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MORPHO-FUNCTIONAL CHARACTERISTICS OF THE SCIATIC NERVE IN THE LATE TERMS OF EXPERIMENTAL PACLITAXEL-INDUCED PERIPHERAL NEUROPATHY UNDER THE CORRECTION OF 2-ETHYL-6-METHYL-3-HYDROXYPYRIDINE SUCCINATE

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6 out of 10 patients undergoing treatment for breast cancer, ovarian cancer, and non-small cell lung cancer suffer from the neurotoxicity of the chemotherapy drug Paclitaxel, namely paclitaxel-induced peripheral neuropathy. Among them, one in four needs to reduce the dose, postpone the treatment or even stop the therapy. Previous attempts to use various neuroprotective agents in humans and animal models have not shown sufficient effectiveness in preventing or significantly reducing the intensity of paclitaxel-induced peripheral neuropathy manifestations. The purpose of our study was to establish the effect of the neuroprotective agent 2-ethyl-6-methyl-3-hydroxypyridine succinate on the morpho-functional parameters of the sciatic nerve in experimental paclitaxel-induced peripheral neuropathy. In the experiment, 56 white rats weighing 150–200 g were used. Paclitaxel was administered intraperitoneally to the animals at a dose of 2 mg/kg body weight 4 times after one day, after which the animals were divided into an experimental group – 24 animals that were administered 2-ethyl-6-methyl-3-hydroxypyridine succinate and a control group (24 animals, introduction of water for injections) groups. The results of the "hot plate" tests and von Frey monofilaments showed that the use of 2-ethyl-6-methyl-3-hydroxypyridine succinate reliably reduces the manifestations of peripheral neuropathy caused by paclitaxel on the 28th and 60th days of the experiment. In rats treated with HS, destructive-dystrophic phenomena in the myelin nerve fibers of the sciatic nerve are less pronounced on the 60th, 90th, and 120th days of the experiment. The results of the electron microscopic study are fully consistent with the data of neurophysiological studies and indicate the possibility of using 2-ethyl-6-methyl-3-hydroxypyridine succinate as an effective neuroprotector in paclitaxel-induced peripheral neuropathy.

Key words: paclitaxel, chemotherapy, neuropathy, nerve, peripheral nervous system.

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МОРФО-ФУНКЦІОНАЛЬНА ХАРАКТЕРИСТИКА СІДНИЧОГО НЕРВА НА ПІЗНІХ ТЕРМІНАХ ЕКСПЕРИМЕНТАЛЬНОЇ ПАКЛІТАКСЕЛ-ІНДУКОВАНОЇ ПЕРИФЕРІЙНОЇ НЕЙРОПАТІЇ ЗА УМОВ КОРЕКЦІЇ 2-ЕТИЛ-6-МЕТИЛ-3-ГІДРОКСИПІРИДИНУ СУКЦИНАТОМ

6 із 10 пацієнтів у процесі лікування раку грудної залози, раку яєчників, недрібноклітинного раку легень страждають від нейротоксичності хіміопрепарату Паклітаксел, а саме паклітаксел-індукованої периферійної нейропатії. Серед них кожен четвертий потребує зниження дози, відкладення лікування чи навіть припинення терапії. Попередні спроби використання різноманітних нейропротекторних середників у людей і на тваринних моделях не показали достатньої ефективності щодо запобігання або суттєвого зниження інтенсивності проявів ПІПН. Метою нашого дослідження стало вивчення впливу нейропротекторного засобу 2-етил-6-метил-3-гідроксипіридину сукцинату на морфо-функціональні параметри сідничого нерва при експериментальній паклітаксел-індукованій периферійній нейропатії. В експерименті використали 56 білих щурів масою 150–200 г. Тваринам вводили внутрішньоочеревинно Паклітаксел у дозі 2 мг/кг маси тіла через одну добу 4 рази, після цього тварин поділили на дослідну групу – 24 тварини, яким вводили 2-етил-6-метил-3-гідроксипіридину сукцинат і контрольну (24 тварини, введення води для ін'єкцій) групи. Результати тестів «гаряча пластинка» та використання монофіламентів фон Фрея показали, що застосування 2-етил-6-метил-3-гідроксипіридину сукцинату достовірно знижує прояви периферійної нейропатії, викликаної паклітакселом на 28-у, 60-у доби експерименту. У щурів, що отримували лікування 2-етил-6-метил-3-гідроксипіридину сукцинатом, деструктивно-дистрофічні явища в мієлінових нервових волокнах сідничого нерва є менш вираженими на 60-у, 90-у та 120-у доби досліду. Результати електронномікроскопічного дослідження повністю узгоджуються з даними нейрофізіологічних досліджень і вказують на можливість використання 2-етил-6-метил-3-гідроксипіридину сукцинату як ефективного нейропротектора при паклітаксел-індукованій периферійній нейропатії.

