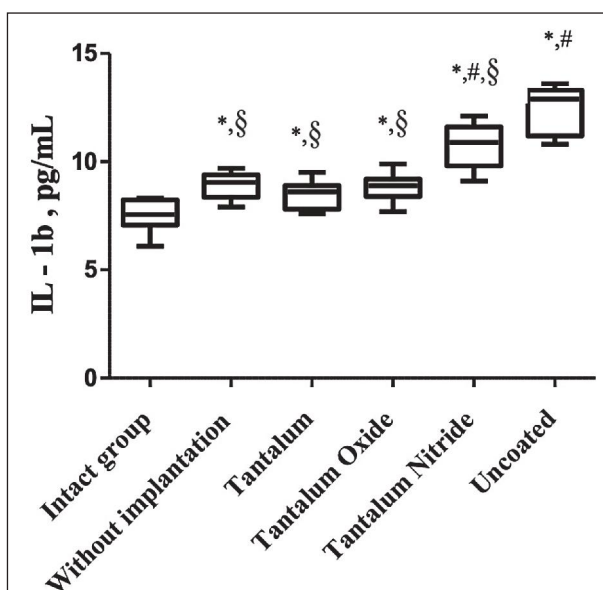


Figure 1 – The content of IL – 1β (pg/ml) in the blood of experimental animals after implantation of surgical meshes without a coating, with a coating based on tantalum and its derivatives.

Notes: \* – significant (p<0.05) difference compared to the indicators of the intact group; # – significant (p<0.05) difference compared to the indicators of the group without implantation; § – significant (p<0.05) difference compared to the indicators of the group without coverage.

by 4.6% and 6.8%, respectively, compared to the results of the second group.

After implantation of a surgical mesh with a coating based on tantalum oxide in the group of experimental animals, the content of IL-1β and IL-6 was statistically higher by 18.7% and 36.6%, respectively, compared to the results of the group of intact animals. Compared with the control group that underwent surgery without implantation, the content of IL-1β was not statistically different, and the content of IL-6 tended to increase according to the results of the control group.

In the fifth group of rats, which were implanted with polypropylene surgical mesh with a coating based on tantalum nitride, the content of IL-1β and IL-6 was statistically higher by 45.3% and 70%, respectively, compared to the results of intact animals. At the same time, compared with the control group, which underwent surgery without implantation, the IL-1β and IL-6 content were statistically higher by 21.1% and 30.7%, respectively, according to the results of the control group.

After implantation of polypropylene surgical mesh without coating (sixth group), the content of IL-1β and IL-6 was statistically significantly higher by 72% and 81.6%, respectively, compared to the values of intact animals. The obtained results indicate a persistent long-term inflammatory process that occurs at the site of surgical mesh implantation, which is confirmed by a morphological study. At the same time, compared with the control group that underwent surgery without implantation, the content of IL-1β and IL-6 was statistically higher by 43.3% and 39.7%, respectively, according to the results of the control group (second group).

The obtained data indicate that coatings based on tantalum and tantalum oxide do not contribute to the inflammatory process in comparison with the results of a group of experimental animals that were implanted with a surgical mesh without a coating.

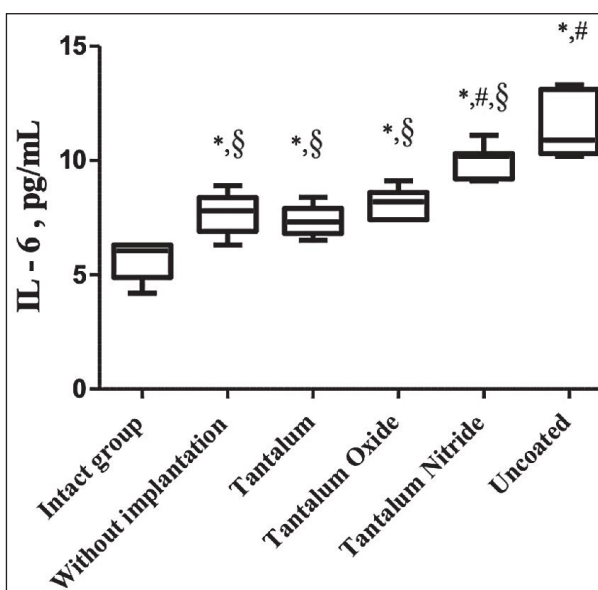


Figure 2 – The content of IL – 6 (pg/ml) in the blood of experimental animals after implantation of surgical meshes without a coating, with a coating based on tantalum and its derivatives.

Notes: \* – significant (p<0.05) difference compared to the indicators of the intact group; # – significant (p<0.05) difference compared to the indicators of the group without implantation; § – significant (p<0.05) difference compared to the indicators of the group without coverage.

