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INFLUENCE OF POLYPROPYLENE IMPLANTS COATED WITH TANTALUM AND ITS DERIVATIVES ON INFLAMMATION AND REGENERATION PROCESSES

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Abstract

Introduction. Polypropylene implants are widely used in surgical practice; however, some authors point to numerous postoperative complications after their use, the main cause of which is the development of aseptic inflammation. This necessitates the search for effective anti-inflammatory coatings.
Aim. To evaluate the influence of polypropylene implants coated with tantalum and its derivatives on inflammation and regeneration processes.
Materials and methods. The study used 40 male rats, divided into 6 groups: intact (1); with surgical intervention without an implant (2); with an uncoated polypropylene implant (3); with a tantalum-coated implant (4); with a tantalum pentoxide-coated implant (5); with a tantalum nitride-coated implant (6). Morphological and immunohistochemical studies were performed.
Results. In rats of groups 3 and 6, pronounced neutrophilic infiltration, purulent exudate, and a thin layer of immature granulation tissue were detected. Multinucleated foreign body giant cells were often observed in the granulation tissue. In rats of groups 4 and 5, neutrophilic infiltration was absent, granulation tissue was mature, and its layer thickness was one-third greater compared to groups 3 and 6. In rats of groups 4 and 5, a greater number of Ki-67 positive and a smaller number of p53 positive cells were detected, and a higher proliferative-apoptotic ratio (Ki-67/p53) was found compared to rats of groups 3 and 6.
Conclusions. Polypropylene implant induces aseptic inflammation, leading to increased apoptosis and decreased regeneration. Coating the implant with tantalum or tantalum pentoxide prevents inflammation, reduces apoptosis, and increases cell proliferation. Coating the implant with tantalum nitride does not change it, while coating with tantalum or tantalum pentoxide improves its biointegration.

Keywords: **rats, tantalum, inflammation, apoptosis, proliferation**

INTRODUCTION

Polypropylene implants (PPI) are widely used in surgical practice for the correction of inguinal and hiatal hernias, reconstruction of the chest and abdominal wall, and more. Although PPI is traditionally used to reinforce soft tissues, there are works according to which PPI is considered a cheap and effective material for the reconstruction of small or medium-sized skull defects [1] and may be a promising adjunct for the treatment of critical-sized bone defects [2]. PPI is considered to have advantages due to its non-toxicity, high biocompatibility, and minimized contamination during processing [3].

However, some authors point to numerous postoperative complications after PPI use, the main cause of which is the development of aseptic inflammation of the abdominal wall tissues as a result of their contact with the classic PPI. Prolonged aseptic inflammation inhibits the process of PPI germination by connective tissue, leading to PPI shrinkage, and in case of infection, to implant migration and hernia recurrence [4]. Other studies have also shown that PPIs cause severe inflammation [5] and induce lipid peroxidation [6]. All this necessitates the search for effective anti-inflammatory coatings.

Tantalum (Ta) attracted our attention as a substance that can improve the biocompatibility of PPI and reduce its pro-inflammatory effect. There are many scientific papers indicating the significant potential for the use of Ta and its derivatives in orthopedic and dental implants [7]. Ta particles have been shown to inhibit the pro-inflammatory effects and bone resorption of titanium (Ti) particles in vivo and in vitro [8]. In a rat femoral

condyle bone defect model, artificial bone loaded with Ta particles promoted the differentiation of macrophages at the defect site to M2, accelerating bone repair [8]. In cell experiments, it was shown that coating the surface of polyimide (a promising implant in orthopedics) with tantalum pentoxide (Ta_2O_5) promotes proliferation, adhesion, and osteogenic differentiation of bone marrow stromal cells [9]. Qi W. et al. (2025) noted that tantalum sulfide has significant promise for the treatment of acute liver injury due to its exceptional biocompatibility and powerful ability to scavenge reactive oxygen species (ROS) [10].

The need for an inexpensive, biocompatible material for the chest and abdominal wall reconstruction increases the relevance of research aimed at eliminating postoperative complications of PPIs. This issue is becoming especially acute in the context of full-scale hostilities in Ukraine with severe chest and abdominal injuries among military personnel and civilians.