Ключові слова: паклітаксел, хіміотерапія, нейропатія, нерв, периферійна нервова система.

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6 out of 10 patients undergoing treatment for breast cancer, ovarian cancer, and non-small cell lung cancer suffer from the neurotoxicity of the chemotherapy drug Paclitaxel, namely paclitaxel-induced peripheral neuropathy (PIPN) [13, 14]. The main symptoms of such neuropathy - burning pain and numbness in the hands and feet, loss of fine motor skills are so pronounced that every fourth patient needs modification of the paclitaxel treatment regimen, including dose reduction, treatment delay or even discontinuation of therapy [4, 14].

The use of models with cell lines of rat spinal cord neurons, induced human pluripotent stem cells, as well as in vivo models in rodents revealed a number of molecular pathways affected by paclitaxel: axons

of sensory neurons, peripheral neuroglia, perikaryons of segmental centers, cells of the immune system. These studies showed that paclitaxel induces altered transmission of calcium ions, the release of neuropeptides and growth factors, mitochondrial damage and the formation of reactive oxygen species, and has a direct effect on the disruption of microtubule transport [10]. However, today there are still insufficient neuromorphological data on the patterns of pathomorphogenesis of peripheral neuropathies caused by paclitaxel.

Previous attempts to use various neuroprotective agents in humans and in animal models have not shown sufficient effectiveness in preventing or significantly reducing the intensity of PIPN manifestations. The method of electroacupuncture, the action of magnetic fields, the use of cryotherapy and chylotherapy, the use of vitamin E, B vitamins, omega-3 fatty acids, glutathione, acetyl-L-carnitine, amitriptyline, progesterone, minoxidil and a number of other means have been tested, but this did not bring the desired result [5, 8, 12]. Therefore, it is very important to study and develop potential effective approaches during chemotherapy with paclitaxel to prevent and correct this complication. One of the possible ways to prevent damage to the nervous system during chemotherapy could be the use of metabolic drugs that have antioxidant, antihypoxic, and membrane-stabilizing properties. One of them - 2-ethyl-6-methyl-3-hydroxypyridine succinate (HS) is quite widely used in endocrinology, neurology, cardiology, and previously a significant positive effect of HS was established in the correction of paclitaxel-induced retinotoxicity in an experiment [2]. Previously, we conducted a study on the stages of development of this neuropathy [7] and found that by the 28th day, its development reaches a maximum, then there is a gradual decrease in the morphological manifestations of neurotoxicity. In order to comprehensively understand the pathomorphogenesis of this neuropathy and the effectiveness of HS as a correction of PIPN, a decision was made to continue the study at later times - 60th, 90th and 120th days.

The purpose of the study was to investigate the effect of the potential neuroprotectant 2-ethyl-6-methyl-3-hydroxypyridine succinate on the morpho-functional parameters of the sciatic nerve in the late stages of experimental paclitaxel-induced peripheral neuropathy.

