SILICON WIRES FOR NERVE GAP MANAGEMENT: ROLE OF SURFACE PROPERTIES IN NERVE REGENERATION

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Population of individuals with partial or complete disability resulting from severe peripheral nerves injuries, create significant social and economic burden on society. According to large body of statistical studies samples peripheral nerves injuries accompany 2 to 5% of all limb injuries. Among those injured in a combat 8.1 to 15.6% had peripheral nerves injuries. The mean age of these patients was 34.6 years, with the majority of them (59%) being young adults of 18-35 years of age [3,5,27,28,32,33].

According to epidemiological studies amputations represented 11% of orthopaedic trauma in combat casualties during 2003-2011 Iraq and Afghanistan campaign. Mean injured patients age was 25,9 years [37]. High-level amputations, occurring at the level of the shoulder or pelvic girdle, were prominent, comprising nearly 10% of all amputation injuries [4].

In human with severe nerve injuries, such as neurotemesis, when a peripheral nerve damage is of considerable length [40], with the distance between the stumps of the nerve trunk being more than 10 mm, primary nerve suturing without tension is not feasible, which necessitates the use of alternative surgical techniques [33,38]. These techniques include grafting with conduit and nerve transfer [7,23,30,39].

Over the past 25 years, the concept of nerve conduits in the form of tubes has evolutionized from a means to stud1y regeneration to devices that can be used in clinical practice in patients as an alternative to neurografting [12].

Constructing highly technological devices for appropriate replacement of the lost limbs with many degrees of freedom and for recovery of both motor and sensory functions is another challenge in amputees rehabilitation and patients with severe nerve and spinal cord injuries [5,14].

All this ideas are realized in Peripheral Regenerative Nerve Interfaces that have hight invasivnes and high selectivity, and composed from hollow tube, and inserted inside electrodes, by which nerve impulses can be recorded or sent by external devices for artificial limb control The key element of successful connection between the external devices and nervous system organs is creation of a functional interface that consists from nerve fibers and both safe and effective electrodes. Major point of such electrodes characteristics is ts material to provide stable in-time connection and with low noize ratio [9].

Recently the interest to using silicon in regenerative medicine and nanomedicine has risen considerably [15,22]. This is explained by the fact that silicon is a semiconductor with unique properties. It has various degrees of oxidation. Doping silicon crystal volume with other chemical elements or modification of its surface leads to changes in its physical and chemical properties. Silicon is one of ideal materials for making microelectronic circuits in constructing micro- and nanocomputers, implantable devices and electrodes [29].

At the present stage of development of medicine the use of such micro- and nanocomputers for replacing the damaged areas of the nervous system and ensuring their interaction with the healthy parts is considered promising [20,41]. Thus, the study of morphological changes occuring in the nervous tissue during interaction with silicon crystals with different physical and chemical properties is quite relevant.

This study aimed at evaluating and assessment of interaction between nerve fibers and silicon wires with different surface properties on severe injured peripheral nerve model.

Material and methods. Experiment was carried-out on 50 male Wistar rats, weighing 180-250 g that were housed in standard conditions with free access to food and water, and natural light-dark cycle. The rats were randomly divided into three groups.

The right sciatic nerves of rats from each experimental group were exposed and transected in the mid-thigh by sharp blade under general anesthesia (40 mg/kg thiopentone, intraperitoneally). After transection 10 mm of nerve trunk were removed to form a gap.

In group I (experimental) the nerve gap was managed by conduit made of decellularized allogenic aorta filled with 4% carboxymethylcellulose gel ("Mesogel", Linteks ltd, Russian Federation) and the longitudinally oriented p-type silicon wires 2-20 μm in diameter.

Both nerve stumps were inserted 2 mm into 10 mm conduit and sutured to nerve stumps with 2-3 u-shaped polyamide sutures with (10/0 Daflon, B.Braun, Germany) [13]. Allogenic aortas were decellularized by single freeze-thaw cycle and incubated in sodium dodecyl sulfate as described in [34] Headlight Magnifier Konus vuemax-pro (Konus, PRC) (magnification x3.5) was used during surgery.

Rats from group I were subdivided into four subgroups in accordance to silicon wire type used for conduit preparation:

Ia received p-type whiskers with 0,3 nm of native oxide on the surface;

Ib - p-type whiskers with hydrogen-cleaned surface and 0,2 nm of oxide on the surface

Ic - p-type whiskers with 15,5 nm of the structured thermally grown oxide on the surface.