AIM

The aim of this study is to evaluate the influence of polypropylene implants coated with tantalum and its derivatives on the processes of inflammation and tissue regeneration.

MATERIALS AND METHODS

The study used 40 male WAG rats weighing 200-240 g, divided into six groups: intact (6 rats, group 1); with surgical intervention without PPI (6 rats, group 2); with uncoated PPI (7 rats, group 3); with Ta-coated PPI (7 rats, group 4); with Ta_2O_5-coated PPI (7 rats, group 5); with tantalum nitride (TaN)-coated PPI (7 rats, group 6). The PPI size was 15×15 mm. The surgical implantation was performed between the abdominal wall and the colon. A drug «Relax» (the active ingredient is 1% propofol) was used as an anesthetic (intraperitoneal administration at a dose of 8 mg/kg). The coatings on PPI were applied by 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.

After 28 days, the rats were decapitated. Fragments of the anterior abdominal wall in group 1 and fragments of the anterior abdominal wall in the surgical area in the other groups were collected. The obtained experimental material for morphological and immunohistochemical studies was fixed in 10% neutral formalin solution (pH 7.4) for 24-48 hours, carried out according to the generally accepted method and embedded in paraffin.

Sections 4-5 μm thick were made from paraffin blocks for staining with hematoxylin, eosin and picrofuchsin according to van Gieson. Studies of the prepared micropreparations were carried out using ZEISS Primostar 3 microscopes (Carl Zeiss, Germany) with a built-in color digital camera, BRESSER Science TFM-301 Trino with a BRESSER Full HD camera (Bresser GmbH, Germany). The severity of the detected general pathological processes was assessed using a semi-quantitative scale: «-» – absent, «+» – weak, «++» – moderate, «+++» – moderately pronounced, «++++» – pronounced, «+++++» – strongly pronounced. The thickness of the granulation tissue layer formed around the PPI was determined using the Labscope program.

Determination of Ki-67 (proliferation marker) and p53 (apoptosis marker) in granulation tissue formed around the PPI was performed by immunohistochemical methods. Rabbit monoclonal antibodies (MABs) to Ki-67 (clone SP6, Master Diagnostica, Spain), to p53 (clone SP5, Master Diagnostica, Spain) were used as primary antibodies. The Master Polymer Plus Detection system (Peroxidase, DAB chromogen) (Master Diagnostica, Spain) was used for visualization. The nuclei of cells containing, respectively, either Ki-67 or p53 were stained brown. For contrast, the micropreparations were stained with hematoxylin and eosin. The absolute number of Ki-67-positive and p53-positive cells in the ×400 field of view of the microscope was counted. The PAST program (version 4.15, Natural History Museum, University of Oslo, Norway) was used to process the indicators in groups. The parameters between groups were compared using the nonparametric Mann-Whitney U-test using the GraphPad Prism program (Graph Pad, USA). The results were presented as median (Me) and interquartile range (25%, 75%). A difference was considered statistically significant at $p<0.05$.

RESULTS

According to the morphological study results, in the intact group rats, between connective tissue fibers in dermis, hypodermis, lumbar striated muscle tissue, connective tissue layer, focal, weakly expressed (+) cellular infiltration was determined, represented mainly by macrophages, lymphocytes, and fibroblastic cells. In rats with surgical intervention without implantation, diffuse, moderate (++) polymorphic cellular infiltration was found, but it was also represented by macrophages, lymphocytes, and fibroblastic cells.

In rats with PPI without coating (group 3), pronounced (+++) hemodynamic disorders; strongly pronounced (+++++) diffuse-focal cellular infiltration, represented by neutrophilic leukocytes, macrophages, lymphocytes, and fibroblastic cells; foci of mature and immature granulation tissue were detected. Ischemic-dystrophic and necrotic changes were observed in the muscle fibers of the muscle layer (Fig. 1).