Materials and methods. The study was conducted on the basis of the Department of Histology, Cytology and Embryology of the Ivano-Frankivsk National Medical University. 56 white rats weighing 150–200 g were used in the experiment. The animals were housed in vivarium conditions at a temperature of 21–24 ℃, under a normal light regime (day-night) and on a diet with access to food and water ad libitum. The experiment was conducted in accordance with the recommendations of ARRIVE and EU Directive 2010/63 / EU on the protection of animals used for scientific purposes, in accordance with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experiments and Other Scientific Purposes" (Strasbourg, 2005), Law of Ukraine "On the Protection of Animals from Cruel Treatment" (2006, Article 26), "General Ethical Principles of Animal Experiments", adopted by the Fifth National Congress on Bioethics (Kyiv, 2013). Animals were injected intraperitoneally with paclitaxel (Actavis, Romania) at a dose of 2 mg/kg of body weight after one day 4 times before reaching a total dose of 8 mg/kg according to the Polomano method [11]. After that, the animals were divided into an experimental group – 24 animals, which were injected with 2-ethyl-6-methyl-3-hydroxypyridine succinate (the preparation "Armadine", manufactured by Scientific and Production Firm "Microchem" LLC), and a control group (24 animals, injection of water for injections) group. Neurophysiological studies and electron microscopic picture of the normal nerve were determined on 8 intact animals. Neurophysiological studies were performed at 3-hour intervals on the 28th, 60th, 90th, and 120th days after the last administration of the HS drug. The hallmark sign of PIPN, mechanical allodynia, was defined as withdrawal of the hind paw of rats in response to irritation with von Frey monofilaments using the "up-down" method [1]. The main method of studying thermal hyperalgesia is the Hot Plate test. During its performance, rats were alternately placed on a metal plate heated to 55 ±1℃. A stopwatch was used to measure the time from the moment the animal was placed on the plate to the end point of the test - licking the pads of the front and/or hind paws or jumping up. This time was the time of latent pain reaction. The maximum time the animals stay on the plate is 35 seconds [3].

On the same day, the animals were removed from the experiment by applying ether anesthesia. Research material – sciatic nerves (SN) were collected on the 28th, 60th, 90th and 120th (6 animals for each period of research) days after the last administration of HS. Electron microscopic research was carried out according to generally accepted methods and studied according to using a PEM-125K electron microscope, images were photographed at a magnification of 4000–12000 times.

Results of the study and their discussion. Administration of paclitaxel caused signs of peripheral neuropathy in the form of thermal hyperalgesia and mechanical allodynia in experimental animals. When conducting the von Frey test, the mechanical pain threshold in intact animals was 55.34±7.58 g. In animals

of the control group, on the 28th day of the experiment, the mechanical pain threshold decreased to 27.72±5.738 g, p<0.01. The following periods demonstrated the dynamics of the approach of the mechanical pain threshold to the initial indicator: on the 60th day it was 47.60±14.66 g, and on the 90th day it was caused by monofilaments with a pressure force of 53.00±17.60 g. In remote no manifestations of mechanical allodynia were observed during the experiment: on the 120th day, the pain threshold reached 73.33±13.33 g, which probably exceeded the values of intact animals p<0.05. In the animals of the experimental group, which underwent HS correction, the threshold of pain sensitivity on the 28th day was 54.94±8.29 g, p<0.05, which differs by 98.17% from the similar indicator in the control group of animals. On the 60th day, manifestations of mechanical allodynia were no longer observed: the threshold was 57.61±12.36 g, and on the 90th day, it was caused by monofilaments with a pressure force of 59.02±11.60 g.

The duration of stay of intact animals on the "Hot Plate" was 17.20±0.92 s. Animals of the control group on the 28th day after the last injection of the drug showed signs of thermal hyperalgesia: the indicator decreased to 13.02±0.96 s, p<0.01. Manifestations of thermal hyperalgesia reliably disappear already on the 60th day of the experiment: the latent time of pain sensitivity was 15.62±1.61 s, on the 90th day – 15.58±1.53 s. In the long term of the experiment, manifestations of thermal hyperalgesia were rarely observed. Thermal hyperalgesia was significantly less pronounced in the animals of the experimental group: already on the 28th day, the time spent on the "Hot Plate" remained close to the initial level – 17.14±1.01 s, p<0.01. On the 60th day and until the end of the experiment, no manifestations of thermal hyperalgesia were observed in the animals of the experimental group.

Electron microscopic examination of the SN preparations of rats in the control group established that on the 28th day of the experiment, the phenomena of destruction in the myelin nerve fibers (MNF) increased. In most MNF, the myelin sheath is thickened due to swelling of neuroleumocytes and intralamellar vacuolation. We often observe MNF with near-to-complete degeneration of the axial cylinders (AC) and pronounced edema. The vast majority of mitochondria are increased in size, with the phenomena of lightening of the matrix and destruction of crystals. Small and large vacuoles, including periaxonal vacuoles, are found in the axoplasm of AC.

Compared with the previous terms of the experiment, on the 60th day of the experiment, we see a significant difference in the morphological picture of the SN of the control group of rats - the presence of degenerated nerve fibers (Fig. 1).