Silicon microwires were obtained by Vapor-Liquid-Solid (VLS) method in a cold wall Catalytic Chemical Vapor Deposition (Cat-CVD) chamber.

Nerve stumps in groups Ia-Ic were inserted 2 mm into 10 mm conduit and sutured with 2-3 u-shaped polyamide sutures (10/0 Daflon, B.Braun, Germany) [13].

In group II (control 1) the nerve gap was managed by decellularized allogenic aorta filled with 4% carboxymethylcellulose gel. The ends of aorta were sutured to nerve stumps in same way as in I group.

In group III (control 2) the removed 10 mm nerve fragment was rotated at 180^0 and sutured to proximal and distal nerve stumps with 3-4 simple epineural polyamide sutures (Daflon, B.Braun, Germany). The surgical wound was closed with silk sutures (4/0 Silkam, B.Braun, Germany).

6 weeks after the surgery the animals were sacrificed by decapitation after thiopentone overdosage (200 mg/kg). The nerve graft site with fragments of proximal and distal nerve stumps was harvested and fixed in 4% neutral formalin solution. Frozen longitudinal sections 30 μm thick were prepared and impregnated with modified Bielshowsky nitric silver impregnation [19] and stained with hematoxylin-eosin, and studied using Olympus BX51 (Olympus, Japan) light microscope with attached digital camera Olympus zoom 4040 (Olympus, Japan).

The obtained images were analyzed with ImageJ v.1.51 (National Institutes of Health, USA).

Quantative analysis was performed at nerve site 2 mm distally to conduit beginning.

Average nerve fibers deviation angle from longitudinal nerve axis was determined. Longitudinal nerve axis considered as line parallel to both conduit walls. Average nerve fibers density was estimated with formula (10^6 x N)/(L_n * T), where N – number of fibers intersecting the line perpendicular to the nerve axis, L_n – perpendicular line length, T – slice thickness.

The obtained results were statistically processed with open-source GNU PSPP (Open-source) and compared with Kruskal-Wallis and Mann-Whitney tests.

Animal care, housing and all experiments were performed in accordance with the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978). The research was approved by Bioethical committee for human subjects or animal research at Bogomolets National Medical University, Minutes N 12, 30 December, 2015.

Results aand their discussion. All the experimental animals survived after the surgery and their postoperative wounds healed by primary intention. 6 weeks after the surgery animals from all groups developed two regenerative neuromas: the proximal, located between the central stump of the injured sciatic nerve and the graft; and the distal, located between the graft and the peripheral stump of the injured sciatic nerve.

In group Ia we revealed a significant number of the newly formed nerve fibers in the conduit. Axons in the conduit formed bundles and went in the direction of distal neuroma, having predominantly longitudinal orientation and relatively orderly arrangement. At this term most of the newly formed nerve fibers in this group of animals reached the distal part of the conduit and distal neuroma.

Close adherence of young axons to the surface of the longitudinally located silicon wires with native oxide on the surface was found in this group of animals (Fig. 1).

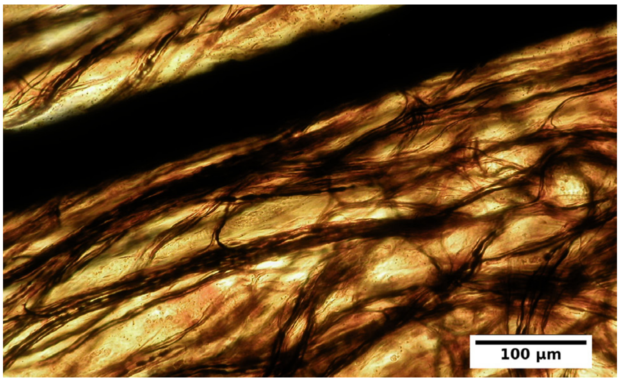

Fig. 1. Proximal regenerative neuroma in rats from Ia group (native oxide). Nerve fibers close to silicon wire. Nitric silver impregnation

Morphometric assessment of the proximal neuroma in group Ia rats showed the density of nerve fibers at the site to be 5885.43±550.27/mm^2, with the average angle of axon deviation from the longitudinal axis of the nerve being 8.48±4.5^0.