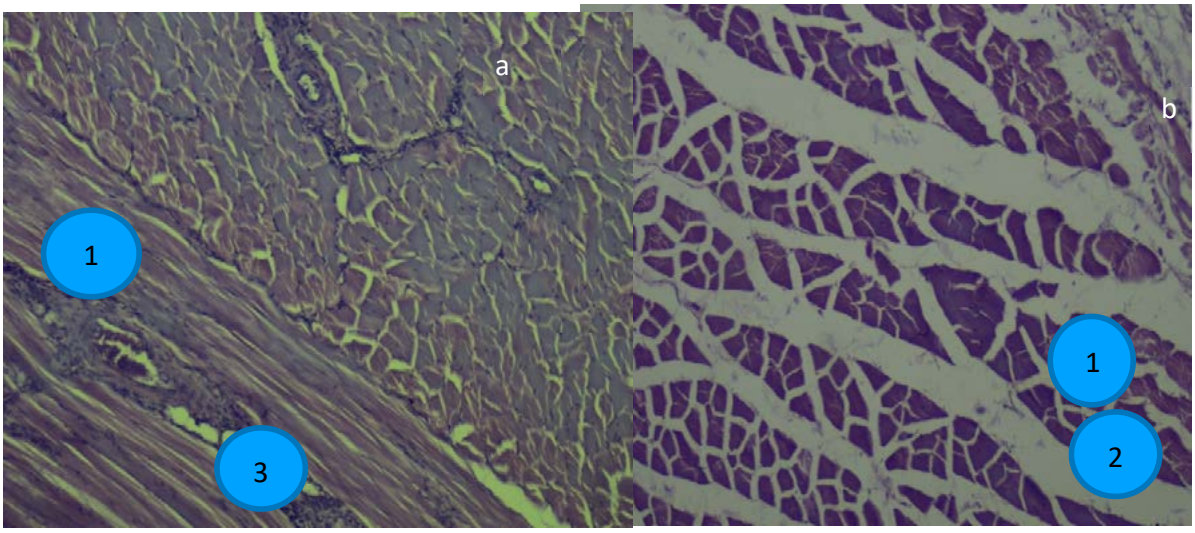


Figure 1. Ischemic-dystrophic and necrotic changes in muscle fibers (1), hemodynamic disturbances (2) and focal polymorphic cellular infiltration (3) in the muscle layer of rat No. 1 of group 3. Hematoxylin a) × 100 and eosin b) × 100 staining.

Multinucleated giant cells of foreign bodies were often found in the granulation tissue. The thickness of the granulation tissue layer was 956.67 [899.52; 1012.16] μm. In six of the seven rats in group 3, a layer of purulent and purulent-fibrinous exudate was adjacent to the granulation tissue layer, and in five of them, purulent exudate was observed to leak outward.

In rats with PPI coated with TaN, changes in the anterior abdominal wall were similar to those in group 3 rats. The thickness of the granulation tissue layer was 1003.75 [887.54; 1041.89] μm. In all rats of this group, behind the layer of immature granulation tissue surrounding the implant, purulent or purulent-fibrinous exudate was observed, and its discharge was noted in 6 cases.

In rats with PPI with Ta coating (group 4), moderate diffuse polymorphic cellular infiltration (++), represented by lymphocytes, macrophages, and fibroblastic differon cells, was observed. Behind the connective tissue layer was mature granulation tissue, which overgrew the PPI (Fig. 2). The thickness of the granulation tissue layer was 1532.92 [1466.47; 1621.25] μm.