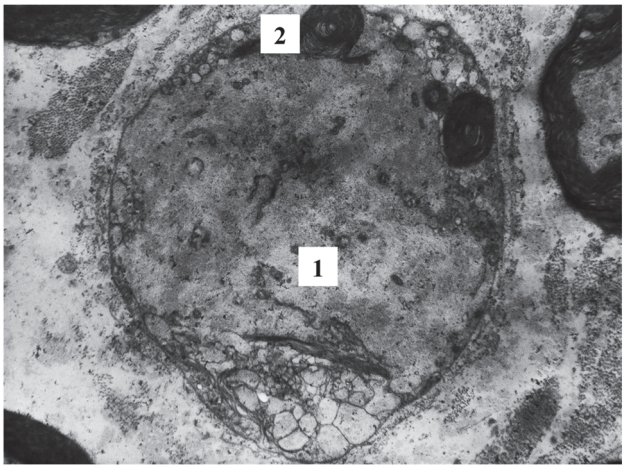

Fig. 1. Myelin nerve fiber of the sciatic nerve of an animal of the control group on the 60th day of the experiment. Electron micrograph. Magnification: x4000. Designation: 1 – axial cylinder, 2 – remnants of the myelin sheath.

Usually, these are single MNF of large diameter, represented by AC with extensive areas of destroyed axolemma, destroyed mitochondria, clusters of vacuoles. The cytoplasm of neurolemocytes is filled with vacuoles with optically transparent contents. The basement membrane is often palpable over a considerable length. We observe myelin sheath (MS) fragments with concentric layers of myelin.

In the animals of the experimental group that received HS correction, at this time of the experiment, the changes in the MNF are significantly less pronounced – small and medium-caliber fibers with a normal AC structure and a thin myelin sheath predominate, which can be interpreted as newly formed nerve fibers. In schwannocytes, synthetic processes slow down: part of the cisterns of the granular endoplasmic reticulum is flattened, the lamellar component prevails in the Golgi complex and the vacuole component is limited (Fig. 2a). At the same time, the number of large-caliber MNF increases, in which destructive processes deepen: large intramyelin vacuoles with the appearance of demyelination foci, deformation of MNF. We regularly observe how distorted chimeric myelin plates form intramyelin inclusions (Fig. 2b). The axial cylinder is thus delimited to one side and a large cavity is formed between the myelin layer and the axolemma with fragments of myelin. In the axoplasm of AC, microfilaments and microtubules are disoriented and disorganized, forming clusters between which areas of edema are located. That is, during this term both normal and newly formed MNF are present, and at the same time they are significantly damaged. Their structural components show signs of violations of compensatory and regenerative processes.