Small number of the newly formed nerve fibers, with the prevalence of cellular elements of connective tissue was found in the conduit of group Ib rats (Fig. 2). Axons in the conduit formed bundles and went from proximal to distal neuroma, having partly longitudinal orientation and partly irregular arrangement. Only about a half of the newly formed nerve fibers have reached the middle part of the conduit. Bundles of the newly formed nerve fibers did not adhere to the longitudinally located wires.

Morphometric assessment of proximal neuroma in group Ib showed the density of nerve fibers at the site to be 2539.03±246.55/mm^2, with the average angle of axon deviation from the longitudinal axis of the nerve being 17.92±5.4^0.

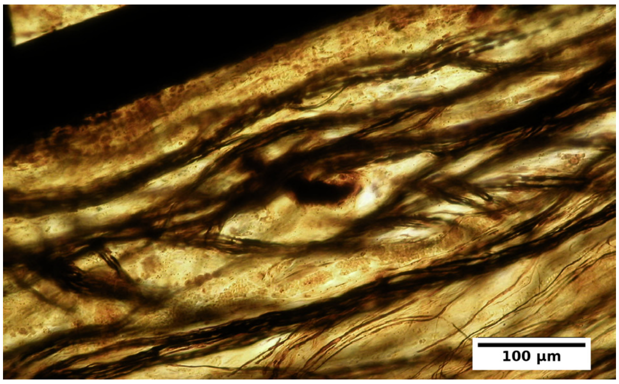

Fig. 2. Proximal regenerative neuroma in rats from Ic group (thermally grown oxide). The wire is surrounded by connective tissue layer. Nitric silver impregnation

In rats of the experimental group Ic non-sugnificant number of the newly formed nerve fibers with the prevalence of cellular elements of connective tissue was found in the conduit within 6 weeks, which is similar to the previous group. Axons in the conduit went from the proximal to the distal neuroma and had both longitudinal direction and disordered arrangement. Only a few of the newly formed nerve fibers have reached the middle of the conduit. Bundles of the newly formed nerve fibers did not adhere to the longitudinally located wires.

Morphometric assessment of proximal neuroma of group Ic rats showed the density of nerve fibers at the site to be 2341.24±321.44/mm^2, with the average angle of axon deviation from the longitudinal axis of the nerve being 18.41±4.20.

The thin newly formed nerve fibers, blood vessels and connective tissue were observed in the area of proximal neuroma and in the graft in group II rats. The number of the newly formed axons in the graft was non-significant. Only a few of them have reached distal neuroma and distal stump.

Morphometric assessment of the proximal neuroma in group II animals showed the density of nerve fibers at the site to be 1755.61±391.91/mm^2, with the average angle of axon deviation from the longitudinal axis of the nerve being 38.66±7.2^0.

In group III rats the thin newly formed nerve fibers, blood vessels and connective tissue were present at the site of proximal neuroma and in the graft, similar to group II. Along the graft we have observed small ovoids of degeneration.

Only small number (however higher than in group II) of the newly formed axons were observed in the distal neuroma and distal stump. Such regenerating nerve fibers had a disordered arrangement and tortuous course, with growth cones occurring at their ends. Maturation of connective tissue in the proximal and distal neuromas was relatively heterogeneous, as evidenced by the presence of hypovascular zones with reduced number of cells.

Morphometric assessment of proximal neuroma showed that the density of nerve fibers of the site in group III animals was 4561.43± 256.46/mm^2, with the average angle of deviation from the longitudinal axis of the nerve being 11.24±6.1^0.

The data of the morphological study are confirmed by the data of morphometric methods. The indicator of the nerve fibers density in the proximal regenerative neuroma 6 weeks after the operation was significantly higher in animals of all subgroups of experimental group I than that of the animals of the second group. This indicator was higher by by 220.52% ($p<0.01$) in group Ia in comparison to group II, in group Ib by 43, 99% ($p<0.01$) and in the Ic group by 35.52% ($p<0.01$).

Comparison of the nerve fibers density in the proximal regenerative neuroma in the subgroups of experimental group I and group III revealed the following: in group Ia it was higher by 22.44% ($p<0.01$), in group Ib being lower by 44.99% ($p <0.01$), and in group Ic lower by 48, 23% ($p<0.01$).

