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# REACTIVE OXYGEN SPECIES GENERATION BY BLOOD LEUKOCYTES OF RATS AFTER IMPLANTATION OF SURGICAL MESH WITH TANTALUM-BASED COATING

***Introduction.*** *Over the past 20 years, polypropylene has become the main material used in hernioplasty, and has proven itself as an excellent material for the restoration of the abdominal wall during hernia repair. Since polypropylene surgical meshes do not decompose well in the body, they can stimulate the development of an inflammatory process in the surrounding tissues, which subsequently causes adhesions. The development of a postoperative inflammatory process after implantation of polypropylene surgical meshes is observed in 30–40 % of patients. This affects the management of the postoperative period, increases the time of stay of patients in the hospital and their period of convalescence. These data force scientists to continue the search for the optimal surgical mesh, 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. Tantalum is successfully used to produce biocompatible medical implants in surgery, orthopedics and dentistry. In previous studies, we have repeatedly noted its excellent anti-inflammatory and antibacterial properties, indicating the possibility of its use as a coating for mesh implants. One of the typical responses to surgical intervention is the generation of reactive oxygen species by leukocyte neutrophils, which are signaling molecules that damage the endothelium of vessels and promote the migration of cells of the immune system to the center of inflammation.*

***The aim of the study*** *– to determine the generation of reactive oxygen species in leukocytes of rats of the control group and experimental rats with implantation of uncoated and tantalum-based surgical meshes.*

***Research Methods.*** *ROS generation was assessed in rat blood leukocytes using the dye 2,7-dichlorodihydrofluorescein diacetate (H2DCFDA) by flow cytometry 28 days after implantation of uncoated and tantalum-coated surgical meshes.*

***Results and Discussion.*** *Analyzing the obtained results, it was determined that the use of tantalum-based surgical meshes does not cause excessive generation of ROS by leukocytes, in contrast to the use of an implant without a coating. Implantation of uncoated surgical mesh caused excessive production of reactive oxygen species in blood leukocytes of rats, as evidenced by statistically significant differences in the mean fluorescence intensity of 2,7- dichlorodihydrofluorescein diacetate.*

***Conclusions.*** *The use of tantalum-based surgical meshes causes less generation of ROS in leukocytes compared to the use of uncoated surgical meshes, and does not provoke the development of adhesions and purulent-septic processes in the postoperative period, which is confirmed by a morphological study. This determines the possibility of their use in surgical practice to improve the durability and stability of use as biomedical implants and prevention of adhesion formation.*

KEY WORDS: **tantalum; leukocytes; reactive oxygen species; surgical meshes; rats.**

INTRODUCTION. According to the data from the International Society of Herniologists, inguinal hernia repair is one of the most common operations in the world, which is performed annually by more than 20 million patients. Surgical treatment is successful in most cases, but the occurrence of intra-abdominal adhesions and purulent-septic processes require repeated surgical interventions in 10– 15 % of patients, and long-term disability due to chronic pain (lasting more than 3 months) occurs in 10–12 % of patients [1, 2].



Nowadays, there is an acute problem of creating and using the most modern materials for hernioplasty, which will suit doctors not only in terms of design, construction, thread thickness and pore width, but also in terms of the chemical nature of the coatings and biological compatibility, which will help prevent the occurrence of pathological processes in the postoperative period, in particular, the formation of adhesions at the point of contact of the surgical mesh with the intestine [3]. Under such circumstances, tantalum (Ta) and its derivatives, in particular tantalum oxide and tantalum nitride, which

can be successfully used in surgery, orthopedics and dentistry, have attracted considerable attention [4].

One of the typical responses to surgical intervention is the generation of reactive oxygen species by leukocyte neutrophils, which are signaling molecules that damage the endothelium of vessels and promote the migration of cells of the immune system to the center of inflammation. Reactive oxygen species are free oxygen-containing radicals, ions or molecules that have one unpaired electron in their outer shell. Due to this nature, ROS have high reactivity. ROS can be divided into two groups: oxygen free radicals and non-radical ROS. Free oxygen radicals include superoxide ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), nitric oxide ($NO^{\bullet}$), organic radicals ($R^{\bullet}$), peroxyl radicals ($ROO^{\bullet}$) [5].