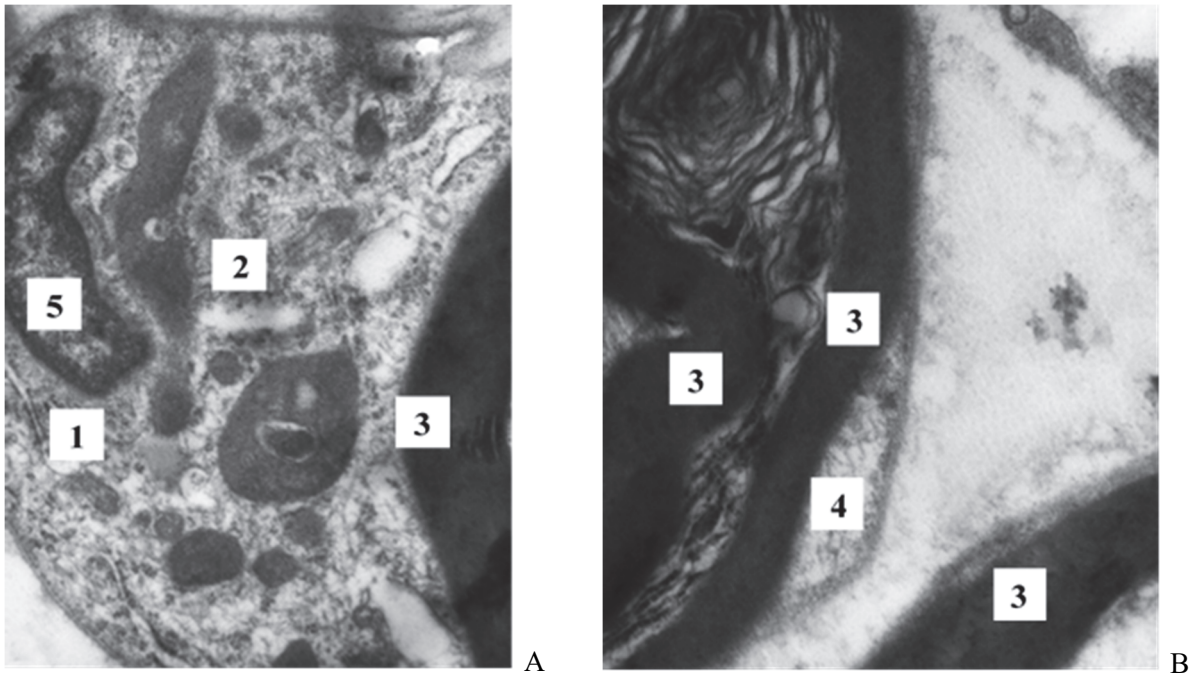

Fig. 2. Disruption of the neuroleumocyte (a) and myelin sheath (b) structure of the myelinated nerve fiber of the sciatic nerve on the 60th day after administration of 2-ethyl-6-methyl-3-hydroxypyridine succinate against the background of paclitaxel-induced peripheral neuropathy. Electron micrographs. Magnification: a, b – x 16000. Designation: 1 – Golgi complex, 2 – agranular endoplasmic reticulum, 3 – myelin sheath, 4 – periaxonal edema, 5 – neuroleumocyte nucleus.

On the 90th day of PIPN, animals of the control group have both preserved and destructively changed MNF (Fig. 3a). Violations of the structure of their MNF are accompanied by pronounced changes in the MS, the formation of concentric detachments of myelin, and the appearance of small interlamellar vacuoles. Numerous unchanged mitochondria are found in the cytoplasm of schwannocytes. The inner and intermediate layers of the MS are represented by separate rounded fragments with concentric layers of myelin, the surface layers of the MS appear to be relatively preserved. Single mitochondria, a large number of cisterns of the endoplasmic reticulum, and dictyosomes of the Golgi complex can be found in the cytoplasm of neurolemocytes. The total degeneration of the MNF is manifested by the shrinkage of the AC and the destruction of the MS (Fig. 3b).