The assessment of the nerve fibers density in the proximal regenerative neuroma between the subgroups of experimental group I has shown this value to be the highest in subgroup Ia, being higher than this value in the subgroup Ib by 122,60% ($p<0,01$), and higher than the corresponding value in the subgroup Ic by 136,50% ($p<0,01$).

The angle of nerve fibers deviation from the longitudinal nerve axis in the region of the proximal regenerative neuroma at 6 weeks after surgery this indicator in all subgroups of experimental group I was significantly lower than that in group II animals. Compared with group II, the angle of deviation of nerve fibers from the longitudinal axis of the nerve in group Ia by 312.26% ($p<0.01$), in group Ib by 105.58% ($p<0.01$) and in the Ic group by 112.76% ($p<0.01$).

Assessment of the angle of nerve fibers deviation from the longitudinal nerve axis of the subgroups of experimental group I and group III revealed the following: in subgroup Ia it was lower by 19.83% (<0.01), being higher in the subgroup Ib by 37.80% ($p<0.01$), and higher by 35.63% ($p<0.01$) in the subgroup Ic.

Comparison of the angle of nerve fibers deviation from the longitudinal nerve axis in the area of the proximal regenerative neuroma in the experimental group I subgroups 6 weeks after the operation has demonstrated this value to be the lowest in subgroup Ia, being also lower than the corresponding value in subgroup Ib by 50.13% ($p<0.01$), and lower than the corresponding value in the subgroup Ic by 48.39% ($p<0, 01$).

The modern concept of conduit development presupposes the availability of means for mechanical support of directed nerve fibers growth using filamentary structures of micro- and nano-chitosan, collagen, fibrin and other materials [1] and creating conditions for sufficient filling of conduit with Schwann cells, and neurotrophic factors. However, inadequate neurotization of the peripheral segment to restore the function of the affected limb is the drawback of this method.

At the present stage of regenerative medicine development controlled high-tech prostheses that ensure recovery of functions, not only the motor, but also the sensory ones, have already been developed [14, 20, 35]. The main disadvantages of interfaces between the nervous tissue and external devices in such prostheses are the low selectivity and instability over time due to the development of connective tissue around the electrodes implanted into the nerve and different other causes as were shown in R. Collins Watson work.

Various electrodes have been created, which are implanted into the limb stump to enable control of the prosthesis, and form interface with the peripheral nerve [36]. These interfaces are characterized by stability over time, electrical characteristics, selectivity and invasiveness. The developed cuff electrodes are non-invasive, but non-selective. Conversely regenerative sieve-like implants in the form of hollow tubes with longitudinally oriented electrodes are highly selective but the most invasive [16]. Prototypes of these electrodes were made of stainless steel, gold, titanium, tungsten and other materials, however optimal interface between the electrode and the nerve fiber, being sustainable over time, selective, non-invasive and having the appropriate physicochemical properties are yet to be found [9].

Inspite fact that majority of researchers used rat's sciatic nerve injury model with gap 6 -10 mm, substantial part of researces devoted to 5-10 mm nerve gap managing [1]. Both with this some works that dealing with microelectrode testing are performed on 5 to 10 mm nerve gap managing [2,21,24], thats' why we consider 10 mm gap modeling in rat's sciatic nerve as adequate fitting to research aim.

Considering requirements for mechanical stability of conduit's wall such as non-collapsing, minimal foreign body reaction, easy of obtaining we believe that allogenic decellularized aorta fits to our experiment aims and conditions as was shown in similar research [8]. Due to obtained results, we didn't observe any signs of collapsing in animals from all groups, also we didn't observe any signs of immune rejection.

Many researches that devoted to electrode choose consider silicon as perspective material [11], other revievs also consider that silicon matches requirements of safe and effectiveness [26]. Physical and mathematical analysis of the interaction between silicon whiskers and regenerating axon membrane resulted in the establishment of Coulomb interaction model between the crystal surface and the outer side of the regenerating axons membrane. The concept of this model was developed based on the known data that after etching the surface of filamentous silicon crystal in hydrofluoric acid, under the effect of atmospheric conditions its surface is covered with a thin film of silicon oxide, where the atoms are in the underoxidized state, and have oxidation grades such as Si^{1+} (Si_2O) , Si^{2+} (SiO) and Si^{3+} (Si_2O_3). [10].