ROS also include hydrogen peroxide ($H_2O_2$), singlet oxygen ($O_2$), ozone ($O_3$), nitrocarbonate anion ($ONOCO_2^-$), nitrogen dioxide ($N_2O_2$) and highly reactive carbonyl compounds, derivatives of lipids or carbohydrates. Among them, superoxide anion, hydrogen peroxide, and hydroxyl radicals are the most well-studied forms of ROS [6, 7].

Under normal physiological conditions, intracellular ROS levels are stably maintained to prevent cell damage. ROS detoxification is facilitated by antioxidants: non-enzymatic molecules (glutathione, flavonoids, and antioxidant vitamins A, C, E, and β-carotene) or enzymes that specifically remove ROS. The enzymatic link of antioxidant protection is superoxide dismutase (SOD), which catalyzes the dismutation of superoxide anion to oxygen and hydrogen peroxide, using metal ions: copper (Cu), zinc (Zn), manganese (Mn) or ferrum (Fe) as cofactors. Isoenzyme forms of SOD are located in different compartments of the cell and are highly specific in the regulation of biological processes. The next enzyme of the antioxidant system is catalase, which contributes to the decomposition of hydrogen peroxide into water and oxygen, is located in the cytosol and peroxisomes [8]. Peroxiredoxins are thioredoxin peroxidase enzymes that catalyze the reduction of hydrogen peroxide, organic hydroperoxides, and peroxynitrite [9].

A disproportionate increase in intracellular ROS can subsequently cause cell apoptosis and necrosis. This process can occur after surgical interventions and associated inflammatory processes.

Apoptosis is known to be associated with an increase in mitochondrial oxidative stress, which causes the release of cytochrome c, which leads to the activation of caspases and cell death [10, 11]. In addition, superoxide generation can also induce pro-apoptotic signaling [12]. Our study will determine the effect of uncoated and coated tantalum-based implants on the generation of ROS by blood leukocytes of experimental animals.

RESEARCH METHODS. The experimental group included 18 male rats of the WAG population weighing (250±10) g. They were randomly divided into three groups (n=6 each) after acclimatization in the vivarium of the Kharkiv National Medical University for 14 days. Animals received the same amount of water, access to food was free in all groups. Rats were in standard laboratory conditions in accordance with the "Standard Rules for the Arrangement, Equipment and Maintenance of Experimental Biological Clinics (vivariums)", adhering to the general principles of bioethics in accordance with the Declaration of Helsinki (World Medical Assembly, 1964). The guidelines of EU Directive 2010/63/EC 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 (Strasbourg, 1986) were strictly followed when handling rats. The study was approved by the Bioethics Committee of the Kharkiv National Medical University (protocol No.3 dated September 21, 2020).

A polypropylene surgical mesh "Omega II standard" (Ukrtechmed, Ukraine) measuring 15×15 mm was implanted surgically between the abdominal wall and various sections of the colon. Anesthesia was carried out by intraperitoneal administration of the drug "Relax" in a dose of 8 mg/kg, the active substance of which is propofol (1 %). Coatings were applied to polypropylene surgical meshes using the method of reactive magnetron sputtering in a vacuum chamber on the basis of the Educational and Scientific Institute "Physical and Technical Faculty" of Kharkiv National University named after V. N. Karazin.

The first group of rats was implanted with uncoated surgical mesh, the second group was implanted with tantalum-based surgical mesh. The third (control) group consisted of intact animals that did not undergo surgery. After 28 days, decapitation was performed by cervical dislocation, blood was collected in sterile K2 EDTA VACUTAINER tubes (BD Vacutainer®). Blood samples were used to prepare leukocyte suspensions for the assessment of ROS production using 2'-7'-dichlorodihydrofluorescein diacetate (H2DCFDA) by flow cytometry.

The generation of ROS in leukocytes was determined by the reaction with a working solution of 2,7-dichlorodihydrofluorescein diacetate (H2DCFDA, Invitrogen TM, USA) with a final concentration of ROS – a sensitive dye equal to 10 μM. H2DCFDA is widely used to determine intracellular ROS content. When H2DCFDA enters

the cell, it is deacetylated by esterases and upon interaction with ROS, it is transformed into DCF (Dichlorofluorescein), the fluorescence intensity of which is proportional to the content of ROS in the cell. Cells were washed twice to remove residual H2DCFDA. The samples were analyzed on a BD FACSCanto II flow cytometer (Becton Dickinson, USA) at 488 nm & emission detection at 525 nm with registration of the average DCF fluorescence intensity. To compare the numerical values of the mean fluorescence intensity (MFI) indicators of DCF of independent groups, the Kruskal-Wallis test was used, followed by the calculation of Dunn's test.