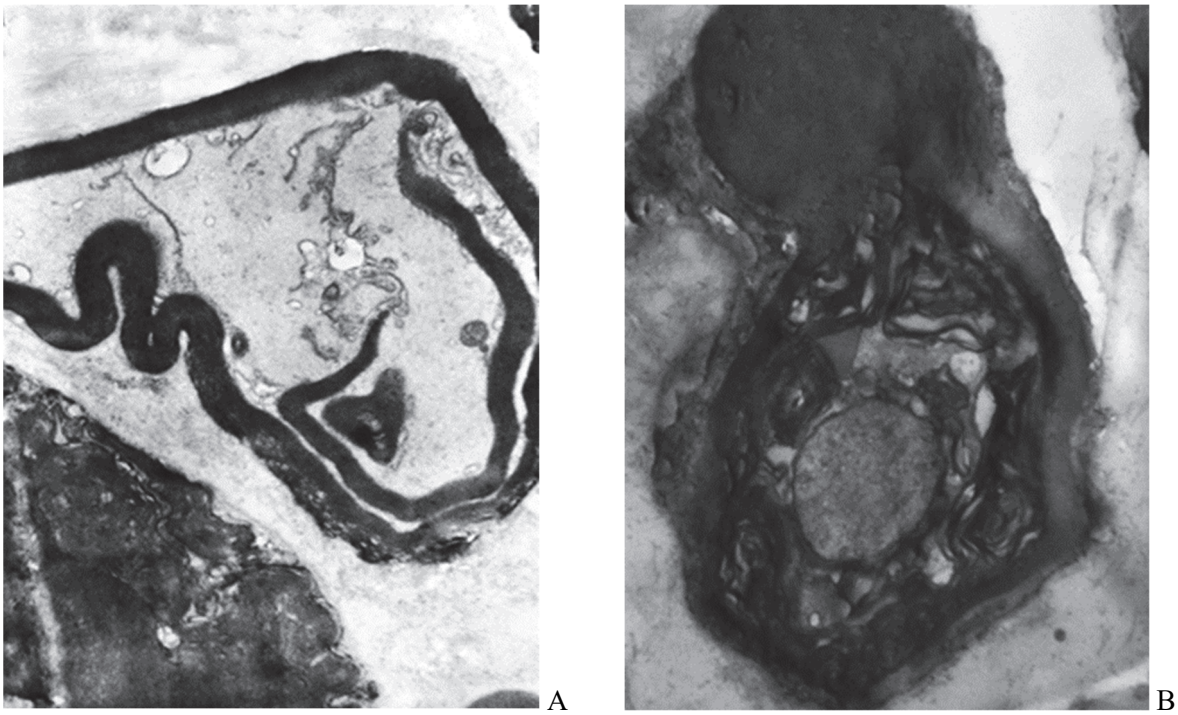

Fig. 3. Shrinkage of axial cylinders, deep disorganization of the myelin sheath and partial demyelination of myelin nerve fibers of the sciatic nerve of rats in the control group on the 90th day of the experiment. Electron micrographs. Magnification: a – x6400, b – x9000.

In the neuroplasm of the AC of MNF of the animals of the control group, abnormalities were detected that were not determined in the previous terms - against the background of diffuse swelling of the neuroplasm, we can see multiple inclusions, which are a cluster of expanded neurotubules and neurofilaments of a flake-like appearance. Along with the changed MNF, there are also fibers with signs of regenerative processes, manifested by the appearance of electron-dense young mitochondria.

On the other hand, in the experimental group of animals that were treated with HS, on the 90th day of the experiment, numerous MNF have a normal structure or undergo very insignificant changes. Their AC are oval-shaped, sometimes slightly deformed, the number of neurotubules and neurofilaments, which are oriented along the long axis of the MNF, is moderate, the MS is of the same thickness.

On the 120th day of the experiment, in animals of the control group, the morphological changes of the MNF are characterized by significant polymorphism, which is reflected by the predominance of manifestations of axonopathy, schwannopathy or their combination. A slight deformation of the AC is determined in numerous MNF. MS tightly adheres to the axolemma, of uniform thickness with isolated areas of myelin laminae. An increase in the density of neurofilaments with preservation of their ordered orientation along the long axis of the fiber is typical for AC. The structure of the agranular endoplasmic reticulum and neurotubules is preserved, and in the mitochondria, the inner membrane and cristae are usually destroyed, the matrix is illuminated. There is an increase in the number of mitochondria in the cytoplasm of neurolemocytes, among which there are numerous small mitochondria with an unchanged structure, as well as phenomena of vacuolar transformation. We observe a violation of the organized placement of neurotubules and neurofilaments in the cytoplasm of axial cylinders. In certain MNF, signs of myelinopathy with splitting of the MS, fragmentation of myelin lamellae prevail, while in others the phenomena of axonopathy dominate - periaxonal swelling, violation of the organized orientation of neurofilaments and neurotubules, but with a fully preserved structure of the myelin sheath. Along with them, practically unchanged MNF are observed.

In the experimental group of animals, the MO on the entire perimeter of the MNF is preserved and has a clearly ordered lamellar structure. In the AC, we observe an orderly arrangement of neurofilaments and neurotubules, numerous young mitochondria. In individual MNF, we observe swelling of the periaxonal space, in neurolemocytes there are large rounded nuclei with evenly scattered chromatin granules. The Golgi complex, agranular endoplasmic reticulum, many mitochondria and ribosomes (both free and polysomes) are located near the nucleus.

