DOI: https://doi.org/10.17816/rmmar642372

Morphological Remodeling of the Spinal Cord After Experimental Neurotmesis with Early Ipidacrine Administration: An Electron Microscopy Study

Igor' V. Litvinenko[1], Sergei A. Zhivolupov[1], Lyudmila S. Onishchenko[1], Andrei V. Klimkin[2], Evgeny N. Gnevyshev[3], Kamil' R. Magomedov[4]

[1] Military Medical Academy, Saint Petersburg, Russia;
[2] Pediatric Research and Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency, Saint Petersburg, Russia;
[3] Institute of Applied Psychoanalysis and Psychology of the Autonomous Non-Commercial Organization of Higher Education "University under the Interparliamentary Assembly of the Eurasian Economic Community", Saint Petersburg, Russia;
[4] Saint Luke's Clinic, Saint Petersburg, Russia

ABSTRACT

BACKGROUND: Peripheral nerve injuries represent a significant medical and social concern both in peacetime and during armed conflict. These injuries require prolonged inpatient care and frequently result in long-term disability. In response to peripheral nerve damage, retrograde reactive changes occur in the parent neurons and associated spinal cord cells. Understanding these processes may allow for more accurate predictions of clinical outcomes and recovery timelines. Elucidating the response of the lumbar spinal cord segment to peripheral nerve injury and subsequent treatment may enhance therapeutic efficacy.

AIM: To examine the regularities of reactive changes in the spinal cord segment following neurotmesis in order to improve the strategy and tactics of treating patients with this pathology.

MATERIALS AND METHODS: Experimental neurotmesis of the sciatic nerve was surgically induced in six male Wistar rats. Three animals received ipidacrine for seven days, whereas the remaining three served as untreated controls.

RESULTS: This electron microscopy study examined changes in the lumbar segment of the spinal cord seven days after neurotmesis, with and without ipidacrine treatment. Retrograde processes following sciatic nerve injury affected not only the parent neurons of the damaged fibers but also nerve fibers, glial cells (including oligodendrocytes), and the microcirculatory bed. Qualitative and quantitative differences in spinal cord morphology were observed between the experimental and control groups, and morphological predictors of successful recovery were identified.

CONCLUSION: The results of this study demonstrated that a 7-day course of ipidacrine administration following sciatic nerve neurotmesis exerted a beneficial effect on adaptive neuroplastic processes in the lumbar segment of the spinal cord.

Keywords: ipidacrine; neuroglia; neuron; nerve fibers; regeneration; spinal cord; peripheral nerve injury; electron microscopy.

To cite this article
Litvinenko IV, Zhivolupov SA, Onishchenko LS, Klimkin AV, Gnevyshev EN, Magomedov KR. Morphological Remodeling of the Spinal Cord After Experimental Neurotmesis with Early Ipidacrine Administration: An Electron Microscopy Study. *Russian Military Medical Academy Reports*. 2025;44(1):87–94. DOI: https://doi.org/10.17816/rmmar642372

Received: 29.11.2024 **Accepted**: 11.02.2025 **Published**: 31.03.2025

УДК 616.832-001:611.018.8:612.086.3:615.036.8
DOI: https://doi.org/10.17816/rmmar642372

Морфологическое ремоделирование спинного мозга после экспериментального невротмезиса на фоне раннего применения ипидакрина (электронно-микроскопическое исследование)

И.В. Литвиненко[1], С.А. Живолупов[1], Л.С. Онищенко[1], А.В. Климкин[2], Е.Н. Гневышев[3], К.Р. Магомедов[4]

[1] Военно-медицинская академия, Санкт-Петербург, Россия;
[2] Детский научно-клинический центр инфекционных болезней федерального медико-биологического агентства, Санкт-Петербург, Россия;
[3] Институт прикладного психоанализа и психологии автономной некоммерческой организации высшего образования «Университет при Межпарламентской ассамблее ЕврАзЭС», Санкт-Петербург, Россия;
[4] Клиническая больница Святителя Луки, Санкт-Петербург, Россия

АННОТАЦИЯ

Актуальность. Травмы периферических нервов представляют собой серьезную медико-социальную проблему как в мирное, так и в военное время. Они требуют длительного стационарного лечения и часто приводят к инвалидизации пациентов. В ответ на повреждение нервных волокон в «родительских» нейронах и других связанных с ними клетках спинного мозга происходят ретроградные реактивные изменения, понимание которых даст возможность прогнозирования исходов и сроков восстановления. Знание того, как поясничный отдел спинного мозга реагирует на травму периферического нерва и последующее лечение позволит повысить эффективность терапии.

