LONG-TERM FUNCTIONAL AND HISTOLOGICAL OUTCOMES OF RAT'S SCIATIC NERVE RECOVERY AFTER SEVERE INJURY AND EXPERIMENTAL TREATMENT WITH SILICON MICROWIRES

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LONG-TERM FUNCTIONAL AND HISTOLOGICAL OUTCOMES OF RAT'S SCIATIC NERVE RECOVERY AFTER SEVERE INJURY AND EXPERIMENTAL TREATMENT WITH SILICON MICROWIRES

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Severe peripheral nerve injuries both with traumatic limb amputations constitute a substantial part in all limb injuries especially during armed conflicts.

For nerve grafting, nerve fibers alignment and fabrication of mind-controlled prosthetic limbs the concept of regenerative nerve implants with peripheral nerve interfacing was proposed.

Silicon showed ideal properties not only for microelictronic devices fabrication but also as a favorable growth medium for neurons in vitro.

This study aimed at evaluating the impact of silicon wires as a part of nerve conduit on motor and sensory recovery simultaneously with distal nerve stump neurotization using rat sciatic nerve injury model.

Materials and methods. We performed experiments on 33 male Wistar rats that were divided into the following groups: I – sham-operated, II – those which received right sciatic nerve transection with 10 mm gap formation with autoneurografting, III – with 10 mm nerve gap bridged by allogenic decelullarized aorta with 4% carboxymethylcellulose hydrogel, IV – with 10 mm gap bridged by allogenic decelullarized aorta with 4% carboxymethylcellulose hydrogel and aligned p-type boron-ligated silicon wires.

12 weeks after operation all rats were examined using von Fray filaments and by Walking track analysis method. For histological analysis right sciatic nerves were harvested. Frozen sections were stained with H&E and nitric silver impregnation was performed. At distal nerve stump nerve fibers density was calculated. The obtained results were compared using nonparametric statistical tests.

Results. The histological analysis revealed differences in tissue reaction patterns between rats from autoneurografting group and conduit grafting groups.

Histomorphometric data showed that nerve fibers density in rats from group IV was significantly higher than that in rats from group III (aorta+hydrogel grafting), but remained lower than in group II (autoneurografting).

Morphometric data were supported by functional tests data: rats from group IV demonstrated higher values of SFI than those in group III and same as those in group II.

Conclusions. According to histological and functional data we can presume that use of silicon wires as a part of hollow conduit improves results of injured sciatic nerve regeneration.

Key words: *Peripheral nerve injury, peripheral nerve interface, silicon wires*

Introduction.

According to large retrospective statistical surveys all traumatic extremities injuries are often accompanied by severe injuries of peripheral nerves and nervous plexus both in peace and wartime [3, 15, 18, 22].

At the same time data on extremities injuries among military personnel during wartime show that traumatic amputations and limb loss are also frequently observed especially during current armed conflicts [25, 26].

Nowadays autoneurografting is considered the gold-standard method for severe nerve injury treatment [21], such as Sunderland 5 degree (Class III, Neurotmesis), nevertheless, alternative strategies such as nerve conduits for nerve gap bridging are developing [24].

New concept for amputee's rehabilitation includes applying of new functional prosthetic limbs that can interact with the patient's nervous system [10, 20, 27].

Keeping in mind problems of axonal guidance and the need for peripheral nerve interface formation a new concept of regenerative hollow nerve implants was developed [4, 5 8].

This kind of nerve conduits is composed of hollow tube with longitudinally oriented electrodes. Such regenerative nerve implants can fit not only for axonal guidance but also for nerve interface formation for effective, safe and stable connection between peripheral nerve and the external device [6, 7].

Silicon, as semiconductor, seems to be a promising material not only for microelectronics but also can be used as neuron growing medium due to close adherence of neuronal branches to silicon crystals in vitro [11, 12]. Taking this into account, we can hypothesize that silicon wires are perspective for regenerative implant fabrication .