Scientists testified that an important factor in increasing the level of pro-inflammatory cytokines is not only the biocompatibility of the material and its anti-inflammatory effect, but also the method of surgical intervention. Open methods of surgical intervention contributed significantly to the development of the inflammatory process, in comparison with laparoscopic methods [17]. Determination of the level of cytokines, in particular IL-1β and IL-6, in the blood plasma makes it possible to assess the activity of the inflammatory process in the postoperative process and to adjust the treatment process.

In our study, we used polypropylene surgical meshes of the same type, but with the addition of biocompatible coatings based on tantalum and its derivatives. This is one of the first studies where a team of scientists not only compared types of surgical mesh, but also added a biocompatible coating through magnetron sputtering.

Thus, as a result of our research, tantalum and tantalum oxide-based coatings have demonstrated excellent anti-inflammatory effects and demonstrated excellent biocompatibility, indicating to us the possibility of further improving surgical meshes with biocompatible coatings to achieve better results in surgical practice.

### Conclusions.

According to the results of the study, it was established that the use of polypropylene surgical meshes with a coating based on tantalum and tantalum oxide significantly reduces the inflammatory reaction in the body of rats, compared to the implantation of uncoated meshes and meshes coated with tantalum nitride. This is confirmed by a decrease in blood plasma of IL-1β and IL-6 on the 28th day after surgery, which indicates better biocompatibility and anti-inflammatory effect of tantalum and tantalum oxide coatings. The obtained results were confirmed by morphological studies.

In addition, our study highlights the need for further clinical studies and to explore the possibility of their future use in hernioplasty.

**Prospects for further research.**

Future experiments should focus on longitudinal studies to evaluate the long-term effects of these coatings on the development of oxidative stress and wound surface healing outcomes in clinical settings. In addition,

our team plans to explore other innovative coatings and materials that could minimize the body's physiological response to implanted surgical meshes. Ultimately, the goal of the work is to develop surgical meshes that not only provide mechanical functionality, but also actively promote healing, reducing complication rates and improving patient quality of life.

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**РОЛЬ ПРОЗАПАЛЬНИХ ЦИТОКІНІВ В ОРГАНІЗМІ ЩУРІВ ПІСЛЯ ІМПЛАНТАЦІЇ ПОЛІПРОПІЛЕНОВИХ ХІРУРГІЧНИХ СІТОК ІЗ ПОКРИТТЯМ НА ОСНОВІ ТАНТАЛУ ТА ЙОГО ПОХІДНИХ**

**Наконечна О. А., Кислов О. В.**

**Резюме.** З початку XXI століття поліпропілен став основним матеріалом, який використовується при пластичній грижі. У світі використовується більше 30 видів поліпропіленових хірургічних сіток, однак негативна статистика з приводу розвитку запального процесу після імплантації й досі залишається невтішною. Розвиток запального процесу після імплантації поліпропіленових хірургічних сіток спостерігається у 30-40% пацієнтів. Поліпропіленові сітки, завдяки своїй синтетичній природі та особливим фізико-хімічним властивостям, можуть посилити цю запальну реакцію. Відповідь організму на поліпропіленові матеріали може призвести до інкапсуляції хірургічної сітки у фіброзній тканині, процесу, призначеного для ізоляції стороннього матеріалу. Дана фіброзна реакція може спричинити дискомфорт, біль і порушення функціональності сітки, спричинивши в подальшому деформацію. Протягом останніх років тантал з успіхом використовується для вироблення біосумісних медичних імплантів у хірургії, ортопедії та ортодонції.

Метою нашого дослідження було визначення вмісту прозапальних цитокінів, а саме IL-1 $\beta$  та IL-6, у плазмі крові експериментальних тварин через 28 діб після імплантації поліпропіленових хірургічних сіток з покриттям на основі танталу та його похідних, зокрема оксиду та нітриду танталу.

До експериментальної групи увійшли 40 щурів – самців популяції WAG. Експериментальні тварини були розділені випадковим чином на шість груп. За допомогою хірургічного втручання було імплантовано поліпропіленову хірургічну сітку «Омега II стандарт» (Укртехмед, Україна) розміром 15x15мм із різними типами покриттів між черевною стінкою та товстою кишкою. Через 28 діб після оперативного втручання було проведено декапітацію експериментальних тварин шляхом цервікальної дислокації та відразу зібрано кров для визначення вмісту IL-1 $\beta$  та IL-6 в плазмі крові.