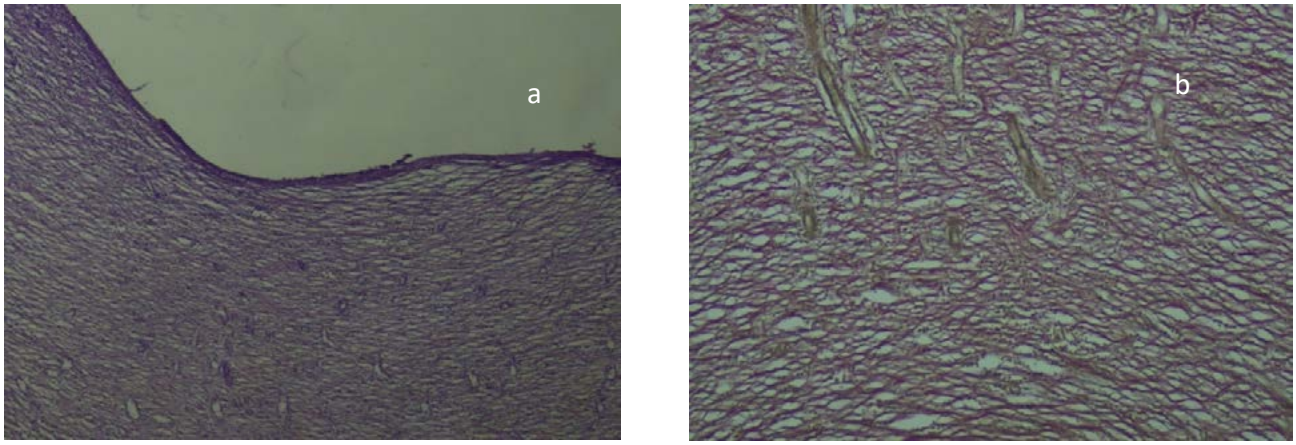


Figure 2. Mature granulation tissue overgrowing the polypropylene implant and growing into its holes in rat No. 2 of group 4. Staining with hematoxylin and eosin (a), × 40; van Gieson's picrofuchsin (b), × 100.

In rats with PPI coated with Ta_2O_5 (group 5), changes in the anterior abdominal wall were similar to those in rats of group 4. The thickness of the granulation tissue layer, located behind the connective tissue layer around the PPI, was 1496.35 [1447.76; 1522.85] μm.

According to the results of immunohistochemical study with MABs to p53 and Ki-67, the expression of these proteins was observed in the granulation tissue in vascular endothelial cells, fibroblasts and lymphocytes. In rats with PPI without coating, the number of Ki-67 positive cells was significantly lower compared to rats with PPI coated with either Ta or Ta_2O_5 and did not differ from rats with PPI coated with TaN (Table 1).

Table 1

Ki-67 and p53 Expression in Granulation Tissue around Polypropylene Implant in Experimental Rats

Animal group	Ki-67 positive cells, absolute number (Me[25%;75%])	p57 positive cells, absolute number (Me[25%;75%])
Group 3: PPI without coating	36 [29;40]	57 [53;62]
Group 4: Ta-coated PPI	47 [46;54]*	32 [28;35]*
Group 5: Ta_2O_5-coated PPI	46 [45;55]*	32 [28;350]*
Group 6: TaN-coated PPI	37 [33;40]**, ***	58 [50;63]**, ***

Note: * – p<0.05 compared to group 3; ** – p<0.05 compared to group 4; *** – p<0.05 compared to group 5.

On the contrary, the number of p53 positive cells in the granulation tissue of group 3 rats was significantly higher compared to rats in groups 4 and 5 and did not differ from group 6 rats. In rats of groups 4 and 5, a higher proliferative-apoptotic ratio (Ki-67/p53) was found compared to rats of groups 3 and 6.

DISCUSSION

According to the results, complete healing of the surgically induced anterior abdominal wall defect was observed on day 28. This is consistent with the literature, which indicates that the healing process of acute wounds usually lasts from 4 to 6 weeks [11]. In rats with implants without coating pronounced signs of the inflammatory process were detected. Thus, in this group of animals, there was a pronounced infiltration of neutrophil leukocytes and macrophages in the dermis, hypodermis, muscle and connective tissue layers. In 85,7% of the rats in this group, a layer of purulent and purulent-fibrinous exudate was adjacent to the granulation tissue layer, and in 71,4% of animals, the release of purulent exudate was detected. The presence of pus and neutrophils on day 28 in the rats in this group indicates that PPI causes aseptic inflammation, which, due to high vascular permeability, quickly turns into an infected focus.