Цель — изучение закономерностей сегментарных спинальных реактивных изменений при невротмезисе для усовершенствования стратегии и тактики лечения больных с данной патологией.

Материалы и методы. Экспериментальный невротмезис седалищного нерва создавался у 6 самцов крыс Wistar хирургическим путем. 3 крысы в течение 7 сут получали лечение ипидакрином, а 3 составили контрольную группу — без лечения.

Результаты. В представленном электронно-микроскопическом исследовании определяли изменения, которые происходили в поясничном сегменте спинного мозга после невротмезиса через 7 сут терапии ипидакрином и без нее. Было установлено, что в ретроградных процессах, происходящих в спинном мозге после травмы седалищного нерва, участвовали не только «родительские» нейроны поврежденных волокон, но и нервные волокна, глиальные клетки (олигодендроциты) и микроциркуляторное русло. Обнаружены качественные и количественные различия в морфологии структур спинного мозга в экспериментальной и контрольной группах и определены морфологические предикторы их успешного восстановления.

Заключение. Результаты исследования показали, что применение ипидакрина в течение 7 дней после невротмезиса седалищного нерва оказало положительное влияние на процессы адаптивной нейропластичности в поясничном сегменте спинного мозга.

Ключевые слова: ипидакрин; нейроглия; нейрон; нервные волокна; регенерация; спинной мозг; травма периферических нервов; электронная микроскопия.

Как цитировать

Литвиненко И.В., Живолупов С.А., Онищенко Л.С., Климкин А.В., Гневышев Е.Н., Магомедов К.Р. Морфологическое ремоделирование спинного мозга после экспериментального невротмезиса на фоне раннего применения ипидакрина (электронно-микроскопическое исследование) // Известия Российской военно-медицинской академии. 2025. Т. 44, № 1. С. 87–94. DOI: https://doi.org/10.17816/rmmar642372

Рукопись получена: 29.11.2024 **Рукопись одобрена:** 11.02.2025 **Опубликована:** 31.03.2025

ЭКО•ВЕКТОР

BACKGROUND

The high incidence of peripheral nerve injuries, especially during armed conflicts, their frequent disabling consequences, and consequent prolonged hospitalizations underscore their significant medical and social impacts. The clinical management of such injuries remains challenging. Despite advances in understanding he mechanisms underlying peripheral nerve regeneration, therapeutic approaches aimed at structural and functional recovery remain fundamentally insufficiently substantiated. Consequently, the effectiveness of treatment strategies directly depends on a thorough understanding of nervous system alterations at multiple levels following nerve injury, as previously reported by our group [1].

It is well established that after peripheral nerve transection, pathological changes extend beyond Wallerian degeneration. Reactive alterations also occur in the proximal nervous system components, including the spinal ganglia, spinal cord, and suprasegmental structures [2]. Nerve fiber damage triggers retrograde changes in the proximal axonal segment and the adjacent, functionally connected neurons. Such changes are linked to the disrupted retrograde transport of trophic factors [2–4].

However, the exact distribution and dynamics of such retrograde responses following peripheral nerve injury remain poorly defined. Evidence indicates that these responses are heterogeneous and variable, influenced by the extent and location of axonal damage, vascular supply to the affected limb segment, and age. Furthermore, the predominant mode of neuronal death during the early post-axotomy period—whether necrotic or apoptotic—has not been established. This lacuna is of critical clinical relevance: a better understanding of retrograde alterations and the development of evidence-based strategies to preserve segmental spinal cord function may enhance regenerative and collateral sprouting, thereby improving clinical outcomes [5, 6].

We previously demonstrated that magnetic stimulation and ipidacrine administration improved adaptive neuroplasticity and nerve regeneration 1 month after traumatic neuropathy [7]. However, data on the early morphological changes within the lumbar spinal cord following neurotmesis (sciatic nerve injury) and ipidacrine administration are limited. The present study was therefore designed to address this knowledge gap.

We aimed to investigate the patterns of segmental spinal reactive changes following neurotmesis by comparing retrograde morphological alterations within the lumbar spinal cord segment during the early stages of treatment with or without ipidacrine, to optimize the therapeutic strategy and procedures for such patients.

MATERIALS AND METHODS

The selected model of traumatic neuropathy resulting in neurotmesis simulates injuries caused by sharp objects or gunshot wounds, incorporating the primary surgical management of wounds.

The experimental model was established through a multistep surgical procedure [7]. For electron microscopy, three male Wistar rats were selected for each study group.

In the experimental group, the animals received intramuscular injections of the anticholinesterase agent ipidacrine at 0.07 mL/day for 7 days, beginning on day 7 post-operation. This regimen mirrored clinical practice. The control group did not receive ipidacrine.