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.

RESULTS AND DISCUSSION. Analyzing the obtained results, it was determined that the MFI value was statistically two times higher (119.8 %) in rats implanted with a surgical mesh without a coating than in the control group. The use of surgical meshes without coating leads to a more than two-fold increase in the generation of ROS by leukocytes. This indicates significantly increased levels of ROS in leukocyte subpopulations such as monocytes and granulocytes compared to the non-operated control group. Excessive generation of ROS can contribute to lipid peroxidation, which leads to the development of oxidative stress and imbalance of intracellular homeostasis, as a result, disruption of cellular metabolism, further development of apoptosis and cell necrosis.

At the same time, the value of MFI (Tab.) after the use of tantalum-based implants was not statistically different from the value obtained in the control group of experimental animals that did not undergo surgery. This proves better biocompatibility of tantalum-coated polypropylene surgical meshes compared to uncoated polypropylene surgical meshes.

After implantation of a surgical mesh without a coating, a sharp hyperproduction of ROS was noted, which led to the rapid onset of inflammatory and adhesion processes, which were observed in the animals during the study. Whereas after implantation of polypropylene surgical meshes with a coating based on tantalum in experimental animals, no signs of the inflammatory process were observed in the postoperative period, which may also indicate its excellent antibacterial properties. Also, differences in inducing excessive generation of ROS by implants is explained by the fact that tantalum coating is relatively inhibiting the occurrence of the inflammatory process and subsequent cell apoptosis, in particular leukocytes, which are involved in the body's immune status. Inhibiting the development of the inflammatory process by tantalum is one of the key factors, which thereby accelerates the healing of the postoperative wound and significantly shortens the convalescence period, as well as prevents the development of adhesions and purulent-septic processes.

For many years, tantalum-based implants and its derivatives have been widely used in dentistry and orthopedics [13]. However, knowledge of the experience with tantalum-based coatings for polypropylene surgical meshes remains limited at present. To the best of our knowledge, this article is one of the first to address the use of a tantalum-based coating to inhibit the inflammatory process at the implant site and prevent oxidative stress. The results we obtained during the experiment suggest a new approach to the use of surgical meshes in hernioplasty and require further study within the framework of the experiment.

After the implantation of a polypropylene surgical mesh with a tantalum-based coating, the generation of ROS was less pronounced, compared to the results after the implantation of a surgical mesh without a coating. This fact allows us to understand that tantalum-based coatings exhibit anti- inflammatory and antibacterial effects, which indicates their inertness and biocompatibility. At the same time, the research of the Chinese scientist Yang with colleagues demonstrated that Ta and its derivatives are able to provoke an acute inflammatory process and oxidative stress, but the results of this discrepancy can be explained by the methods of coating modification and the conditions of use [14].

The French scientist Clave with colleagues noted in their research that the effectiveness of using the implant and its biocompatibility is

Table – **Mean fluorescence intensity (MFI) of 2',7'-dichlorofluorescein (DCF) in rats leukocytes (Me [25 % Percentile; 75 % Percentile])**

| Groups | Median | 25 % Percentile | 75 % Percentile |
|---|---|---|---|
| Control group | 3.286 | 2.833 | 5.252 |
| Experimental group (Ta) | 5.742 | 4.067 | 8.467 |
| Experimental group (uncoated) | 7.224* | 5.465 | 8.613 |

Note: * – p=0.0178 compared to control group.

determined exclusively by the degree of induction of an acute inflammatory process at the site of implantation [15]. Hyperproduction of ROS, as well as suppression of the normal functioning of leukocytes, can have a negative effect on the healing effect of the postoperative wound and on the convalescence period.

In our study, tantalum does not cause excessive production of ROS, which indicates the normal vital activity and functioning of cells, and also confirms the data of the results obtained earlier [16]. In addition, tantalum-based coating implants showed less cytotoxicity, which had a positive effect on the functioning of the implant and reduced the chance of oxidative stress in group of experimental animals.