In rats with PPI without coating, inhibition of wound healing processes was observed (compared to group 2), as evidenced by decrease in the number of fibroblasts, the predominance of apoptosis over proliferation processes and, as a result, a weak intensity of granulation tissue maturation processes around the implant. Multinucleated foreign body giant cells were frequently observed in the granulation tissue. Foreign body giant cells are a characteristic feature of foreign body reaction [12]. The decrease in proliferation processes in rats of group 3 is evidenced by immunohistochemical assessment of the expression of the most common proliferation marker Ki-67, namely a statistically significant decrease in the number of Ki-67-positive cells in the granulation tissue of these animals compared to rats in groups 4 and 5. The increase in apoptosis processes in animals of this group is evidenced by increased expression of p53.

The results of our study indicate that the use of uncoated PPI leads to the development of severe inflammatory changes, which is consistent with the data of other studies [4, 5, 6], and inhibition of wound healing processes.

The use of Ta-coated PPI improves the wound healing process and promotes the formation of a mature granulation tissue layer around the implant. Ta coating reduces the apoptosis process, enhances cell proliferation in the granulation tissue, which contributes to its rapid maturation and transformation into connective tissue. When using PPI coated with Ta_2O_5, the morphological features of wound healing, the thickness of the layer of mature granulation tissue formed around the implant, and the number of Ki-67- and p53-positive cells in it did not differ from the corresponding indicators in the group of rats with an implant coated with Ta. The similarity in the results obtained when using PPI coated with Ta and Ta_2O_5 is explained by the fact that Ta in air quickly forms Ta_2O_5, i.e. the surface of metallic Ta has a natural oxide (Ta_2O_5), which has an important effect on the biocompatibility of Ta [9].

Oxidation of Ta to Ta_2O_5 creates a hydrophilic but very inert film on the surface of PPI. This reduces the perception of the implant by the immune system as a foreign body, and reduces the inflammatory response. As a result, ROS leakage from neutrophils and macrophages is reduced, and therefore apoptosis is reduced and proliferation is increased. In a rat femoral condyle defect model, Ta particles have been shown to modulate macrophage polarization in the M2 direction, thereby enhancing proliferation, migration, and osteogenic differentiation of mesenchymal stem cells [8]. In a culture of bone marrow-derived stromal cells, Ta_2O_5 coating has also been shown to increase cell adhesion, proliferation, and differentiation [9]. According to our results, the proliferative-apoptotic index (Ki-67 to p57 ratio) in rats with PPI with Ta or Ta_2O_5 coating is, respectively, 1.47 and 1.44 versus 0.62 in the group of animals with PPI without coating.

The use of TaN-coated implant causes the development of a pronounced inflammatory process, the prevalence of apoptosis over proliferative processes, and inhibition of granulation tissue maturation. The morphological characteristic of wound healing processes in rats of this group is similar to that observed in rats with implants without coating. No statistically significant difference was observed between these two groups in all studied parameters. The proliferative-apoptotic index was 0.62 (for group 3) and 0.64 (for group 6). It is possible

that this difference in the effects of TaN compared to Ta and Ta_2O_5 is due to the greater fragility of TaN and the possibility of its particles being detached from the surface of the PPI. In addition, it lacks antibacterial properties [13]. Thus, PPI and PPI coated with tantalum nitride even on the 28th day demonstrate a destructive-inflammatory type of reaction. High levels of apoptosis and the presence of neutrophils/pus block normal tissue growth, which is confirmed by a smaller thickness of granulation tissue.

Tantalum and tantalum pentoxide provide a regenerative-plastic type of reaction. High proliferation and low apoptosis allow the body to build up a powerful protective layer, which indicates ideal biointegration.

CONCLUSIONS

Polypropylene implant induces aseptic inflammation, resulting in increased apoptosis and decreased proliferation, as evidenced by neutrophil/pus accumulation, low proliferative-apoptotic index (Ki-67/p57), and the formation of immature granulation tissue. Coating PPIs with TaN does not affect the development of the inflammatory process and does not change the proliferative-apoptotic index compared to uncoated PPI.