Отримані дані після проведених досліджень вказують на те, що покриття з танталу і оксиду танталу не сприяють виникненню запального процесу у порівнянні із результатами групи експериментальних тварин,

яким було імплантовано хірургічну сітку без покриття. У групі експериментальних тварин після імплантації хірургічної сітки з покриттям на основі танталу вміст IL-1 $\beta$  та IL-6 статистично був вищим на 14,6% та 21,6% відповідно до результатів у інтактних тварин. У групі експериментальних тварин після імплантації хірургічної сітки з покриттям на основі оксиду танталу вміст IL-1 $\beta$  та IL-6 статистично був вищим на 18,6% та 36,6% відповідно, у порівнянні з результатами групи інтактних тварин. У той же час, у групі експериментальних тварин після імплантації поліпропіленової хірургічної сітки без покриття вміст IL-1 $\beta$  та IL-6 статистично був вищим на 72% та 81,6% відповідно, у порівнянні з групою інтактних тварин.

У результаті покриття на основі танталу та оксиду танталу продемонстрували відмінний протизапальний ефект та продемонстрували чудову біосумісність, що вказує нам на можливість подальшого вдосконалення хірургічних сіток за допомогою біосумісних покриттів для досягання кращих результатів у хірургічній практиці.

**Ключові слова:** тантал, оксид танталу, інтерлейкін-1 $\beta$ , хірургічні сітки, інтерлейкін-6, нітрид танталу

### **THE ROLE OF PRO-INFLAMMATORY CYTOKINES IN RATS AFTER IMPLANTATION OF POLYPROPYLENE SURGICAL MESH WITH A COATING BASED ON TANTALUM AND ITS DERIVATIVES**

**Nakonechna O. A., Kyslov O. V.**

**Abstract.** Since the beginning of the 21st century, polypropylene has become the main material used in hernia plastic surgery. More than 30 types of polypropylene surgical meshes are available in the world, but negative statistics regarding the development of the inflammatory process after implantation still remain disappointing. The development of the inflammatory process after implantation of polypropylene surgical meshes is observed in 30-40% of patients. Polypropylenenets, due to their synthetic nature and special physicochemical properties, can increase this inflammatory reaction. The body's response to polypropylene materials can lead to encapsulation of the surgical mesh in fibrous tissue, a process designed to isolate the foreign material. This fibrotic reaction can cause discomfort, pain, and dysfunction of the mesh, causing subsequent deformation. In recent years, tantalum has been successfully used to produce biocompatible medical implants in surgery, orthopedics, and orthodontics.

The aim of our study was to determine the content of pro-inflammatory cytokines, namely IL-1 $\beta$  and IL-6, in the blood plasma of experimental animals 28 days after implantation of polypropylene surgical meshes coated on the basis of tantalum and its derivatives, in particular tantalum oxide and nitride.

The experimental group included 40 male rats of the WAG population. Experimental animals were divided randomly into six groups. With the help of surgical intervention, polypropylene surgical mesh «Omega II standard» (Ukrtehmed, Ukraine) measuring 15x15 mm with different types of coatings was implanted between the abdominal wall and the colon. 28 days after surgery, experimental animals were decapitated by cervical dislocation and blood was immediately collected to determine the content of IL-1 $\beta$  and IL-6 in blood plasma.

The data obtained after the conducted studies indicate that coatings made of tantalum and tantalum oxide do not contribute to the emergence of an inflammatory process in comparison with the results of a group of experimental animals that were implanted with a surgical mesh without a coating. In the group of experimental animals, after implantation of a tantalum-based surgical mesh, the content of IL-1 $\beta$  and IL-6 was statistically higher by 14.6% and 21.6%, respectively, compared to the results in intact animals. In the group of experimental animals after implantation of a surgical mesh with a coating based on tantalum oxide, the content of IL-1 $\beta$  and IL-6 was statistically higher by 18.6% and 36.6%, respectively, compared to the results of the group of intact animals. At the same time, in the group of experimental animals after implantation of polypropylene surgical mesh without coating, the content of IL-1 $\beta$  and IL-6 was statistically higher by 72% and 81.6%, respectively, compared to the group of intact animals.

As a result, the coating based on tantalum and tantalum oxide demonstrated an excellent anti-inflammatory effect and demonstrated excellent biocompatibility, which indicates to us the possibility of further improvement of surgical meshes with biocompatible coatings to achieve better results in surgical practice.

**Key words:** tantalum, tantalum oxide, interleukin-1 $\beta$ , surgical meshes, interleukin-6, tantalum nitride.

#### **ORCID and contributionship:**

Nakonechna O. A.: <https://orcid.org/0000-0002-2614-1587><sup>ABDEF</sup>

Kyslov O. V.: <https://orcid.org/0009-0000-9503-7524><sup>BCD</sup>

#### **Conflict of interest:**

The authors declare that there is no conflict of interest.

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#### **Corresponding author**

Kyslov Oleksandr Victorovich  
Kharkiv National Medical University  
Ukraine, 61022, Kharkiv, 4 Nauky avenue  
Tel.: +380992205048  
E-mail: [ov.kyslov@knmu.edu.ua](mailto:ov.kyslov@knmu.edu.ua)

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article.

Received 02.10.2023

Accepted 01.03.2024