Aim

Current experimental study aimed at estimating the silicon wires impact on motor and sensory hind limb recovery both with neurotization of conduit site and distal nerve stump using rat sciatic nerve severe injury model.

Materials and Methods

The experimental research was performed on 33 2-4 mounth old male Wistar rats, housed 4 per cage in conditions of natural light-dark cycle and free access to water and food.

All surgical manipulations were performed under general anesthesia (40 mg/kg thiopentone, intraperitoneally). All manipulations were conducted according to the “Rules of work using experimental animals”, approved by order of the Ministry of Health of Ukraine.

According to experimental aim rats were divided into the following groups:

I sham-operated (n= 3) – only surgical access to right sciatic nerve was performed followed by the surgical wound closure.

II Autoneurografting (n= 10) – the exposure of the right sciatic was followed by its transection at the mid-thigh with 10 mm nerve gap formation (Sunderland V injury model). The removed nerve trunk fragment was used for nerve gap bridging and sutured to proximal and distal nerve stumps with 4 epineural sutures from each side (10/0 Daflon, B.Braun, Germany) [9]

III Allogenic aorta grafting (n= 10) – the right sciatic nerve was exposed and transected with 10 mm gap formation as described before. The nerve gap was bridged with 10 mm allogenic decellularized aorta that was sutured to nerve stumps with two n-like stithes on each side (10/0 Daflon, B.Braun, Germany) [9]. Decellularization was performed by freeze-thaw cycles as described in Rodriguez et al, 2012 [19].

III Silicon wires grafting (n=10) – the right sciatic nerve was exposed and transected with 10 mm gap formation as described before. The nerve gap was bridged with 10 mm allogenic decellularized aorta containing 4% carboxymethylcellulose hydrogel (Mesogel, Linteks, Russian Federation) and longitudinally oriented silicon wires (p-type, Boron-ligated). Conduit was sutured to nerve stumps with two n-like stitches on each side.

During microsurgery x3,5 head magnifier Konus vuemax-pro (Konus, PRC) was used. In each animal surgical wound was closed with silk sutures (4/0 Silkam, Bbraun). All animals were monitored and housed in warm recovery cage until complete recovery from general anesthesia.

We used silicon wires obtained from V.Ye. Laskaryov Institute for semiconductor physics NAS of Ukraine. Silicon whiskers were fabricated by Vapor-Liquid-Solid (VLS) method in a cold wall Catalytic Chemical Vapor Deposition (Cat-CVD) chamber [13].

After fabrication silicon wires were pre-cleaned with isopropanol, deionized water and treated with hydrofluoridic acid to remove surface oxide layer. After surface preparation wires were cleaned with deionized water and sterilized via dry heating.

12 weeks after operation rats from each experimental group were evaluated for motor function recovery using Walking track analysis method with Sciatic Function Index calculation using McKinnon formula [23].

Rats were also evaluated for sensory function recovery using von Fray Filaments set (Aesthesio set, Ugo Basile, Italy).

after the functional testing animals were sacrificed by decapitation under thiopentone overdose. Right sciatic nerve was harvested for histological examination. After formalin fixation, longitudinal frozen slices were prepared and stained with H&E, impregnated with nitric silver [1], examined and photographed using light microscope Olympus BX51 and attached digital camera Olympus Zoom 4040 (Olympus, Japan). Obtained digital photos were processed with ImageJ ver. 1.5 (NIH, USA, freeware) software for biomedical images examination.

At conduit site, distal neuroma and distal nerve stump nerve fibers density were counted using the formula described in Yuri Chaikovsky work (personal communications).

Statistical analysis was performed with SPSS Statistics Base v.22 software (IBM, USA, Bogomolets National Medical University academic license #128 since 01.08.2016).

Distribution of obtained data was analyzed using Kolmogorov-Smirnov test, also Friedman’s and T-test for paired samples tests were used, we consider difference at significance level $p<0.05$.