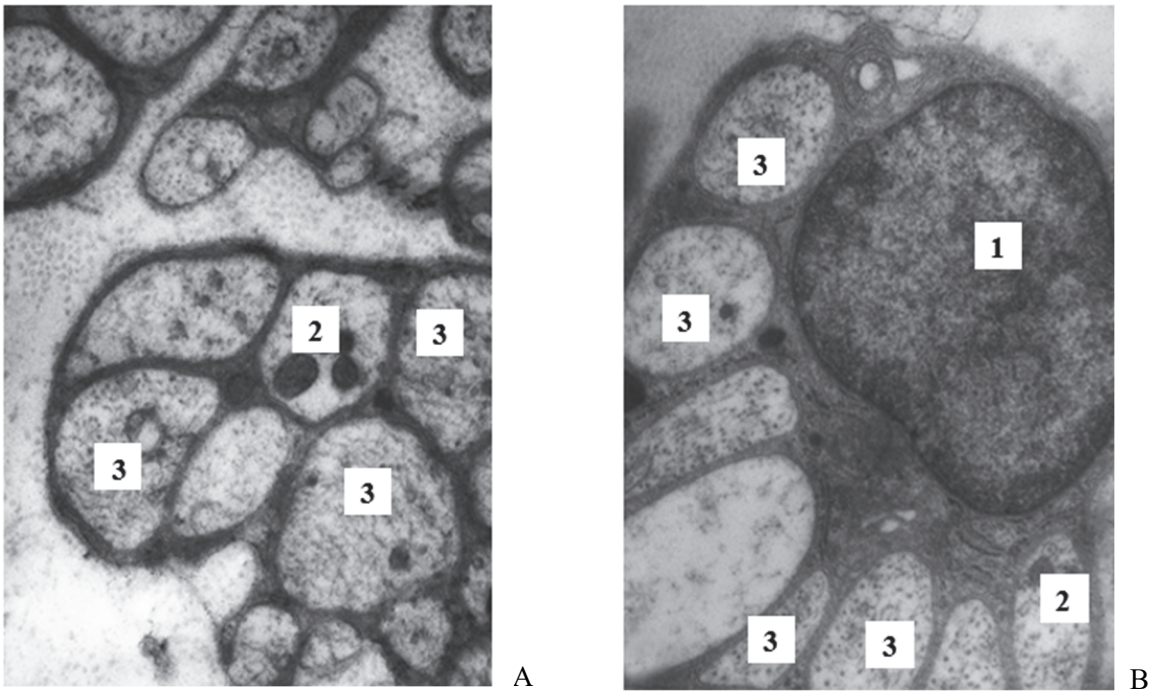

Fig. 4. Polymorphic changes in axial cylinders of unmyelinated nerve fibers of the sciatic nerve of the control (a) and experimental (b) groups of animals on the 120th day of the experiment. Electron micrographs. Magnification: a, b – x16000.
Designation: 1 – neuroleumocyte nucleus, 2 – mitochondria, 3 – neurofilaments.

Changes in unmyelinated nerve fibers (UNF) are expressed to a lesser extent, as in the previous periods of the experiment. In the control group of rats, swelling of the neuroplasm of individual AC prevails (Fig. 4a), vacuolar transformation of mitochondria, rarefaction of neurofilaments and

neurotubules, significant expansion of lumens in the agranular endoplasmic reticulum. In the experimental group of animals, the cytoplasmic organelles do not undergo significant changes, and the nuclei of the UNF neuroleumocytes are mostly irregularly rounded with uniformly scattered chromatin granules (Fig. 4b).

Our study was focused on testing 2-ethyl-6-methyl-3-hydroxypyridine succinate as a potential neuroprotector in experimental paclitaxel-induced peripheral neuropathy based on complex morpho-functional analysis. The morphological changes of the sciatic nerve that we discovered from the 28th to the 120th day of the experiment in the control group of rats coincide with the processes described by other researchers in experimental PIPN, namely: focal destruction and swelling of the MNF, pronounced changes in the lamellar structure of the MS, disruption of division processes in neurolemocytes with further involvement in the pathological process of AC and accumulation of neurofilaments and neurotubules [9]. In rats treated with HS, the destructive-dystrophic phenomena in the MNF of the SN are less pronounced: on the 90th day of the experiment, numerous MNF have a normal structure or undergo very insignificant changes, edema and intralaminar vacuoles in the MS are visualized in the MS. In individual fibers in the AC, phenomena of incomplete splitting of mitochondria with the formation of vacuoles filled with medium electron density content are observed, and small young mitochondria with a matrix of increased electron density are also visualized.

It should be noted that a certain recovery of the myeloarchitectonics of the sciatic nerve in PIPN occurs independently, but the use of HS correction provides faster regenerative and restorative processes, therefore, it will potentially allow preparing the cancer patient for repeated courses of chemotherapy with paclitaxel in the clinic.