CONCLUSIONS. The use of tantalum-based coatings did not provoke hyperproduction of ROS in blood leukocytes of experimental animals, which indicates their excellent biocompatibility and antibacterial activity compared to the use of uncoated surgical mesh. The in vivo results showed that the tantalum-coated surgical meshes implanted by us have good stability, as well as a clear anti-inflammatory effect, which is manifested in the postoperative period during the occurrence of oxidative stress, which is confirmed by morphological research.

This fact confirms the possibility of further use of tantalum-coated implants in surgical practice to improve the course of the postoperative period and guarantees their durability and stability of use as biomedical implants. Our study offers a promising strategy for the use of implants that is expected to be translated into clinical application in elective surgical practice to prevent adhesions in the near future.

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# ГЕНЕРАЦІЯ АКТИВНИХ ФОРМ КИСНЮ ЛЕЙКОЦИТАМИ КРОВІ ЩУРІВ ПІСЛЯ ІМПЛАНТАЦІЇ ХІРУРГІЧНОЇ СІТКИ З ПОКРИТТЯМ НА ОСНОВІ ТАНТАЛУ

**Резюме**

***Вступ.*** *За останні 20 років поліпропілен став основним матеріалом для герніопластики і зарекомендував себе як чудовий матеріал для відновлення черевної стінки при грижі. Оскільки поліпропіленові хірургічні сітки погано розкладаються в організмі, вони можуть стимулювати розвиток запального процесу в навколишніх тканинах, що згодом викликає спайковий процес. Розвиток післяопераційного запального процесу після імплантації поліпропіленових хірургічних сіток спостерігають у 30–40 % пацієнтів. Це впливає на ведення післяопераційного періоду, збільшує час перебування хворих у стаціонарі та період їх одужання. Такі дані змушують учених продовжувати пошук оптимальної хірургічної сітки, яка б влаштовувала фахівців щодо як її фізичних властивостей, так і біосумісних та протизапальних. Тантал успішно використовують для виробництва біосумісних медичних імплантатів у хірургії, ортопедії і стоматології. У попередніх дослідженнях ми неодноразово відзначали його відмінні протизапальні й антибактеріальні властивості, що вказує на можливість застосування танталу як покриття для сітчастих імплантатів. Однією з типових реакцій на хірургічне втручання є генерація активних форм кисню (АФК) нейтрофілами лейкоцитів, які є сигнальними молекулами, що ушкоджують ендотелій судин і сприяють міграції клітин імунної системи до вогнища запалення.*

***Мета дослідження*** *– визначити генерацію активних форм кисню лейкоцитами крові щурів контрольної групи та піддослідних тварин при імплантації хірургічних сіток без покриття і з покриттям на основі танталу.*

***Методи дослідження.*** *Оцінювали генерацію АФК лейкоцитами крові щурів з використанням барвника 2,7-дихлордигідрофлуоресцеїну діацетату ($H_2$DCFDA) за допомогою проточної цитометрії через 28 днів після імплантації хірургічних сіток без покриття і з танталовим покриттям.*

***Результати й обговорення.*** *Аналізуючи отримані результати, встановили, що використання хірургічних сіток на основі танталу не викликало надмірної генерації АФК лейкоцитами крові на відміну від застосування імплантата без покриття. Імплантація хірургічної сітки без покриття спричинила надмірне продукування АФК лейкоцитами крові щурів, про що свідчили статистично значущі відмінності в середній інтенсивності флуоресценції 2,7-дихлордигідрофлуоресцеїну діацетату.*

***Висновки.*** *Використання хірургічних сіток на основі танталу спричиняє меншу генерацію АФК лейкоцитами крові порівняно із застосуванням хірургічних сіток без покриття, не провокує розвитку спайок і гнійно-септичних процесів у післяопераційний період, що підтвердило морфологічне дослідження. Це визначає можливість їх використання в хірургічній практиці для підвищення довговічності й стабільності застосування як біомедичних імплантатів і запобігання утворенню спайок.*

КЛЮЧОВІ СЛОВА: **тантал; лейкоцити; активні форми кисню; хірургічні сітки; щури.**