Results

Histology results

12 weeks after sham-operation histological analysis of sciatic nerve in group I (sham-operated) revealed normal sciatic nerve structure: longitudinally-oriented nerve fibers formed bundles that were separated with thin layers of connective tissue. Myelinated nerve fibers had clear outlines. Blood vessels were equally disturbed (Fig.1).

Nerve fibers density was 10077,33±211,88 mm^{-1}(Mean±S.D.)

12 weeks after operation macroscopic evaluation revealed proximal and distal nerve stumps connected to graft site with two regenerative neuromas: proximal and distal.

In experimental group II (autoneurografting) at graft site light microscopy revealed thin newly-formed myelinated nerve fibers. Despite the relatively poor vascularization, majority of them passed orderly and formed nerve bundles that were separated one from another

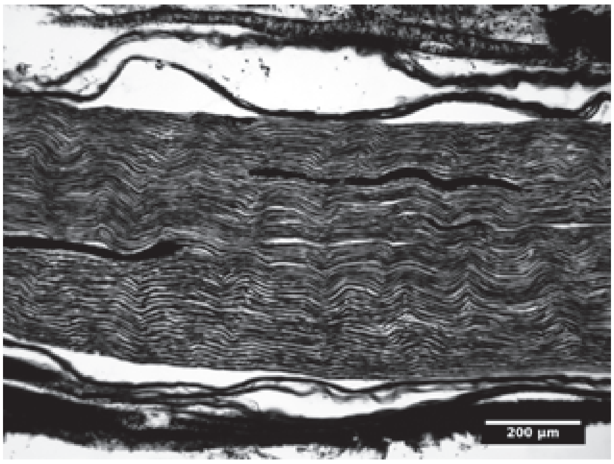

Fig.1. Mid-thigh of sciatic nerve. Sham-operated group. Nitric silver impregnation.

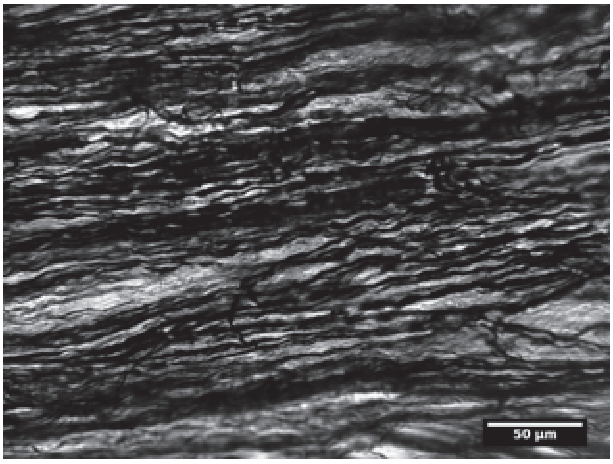

Fig.2. Graft site. II group (autoneurografting), 12 weeks after operation. Nitric silver impregnation.

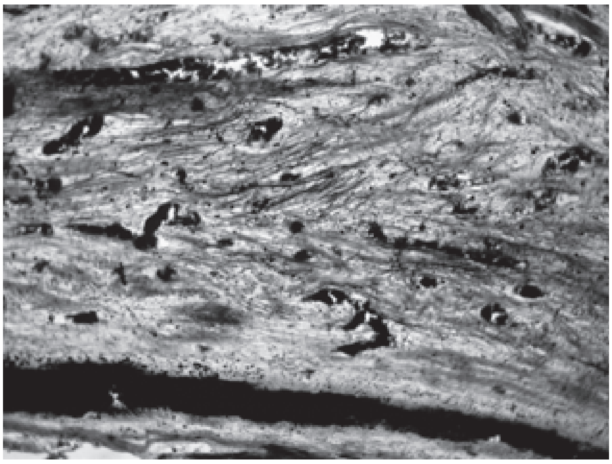

Fig.3. Graft site. III group (Grafting by decell. aorta with hydrogel) Nitric silver impregnation