Therefore, the pathophysiological mechanisms of neurotoxicity when using paclitaxel are degeneration and demyelination of axons, impaired axonal transport, oxidative stress, mitochondrial dysfunction, and immune-mediated reactions [6]. The use of HS neutralizes these processes and leads to regenerative and restorative changes in SN. The results of the electron microscopic study obtained by us are fully consistent with our data of neurophysiological studies and indicate the possibility of using HS as a potentially effective neuroprotector in PIPN.

Conclusions

1. After the correction of paclitaxel-induced peripheral neuropathy with 2-ethyl-6-methyl-3-hydroxypyridine succinate in the electron microscopic picture of the sciatic nerve, pronounced regeneration processes were observed from the 28th to the 120th day.

2. The use of 2-ethyl-6-methyl-3-hydroxypyridine succinate at a dose of 10 mg/kg of body weight within 10 days after the last administration of paclitaxel significantly reduces the manifestations of peripheral neuropathy caused by the latter on the 28th and 60th days of the experiment. Disappearance of manifestations of thermal hyperalgesia when using 2-ethyl-6-methyl-3-hydroxypyridine succinate is observed already on the 28th day of the experiment.

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HISTOLOGICAL AND MICROBIOLOGICAL RATIONALE FOR THE USE OF MATRIX MATERIALS IMPREGNATED WITH ANTIBIOTICS FOR THE RECONSTRUCTION OF BONE TISSUE DEFECTS

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Studying the combination of fibrous scaffold materials with therapeutic agents as a drug delivery system is important for regenerative medicine. The results of the antibiotic-absorbing capacity of the fibrous non-woven polycaprolactone matrices created by us, as well as their influence on the regeneration of bone tissue, were analyzed in the study. The results of microbiological studies indicated the pronounced hydrophilic properties of the matrices we've created; it was confirmed by a decrease in the activity of the antibiotic only at 16.4 % after 7 days ($p<0.05$). Instead, in an experiment on laboratory animals, the specified frame effect of fibers was confirmed by the beginning of the formation of an organized bone structure, namely, by an increase in osteoid up to 34.38 % ($p<0.05$), at an early stage so far.

Key words: matrix materials, polycaprolactone, antibiotic impregnation, cefazolin, lincomycin, histological analysis, bone tissue.

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ГІСТОЛОГІЧНЕ ТА МІКРОБІОЛОГІЧНЕ ОБГРУНТУВАННЯ ВИКОРИСТАННЯ МАТРИКСНИХ МАТЕРІАЛІВ, ІМПРЕГНОВАНИХ АНТИБІОТИКАМИ, ДЛЯ РЕКОНСТРУКЦІЇ ДЕФЕКТІВ КІСТКОВОЇ ТКАНИНИ

Вивчення поєднання волокнистих каркасних матеріалів із лікувальними засобами, як системи доставки ліків має важливе значення для регенеративної медицини. У дослідженні проаналізовано результати антибіотик-сорбуючої здатності створених нами волокнистих нетканих полікапролактонових матриксів, а також їхній вплив на регенерацію кісткової тканини. Результати мікробіологічних досліджень свідчили про виражені гідрофільні властивості створених нами матриксів, що підтверджувалось зниженням після 7 діб активності антибіотика всього на 16,4 % ($p<0,05$). Натомість, в експерименті на лабораторних тваринах вказаний каркасний ефект волокон підтверджувався початком формування організованої структури кістки, а саме, збільшенням остеоїду до 34,38 % ($p<0,05$) вже на ранніх термінах.

Ключові слова: матриксні матеріали, полікапролактон, імпрегнація антибіотиками, цефазолін, лінкоміцин, гістологічний аналіз, кісткова тканина.

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To date, a new direction is being pursued in medicine, including the combination of fibrous materials with therapeutic agents, as a delivery system for medicines and living cells. This approach promotes a purposeful management of the structural-functional condition of cells involved in regenerative processes [1, 11].

Natural polymers (hyaluronic acid, collagen, gelatin, fibrinogen, chitosan, pectins, agarose, alginates, cellulose) and synthetic materials (polycaprolactone, polylactide) are considered to be the most promising tools for the controlled reconstructive tissue repair [5, 6].

An existing method of forming porous non-woven matrices is electrospinning. The three-dimensional frame of the implant due to its architecture and the presence of active functional groups (which is determined by the type of polymer material) promotes the adhesion and migration of cells to the area of