This restructuring of the crystal results in redistribution of charge in its volume with the charge density increasing in close proximity to the surface, which becomes positively charged. When the surface of the silicon crystal comes in contact with body fluids OH^- -groups fix on it, which changes the sign of the surface charge to negative. This mechanism underlies the attraction between the surface of the crystal that becomes negatively charged and the outer side of the regenerating axons membrane that is positively charged according to the laws of Coulomb interaction [17,18,36].

Obtained results that shows large amount of nerve fibers near silicon wires can be sign of spontaneous axonal sprouting or pro-regenerative influence both with increased sprouting due to meeting with mechanical obstacles as shown in Mackinnon rewiew [25]. We think that large amount of new nerve fibers alongside silicon wires with native oxide (group I a) and absence of such picture in groups with other types of whiskers indicates to pro-adhesive properties and promising high effectiveness, but requires further investigations.

Findings of our morphological studies shows how newly formed axons grow near the silicon wires and the accelerated regeneration process in the group of animals in which conduit containing silicon wires with a native oxide on the surface was used as opposed to groups of animals where the conduits have been used with other types of silicon wires treatment.

Thus, both morphological analysis and morphometry data state that the density of nerve fibers in the proximal neuroma was significantly higher in the group of animals where silicon wires with native oxide on the surface were used, unlike other groups of animals.

This indicates to more full implant neurotization in animal group where wires with native oxide on surface were used.

The angle of deviation of the newly formed nerve fibers from the longitudinal axis of the nerve was the lowest in the group of animals, where the wires with a native oxide on the surface were used. This indicates more uniform neurotization of the conduit as compared to other groups of animals.

According to this we can state, that more complete and uniform implant site neurotization indicate to more successful, qualitative and accelerated nerve regeneration in I a experimental group (silicon with thin native oxide) [31].

Thus, the results of our experiments demonstrate that the use of silicon wires with native oxide on the surface can solve the problem I) of mechanical support for directed growth of nerve fibers and acceleration of their growth, which ensures neurotization of the peripheral stump of the injured nerve; II) of time-related interface instability due to the identified close adherence of the newly formed axons to whiskers. Based on the above data it can be assumed that the use of silicon crystals with native oxide on the surface is a promising material for manufacturing regenerative implant electrodes in order to restore function of the denervated limb by analogy to the prototypes of the developed controlled prostheses.

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SUMMARY

SILICON WIRES FOR NERVE GAP MANAGEMENT: ROLE OF SURFACE PROPERTIES IN NERVE REGENERATION

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Up to 15% of combat trauma cases are accompanied by neuroinjuries with nerve gap formation that need to be bridged using various techniques and materials. Both with this prevalence of limb loss, especially traumatic amputations, tends to grow. Loosed limbs must be prosthetized by modern functional mind-controlled prosthesis based on nerve- or brain-computer interfaces.

This study aimed at morphological evaluation of interaction between nerve fibers and silicon wires with different surface properties using peripheral nerve injury and grafting model.

Experiment was performed on 50 male Wistar rats, weighing 180-250 g. Rats from experimental groups underwent sciatic nerve injury Sunderland 5 degree with a 10 mm gap formation that was subsequently filled with conduit consisting of decellularized aorta, carboxymethylcellulose gel and a set of longitudinally oriented p-type silicon wires 2-20 µm in diameter. We used silicon wires with native oxide in group Ia, with hydrogen-cleaned surface in group Ib and thermally grown oxide in group Ic. The gap in control groups was filled with decellularized aorta with gel alone (group II) or by autoneurograft (group III). 6 weeks postoperatively the conduit site was harvested and light microscopy performed. Implantation of conduit with native oxide on silicon wires surface resulted in more complete and equal neurotization of the conduit site with close adherence between the newly-formed nerve fibers and silicon wires, in comparison with groups where wires with other surface properties have been used. P-type silicon wires with native oxide are seems to be more suitable than other types of wires for further electrode preparation as a part of regenerative implants.

Keywords: peripheral nerve injury, silicon wires, peripheral nerve interface.

РЕЗЮМЕ

ПРИМЕНЕНИЕ НИТЕВИДНЫХ КРИСТАЛЛОВ КРЕМНИЯ ДЛЯ ЛЕЧЕНИЯ ТЯЖЕЛЫХ ТРАВМ ПЕРИФЕРИЧЕСКИХ НЕРВОВ: РОЛЬ ПОВЕРХНОСТНЫХ СВОЙСТВ В НЕЙРОРЕГЕНЕРАЦИИ

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До 15% всех случаев боевых травм сопровождаются травмами периферических нервов с формированием дефектов нервных стволов, которые должны быть заполнены с применением различных техник и материалов.