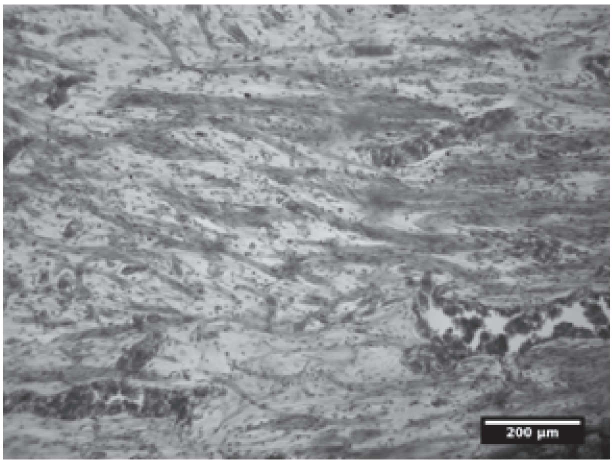

Fig.4. Graft site. III group (Grafting by decell. aorta with hydrogel) Hematoxylin and eosin.

with moderate amount of connective tissue, and had equal distribution (Fig.2).

Distal neuroma site contain and great amount of the newly-formed nerve fibers. Majority of them were thin and passed chaotically, having unequal distribution. Between few bundles of nerve fibers there were broad avascular fields of loose connective tissue. Blood vessels were rare. Some nerve fibers passed in transverse way or even had retrograde orientation.

Distal nerve stump contained small amount of thin nerve fibers separated with thin connective tissue layers. Amount of Schwann cell and blood vessels were low.

Nerve fibers density in distal nerve stump was 7573,70±607,50 mm^{-1} (Mean±S.D.)

In animals from group III (Grafting by decell. aorta with hydrogel) at graft site a moderate amount of the newly formed nerve fibers were found, they formed bundles but were situated chaotically and had unequal distribution among huge amount of different in diameter blood vessels and substantial amount of connective tissue (Fig.3, 4).

Distal neuroma site contained chaotically-oriented and unequally distributed thin nerve fibers, blood vessels and substantial amount of cells.

Distal nerve stump contained unequally distributed small quantity of thin nerve fibers and great quantity of Schwann cells that formed stripes.

Nerve fibers density in distal nerve stump was 3671,78±470,89 mm^{-1} (Mean±S.D.)

In animals from group IV (Grafting by decell. aorta with hydrogel and silicon wires) at graft site a moderate amount of the newly formed nerve fibers were found. Nerve fibers bundles passed relatively orderly with equal distribution. Majority of them passed alongside the silicon wires at the center of conduit among huge amount of different in diameter blood vessels and moderate amount of connective tissue (Fig.5).

Distal neuroma contained a moderate amount of relatively oriented and equally distributed nerve fibers.

Distal nerve stump contained moderate amount of relatively equally distributed thin nerve fibers, and moderate amount of Schwann cells.

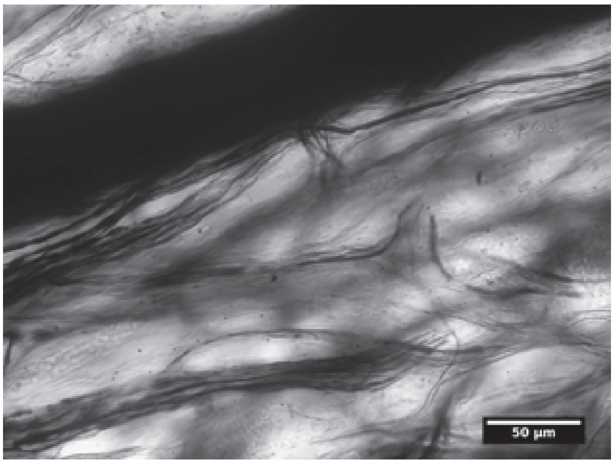

Fig.5. Graft site. IV group. (Grafting by decell. aorta with hydrogel and silicon wires) Nitric silver impregnation.

Nerve fibers density in distal nerve stump was 5544,00±662,26 mm^{-1} (Mean±S.D.)