Coating PPIs with Ta or Ta_2O_5 prevents the development of the inflammatory process, reduces apoptosis, and increases cell proliferation. Coating PPIs with Ta or Ta_2O_5 improves their biointegration.

Perspectives for further research. In the future, it is advisable to study the effect of tantalum derivatives on the biointegration of other implants, taking into account the needs of medicine in the conditions of full-scale hostilities in Ukraine. An important direction is the study of their effect on key markers of osteogenesis and angiogenesis, the crucial apoptosis marker caspase-3, and macrophage polarization.

COMPLIANCE WITH ETHICAL REQUIREMENTS

The research was carried out in accordance with the requirements of Good Laboratory Practice (GLP), the Council of Europe Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes of March 18, 1986, the EU Directive 2010/63/EU on the protection of animals used for scientific purposes. The study was approved by the Ethics and Bioethics Commission of Kharkiv National Medical University (protocol No. 8 dated October 17, 2025).

Study limitations. The limitations of this study include the small sample size, monocenter design, the use of sexually mature male rats. The results are preliminary; confirmation requires multicenter replications, inclusion of both sexes, and different age groups.

Primary data and materials. The authors of the manuscript consciously certify that the work uses the results of their own experimental studies, which were systematized and analyzed by the authors. Primary data include generalized indicators, laboratory results, experimental protocols and obtained quantitative characteristics. All materials are stored in the archive of the research group and can be provided upon reasonable request to the corresponding author, taking into account ethical norms and legal restrictions.

Declaration on the use of generative artificial intelligence in manuscript preparation. No artificial intelligence tools were used in the preparation of this manuscript for text generation, data analysis, or image creation. All content was developed by the authors, who bear full responsibility for its accuracy, originality, and compliance with ethical standards.

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The authors declare no conflict of interest.

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Резюме

ВПЛИВ ПОЛІПРОПІЛЕНОВИХ ІМПЛАНТІВ ІЗ ПОКРИТТЯМ ТАНТАЛОМ ТА ЙОГО ПОХІДНИМИ НА ПРОЦЕСИ ЗАПАЛЕННЯ ТА РЕГЕНЕРАЦІЇ

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Вступ. Поліпропіленові імпланти широко використовуються у хірургічній практиці, однак деякі автори вказують на численні післяопераційні ускладнення після їх використання, основною причиною яких є розвиток асептичного запалення. Це обумовлює необхідність пошуку ефективних протизапальних покриттів.
Мета. Оцінити вплив поліпропіленових імплантів із покриттям танталом та його похідними на процеси запалення та регенерації.
Матеріали та методи. У дослідженні використано 40 самців щурів, розділених на 6 груп: інтактні (1); з хірургічним втручанням без імпланту (2); з поліпропіленовим імплантом без покриття (3); з покритим танталом імплантом (4); з покритим пентаоксидом танталу імплантом (5); з покритим нітридом танталу імплантом (6). Проведено морфологічні та імуногістохімічні дослідження.
Результати. У щурів груп 3 та 6 виявлено виражену нейтрофільну інфільтрацію, гнійний ексудат, тонкий шар незрілої грануляційної тканини. Часто в грануляційній тканині відмічалися багатоядерні гігантські клітини сторонніх тіл. У щурів груп 4 та 5 нейтрофільна інфільтрація відсутня, грануляційна тканина зріла, товщина її шару на одну третину більша порівняно з групами 3 та 6. У щурів груп 4 та 5 виявлено більшу кількість Кі-67 позитивних і меншу кількість p53 позитивних клітин, вищий проліферативно-апоптичний коефіцієнт (Кі-67/ p53) порівняно зі щурами груп 3 та 6.
Висновки. Поліпропіленовий імплант викликає асептичне запалення, що призводить до посилення апоптозу та зниження регенерації. Покриття імпланту танталом або пентаоксидом танталу запобігає розвитку запалення, зменшує апоптоз та збільшує проліферацію клітин. Покриття імпланту нітридом танталу не змінює біоінтеграцію, тоді як покриття танталом або пентаоксидом танталу покращує її.

Ключові слова: **щури, тантал, запалення, апоптоз, проліферація**

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