Цель исследования – морфологическая оценка взаимодействия между нервными волокнами и нитевидными кристаллами кремния с различными свойствами поверхности на модели тяжелой травмы периферического нерва и нейропластики.

Эксперимент проведен на 50 крысах-самцах линии Вистар, весом 180-250 г. Крысам экспериментальных групп моделировали тяжелую травму седалищного нерва (Sunderland 5) с формированием дефекта нервного ствола протяженностью 10 мм, который замещался кондуитом, состоящим из децеллюляризованной аорты, карбоксиметилцеллюлозного геля и продольно ориентированных нитевидных кристаллов кремния p-типа, диаметром 2-20 µm. У крыс группы Ia использованы нитевидные кристаллы с естественным окислом, в группе Ib - кристаллы с поверхностью, очищенной в потоке водорода, в группе Ic - кристаллы с искусственным термически выращенным окислом. Диастаз между концами нервов в контрольных группах был заполнен аортой с гелем (II группа) либо аутонейрографтом (III группа). Спустя 6 недель после операции места кондуита с прилежащими концами нерва были забраны для световой микроскопии. Применение нитевидных кристаллов кремния с естественным окислом приводит к более полной и равномерной невротизации места кондуита. Нитевидные кристаллы кремния p-типа с естественным окислом являются более подходящими для изготовления электродов как часть регенеративного имплантата в сравнении с кристаллами других типов.

რეზიუმე

კრემნიუმის ძაფისებრი კრისტალების გამოყენება პერიფერიული ნერვების მძიმე ტრამვების მკურნალობის დროს: ზედაპირული თვისებების როლი ნეირორეგენერაციაში

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[1]ა. ბოგომოლცის სახ. ნაციონალური სამედიცინო უნივერსიტეტი; [2]ვ. ლაშკარევის სახ. ნახევარგამტარების ფიზიკის ინსტიტუტი,უკრაინის მეცნიერებათა ეროვნული აკადემია, კიევი, უკრაინა

15%-მდე ყველა საბრძოლო ტრავმას თან ახლავს პერიფერიული ნერვების ტრავმები, ნერვული ღეროს დეფექტების ფორმირებით, რომელიც უნდა შეივსოს სხვადასხვა ტექნიკისა და მასალების გამოყენებით.

კვლევის მიზანია - ნერვული ბოჭკოებისა და სხვადასხვა თვისებების მქონე ზედაპირის კრემნიუმის ძაფისებრი კრისტალების ურთიერთქმედების მორფოლოგიური შეფასება პერიფერიული ნერვის მძიმე ტრამვისა და ნეიროპლასტიკის მოდელზე.

ექსპერიმენტი ჩატარდა ვისტარის ჯიშის 50 მამრ-ვირთაგვაზე,წონით 180-250 გ. ექსპერიმენტული ჯგუფების ვირთაგვებზე მოდელირებული იყო საჯდომის ნერვის მძიმე დაზიანება (Sunderland 5), 10 მმ სიგრძის ნერვის ღეროს დეფექტის ფორმირებით, რომელიც ჩანაცვლებული იყო კონდუიტით,დეცელულარიზებული აორტით, კარბოქსიმეთილცელულოზური გელით და გრძივად ორიენტირებული p-ტიპის კრემნიუმის ძაფისებრი კრისტალებით, დიამეტრით 2-20 μm. Ia ჯგუფის ვირთაგვებში გამოყენებული იყო კრემნიუმის ძაფისებრი კრისტალების ბუნებრივი ოქსილი, Iბ ჯგუფის ვირთაგვებში - კრისტალები, რომელთა ზედაპირი გაიწმინდა წყალბადის ნაკადში, Ic ჯგუფის ვირთაგვებში - კრისტალები ხელოვნურად თერმულად გამოყვანილი ოქსილით. დიასტაზი ნერვულ დაბოლოებათა შორის კონტროლის ჯგუფებში შევსებული იყო გელიანი აორტით (II ჯგუფი), ან აუტონეიროგრაფტით (III ჯგუფი). ოპერაციიდან 6 კვირის შემდეგ, კონდუიტის ადგილი, მიმდებარე ნერვული დაბოლოებით ამოღებული იყო სხივური მიკროსკოპიისთვის. კრემნიუმის ძაფისებრი კრისტალების გამოყენება ბუნებრივი ოქსილით იწვევს კონდუიტის ადგილის უფრო სრულ და თანაბარზომიერ ნევროტიზაციას. P-ტიპის კრემნიუმის ძაფისებრი კრისტალები ბუნებრივი ოქსილით, როგორც ნაწილი რეგენერაციული იმპლანტისა წარმოადგენს უფრო შესაფერისს მასალას ელექტროდების დასამზადებლად, ვიდრე სხვა ტიპის კრისტალები.