Motor recovery results

Rats from group I (sham-operated) did not demonstrate significant decrease of SFI. Animas from this group SFI = -6,22±2,64 (Mean±S.D.).

Rats from group II (Autoneurografting) demonstrated significant decrease of to SFI =-48,70±4,07 (Mean±S.D.). Among rats from group III (Grafting by decell aorta with hydrogel) SFI was decreased to -68,89±6,55 (Mean±S.D.)

Rats from group VI (Grafting by decell aorta with hydrogel and silicon wires) showed decrease of SFI to -51,78±6,91 (Mean±S.D.)

Sensory recovery results

Rats from group I (sham-operated) demonstrated 15 -g paw withdrawal threshold on both hind limbs.

Animals in group II (sham-operated) demonstrated increasing paw withdrawal threshold on injured limb to 26 g with unchanged threshold on the contralateral limb.

Animals from group III (Grafting by decell aorta with hygrogel) showed the injured hind limb withdrawal threshold of 60, and 15 g on the contralateral limb.

Animals from group VI (Grafting by decell aorta with hygrogel and silicon whiskers) demonstrated the injured hind limb withdrawal threshold of 60, and 15 g on the contralateral one.

Statistical analysis

One sample Kolmogorov-Smirnov test showed normal distribution of nerve fibers density and Sciatic Function Index in all groups.

Friedman test for k-related samples showed significant differences among values of Nerve fibers density (Chi-Square = 27,00 df=3 $p<0.01$) and SFI (Chi-Square = 25,93 df=3 $p<0.01$) in all groups.

Paired related samples T-test shows that there is no difference in SFI value among rats from II and IV group (t=1,21, p=0.261); with presence of significant differences among Nerve fibers density and SFI values between rest of groups ($p<0,01$)

Discussion

According to large review studies 10 mm gap of rat's sciatic nerve injury model is best-fitting for nerve graft studies and can be considered adequate for experimental purposes.

Revealed histological picture at graft site indicated the differences in regeneration patterns between animals from II (autoneurografting) and III groups with group IV (conduit grafting groups).

Histological structure of the graft site, distal neuroma and distal nerve stump in animals from groups III and IV is similar to such picture in axonal phase of nerve regeneration through hollow tubes and described by Frat et al in 2014 [5].

In rats from group III inside the graft site there were many newly-formed blood vessels and loose connective tissue. Nevertheless the absence of silicon nanocrystals lead to the chaotic orientation of axons and poor functional results.

At the same time in rats from group IV same abundance of blood vessels was also observed. Aligned orientation and relatively equal distribution of the newly-formed nerve fibers indicate the ordering effect of silicon wires. Similar effects were observed in experiments with nerve grafting with hollow tube with inserted filaments [16, 17].

That conduit site of animals from group IV contains bundles of nerve fibers that change their direction and deviate toward the silicon wires is remarkable and may be explained by hypothesis about electrostatic interaction between the silicon wire surface and the polarized nerve fiber membrane [14].

Table 1.

Histomorphometric and functional experimental results.

Group name	Nerve fibers density in proximal nerve stump, mm^{-1}, Mean±S.D.	Sciatic Function Index, units, Mean±S.D.	Paw withdrawal threshold left/right limb grams
I Sham-operated	10077,33±211,88	-6,22±2,64	15 / 15
II Autoneurografting	7573,70±607,50	-48,70±4,07	15 / 26
III Grafting by decell aorta with hygrogel	3671,78±470,89	-68,89±6,55	15 / 60
IV Grafting by decell aorta, hydrogel and silicon wires	5544,00±662,26	-51,78±6,91 *	15 / 26

* No differences between IV and II groups (P=0,261)

The histological structure of distal neuroma has similarities than can be observed in animals from each experimental groups: nerve fibers change their direction and order: bundles are often disintegrated to single-passing fibers with large deviation angles.

In the distal neuromas in rats from groups III and IV a substantial amount of cells are clearly observed. Their presence can be explained by excessive cell proliferation during cellular phase of regeneration but restricted cell migration into conduit site due to delay in microenviroment formation [2].

Such cell accumulation may be the reason of nerve fibers chaotic orientation, especially in rats from group III, where cell proliferation is clearly seen.

Chaotic orientation of nerve fibers in distal neuroma in rats from autoneurografting group can be explained by excessive scar formation due to sprouting nerve fibers.

Relatively unsatisfactory results in groups II (autoneurografting) III (Decell aorta and gel grafting) can be explained by axonal misguidance due to distal neuroma features: lack of blood supply and excessive sprouting with limited endoneural tubes in which they were growing; excessive Schwann cells proliferation both with excessive scar formation. All these reasons result in poor distal nerve stump neurotization that in combination with improper target reinnervation are the cause of poor functional outcomes.

The nerve fibers passage in proximity to silicon wires at graft site can be considered not only as their pro-gerenerative effect, but also as their ability to form stable in time, effective and safe peripheral nerve interface.

Conclusions

According to histological and functional data we can presume that the use of silicon wires as a part of hollow conduit improves results of the injured sciatic nerve regeneration. Boron-ligated p-type silicon wires can be perspective both for improving nerve regeneration and for peripheral nerve interface formation.

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ВІДДАЛЕНІ ФУНКЦІОНАЛЬНІ ТА ГІСТОЛОГІЧНІ РЕЗУЛЬТАТИ ВІДНОВЛЕННЯ ТРАВМОВАНОГО ПЕРИФЕРІЙНОГО НЕРВА ЩУРА ПІСЛЯ ТЯЖКОГО ПОШКОДЖЕННЯ ТА ЕКСПЕРИМЕНТАЛЬНОГО ЛІКУВАННЯ ІЗ ЗАСТОСУВАННЯМ НИТКОПОДІБНИХ МІКРОКРИСТАЛІВ КРЕМНІЮ

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Тяжкі пошкодження нервових стовбурів, ампутації кінцівок становлять суттєву частину всіх травм, особливо у пацієнтів, постраждалих внаслідок збройних конфліктів. Для протезування нервів, впорядкування росту аксонів та створення функціональних, керованих протезів кінцівок було запропоновано створення машинних інтерфейсів із периферійним нервом у концепції трубчастих регенеративних імплантів. Кремній є перспективним матеріалом не тільки для створення мікроелектронних пристроїв, а й для формування сприятливого мікрооточення для росту культивованих нейронів in vitro.

Метою дослідження є визначення впливу ниткоподібних кристалів кремнію на відновлення рухової та чутливої функції одночасно з визначенням впливу на невротизацію дистального відрізка травмованого периферійного нерва.

Матеріали і методи. Проводили дослідження на 33 щурах лінії Вістар, що були розділені на групи: І – псевдооперовані, яким виконувався лише доступ до сідничого нерва, ІІ – формувався дефект нервового стовбура 10 мм та аутонейропластика, ІІІ – пластика дефекта 10 мм аллогенною децелюляризованою аортою, IV – пластика дефекта 10 мм аллогенною децелюляризованою аортою, карбоксиметилцелюлозним гелем та ниткоподібними кристалами кремнію р-типу, легованими бором.

Через 12 тижнів після операції відновлення функції кінцівки оцінювали методом Walking track analysis та волосками вон Фрея. Для дослідження забирали травмовані периферійні нерви, Заморожені зрізи забарвлювали гематоксиліном та еозином, імпрегнували азотнокислим сріблом. В ділянці дистального відрізка нерва підраховували питому щільність нервових волокон. Результати порівнювали непараметричними статистичними методами.