FEATURES OF HISTOCHEMICAL CHANGES IN THE ACTIVITY OF SUCCINATE DEHYDROGENASE OF ARTIFICIAL BLADDER IN DYNAMICS (EXPERIMENTAL STUDY)

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Bladder cancer remains an urgent problem, due to a steady increase in morbidity and mortality. About five thousand new cases and two, three thousand deaths from this pathology are registered in Ukraine every year [1]. The active development and improvement of the quality of anesthetic management, early diagnosis and the emergence of new methods of treating oncological diseases, led to an expansion of indications for reconstructive operations in oncourology.

The gold standard for the treatment of invasive bladder cancer recognized throughout the world is radical cystectomy with orthotopic ileocystoplasty using the ileal intestinal tract [2,3,4]. A segment of the ileum is isolated, to form a reservoir from the gastrointestinal tract. The latter is detubulated, and then sewn as S, W, U, M, N - anastomoses, turning into a capacity of the shape of the ball [11]. The radical cystectomy with orthotopic derivation of urine is performed throughout the world by an open, laparoscopic and robot-assisted method, sometimes with the formation of intracorporeal anastomoses, which reduces the wound surface, the number of complications and quickly restores patient activity [5-8].

The study of the effect of urine on the adaptation of the mucosa of the artificial bladder continues for the last twenty years. According to the researchers, the results are quite contradictory, as some scientists note the hypersecretion of sulphomucins, sialomucins, progressive atrophy of microvilli, adenomatous hyperplasia and dysplasia [9,10].

The changes in the activity of enzymes of oxidation-reduction reactions in the tissues of the artificial bladder remain outside the attention of researchers. Although their activity causes the course of the main processes of vital activity in the tissues of the body.

Aim - to study the features of the histochemically revealed activity of succinate dehydrogenase in the wall of the artificial bladder and ileum in experimental animals.

Material and methods. The material of the present study were the results obtained from the study of 18 female mini-pigs aged 4-5 months and weighing 8-10 kg. The modeling of the artificial bladder was performed in experimental animals, by cystectomy and subsequent ileo-cystoplasty. The choice of an experimental facility is due to anatomical considerations. The urethra in female is straight and 5-7 times shorter than males.

The procedure for surgical intervention was as follows. A cut of the abdominal wall in the middle line from the pubic symphysis to the navel is performed under intravenous anesthesia (thiopental) in the position on the back of the pig. The top of the bladder is captured by forceps and tucked up. The front wall of the bladder is separated. The urethra resects, the bladder is separated from the rectum. The bladder is removed. Hemostasis. Retreating 15 cm from the ileocecal valve, sew the end of the isolated intestinal segment with continuous serous-muscle sutures vikryl 4-0. During the antibriated region, the distal part of the idiopathic segment is dissected within about 10 cm. The cut part of the segment is U-shaped, the adjacent edges of both knees are sewn together by a series of continuous serous-muscle sutures, cured 4-0. The lower part of the resulting U-shaped segment is placed transversely upwards. The distal portion of the ileo-intestinal segment is dissected approximately 10 cm long in mesenteric margin. The dissected part of the segment is U-shaped, adjacent edges of both knees sewed together by one row of continuous serous-muscular sutures vikryl 4-0. The lower part of the resulting U-shaped segment is enclosed transversely upwards. The ureteral catheters №3 Fr are inserted, the ends of which are removed through the wall of the reservoir before stitching the free margins of the dissected segment into the ileal lobe. An orifice is made, in the most caudal part of the reservoir, to which the urethra is sutured with 6 seams of vicryl 4-0. The sutures are tied after conducting the urethra of the Foley catheter