Результати. В результаті проведеного гістологічного аналізу встановлені відмінності у перебудові периферійного нерва тварин з групи виконання аутонейропластики та груп із використанням кондуїтів. Дані гістоморфометрії свідчать, що показник щільності розподілу нервових волокон в ділянці дистального відрізка травмованого нерва у щурів IV групи був суттєво вищим, ніж даний показник у тварин ІІІ групи, але залишався меншим, ніж у тварин ІІ групи. Дані морфометрії підтверджуються ре-

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ОТДАЛЕННЫЕ ФУНКЦИОНАЛЬНЫЕ И ГИСТОЛОГИЧЕСКИЕ РЕЗУЛЬТАТЫ ВОССТАНОВЛЕНИЯ ТРАВМИРОВАННОГО ПЕРИФЕРИЧЕСКОГО НЕРВА КРЫСЫ ПОСЛЕ ТЯЖЕЛОГО ПОВРЕЖДЕНИЯ И ЭКСПЕРИМЕНТАЛЬНОГО ЛЕЧЕНИЯ С ИСПОЛЬЗОВАНИЕМ НИТЕВИДНЫХ МИКРОКРИСТАЛЛОВ КРЕМНИЯ

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Тяжелые повреждения нервных стволов, ампутации конечностей составляют существенную часть всех травм, особенно у пациентов, пострадавших вследствие вооруженных конфликтов. Для протезирования нервов, упорядочивания роста аксонов и создания высокофункциональных, управляемых протезов конечностей было предложено создание машинных интерфейсов с периферическим нервом в концепции полых регенеративных имплантов. Кремний является перспективным материалом не только для создания микроэлектронных устройств, а и для формирования благоприятного микроокружения для роста и культивирования нейронов in vitro.

Целью исследования является определение влияния нитевидных кристаллов кремния на восстановление двигательной и чувствительной функции одновременно с определением влияния на невротизацию дистального отрезка травмированного периферического нерва.

Проводили исследования на хх крысах линии Вистар, которые были разделены на группы: І – псевдооперированные, которым выполнялся доступ к седалищному нерву. ІІ – формировался дефект нервного ствола 10 мм и проводилась аутонейропластика, ІІІ – пластику дефекта 10 мм выполняли аллогенной децелюлляризованной аортой и карбоксиметилцеллюлозным гелем, IV – пластику дефекта 10 мм выполняли аллогенной децелюлляризованной аортой, карбоксиметилцеллюлозным гелем и нитевидными кристаллами кремния р-типа, легированными бором.

Через 12 недель после операции восстановление функции конечности оценивали методом Walking track analysis и волосками вон Фрея. Для гистологического исследования забирали травмированные периферические нервы. Замороженные срезы окрашивали гематоксиллином и эозином, импрегнировали азотнокислым серебром. В дистальном отрезке нерва подсчитывали удельную плотность нервных волокон. Результаты обрабатывали непараметрическими статистическими методами.

В результате проведенного гистологического анализа установлены отличия в перестройке периферического нерва животных в группе выполнения аутонейропластики и групп с использованием кондуитов. Данные

зультатами функціональних тестів: тварини IV групи демонстрували більший показник SFI, ніж тварини III групи.

Висновки. Враховуючи дані гістологічного, морфометричного та функціонального досліджень можна припустити, що застосування ниткоподібних кристалів кремнію як компонента трубчастого кондуїта покращує результати регенерації сідничого нерва після тяжкого пошкодження.

Ключові слова: Травма периферійного нерва, інтерфейс нерв-комп’ютер, ниткоподібні кристали кремнію.

гистоморфометрии свидетельствуют, что показатель удельной плотности распределения нервных волокон в дистальном отрезке травмированного нерва у крыс IV группы был существенно больше, чем данный показатель у животных III группы, однако, оставался меньше, чем у животных II группы. Данные морфометрии подтверждаются результатами функциональных тестов: Животные IV группы имели больший показатель SFI, чем животные III группы.

Таким образом, учитывая данные гистологического, морфометрического и функционального исследований, можно предположить, что применение нитевидных кристаллов кремния как компонента трубчатого кондуита улучшает результаты регенерации седалищного нерва после тяжелого повреждения.

Ключовые слова: Травма периферического нерва, интерфейс нерв-компьютер, нитевидные кристаллы кремния.