Tissue samples were harvested from the corresponding lumbar spinal cord segment and prepared for electron microscopy using standard protocols [8]. Ultrathin contrasted sections were examined using a JEM-100CX transmission electron microscope (JEOL Ltd., Tokyo, Japan). The electron micrographs obtained were scanned and analyzed descriptively.

RESULTS

In the control group, the lumbar segment of the spinal cord predominantly contained hyperchromic neurons, characterized by densely structured nuclei and cytoplasm. These neurons exhibited a greater number of mitochondria; however, many exhibited indistinct structural features, suggesting low activity (Fig. 1). The surrounding myelinated and unmyelinated fibers were markedly altered.

A small number of normochromic neurons were also observed. These had pale nuclei with diffuse chromatin distribution and, occasionally, dense, inactive nucleoli. Their cytoplasm contained dilated cisternae of the rough endoplasmic reticulum (RER) and, in some instances, dense lipid inclusions. Numerous ribosomes surrounded the nucleus, and a majority of the mitochondria exhibited a normal matrix and cristae structure.

These findings indicate the morphological and functional reactivity of the neurons. The axonal cylinders and myelin sheaths of the adjacent nerve fibers exhibited moderate alterations (Fig. 2).

Further, in the control group, the chromatin distribution of some oligodendrocyte (OL) nuclei was consistent with apoptosis. The surrounding myelinated and unmyelinated fibers exhibited varying degrees of degeneration (Fig. 3). Such a morphology is indicative of the apoptosis-mediated functional inactivation of OLs.

One week after initiation of ipidacrine therapy, small neurons with pale nuclei, irregularly contoured, and mildly altered chromatin architecture were observed in the experimental group. Their cytoplasm comprised various

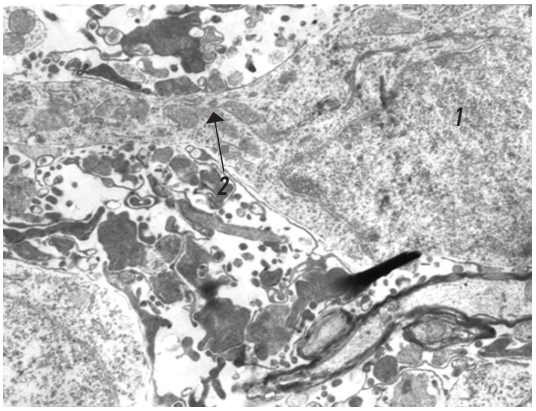


Fig. 1. Hyperchromic neuron rat spinal cord without treatment: *1* — nucleus; *2* — mitochondria (arrow), ×8,300.
Рис. 1. Гиперхромный нейрон спинного мозга крысы без лечения: *1* — ядро; *2* — митохондрии (стрелка), ×8 300.

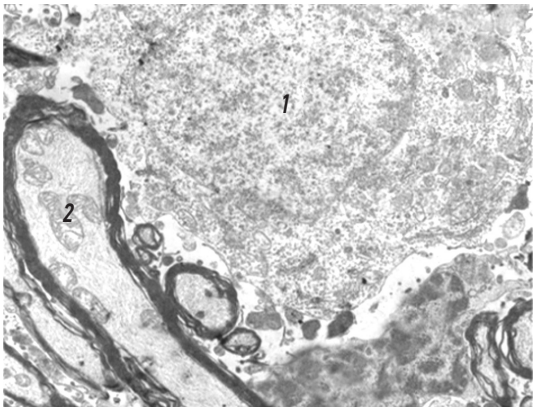


Fig. 2. Normochromic neuron rat spinal cord without treatment: *1* — nucleus; *2* — myelin fiber, ×5,000.
Рис. 2. Нормохромный нейрон спинного мозга крысы без лечения: *1* — ядро; *2* — миелиновое волокно, ×5 000.

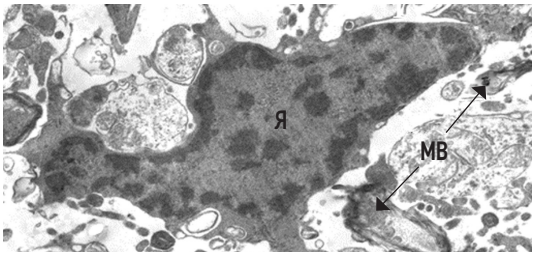


Fig. 3. Oligodendrocyte rat spinal cord without treatment with signs of apoptosis. Я — nucleus with uneven and dense accumulations of heterochromatin in the karyoplasm; MB — myelin fibers, ×10,000.
Рис. 3. Олигодендроцит спинного мозга крысы без лечения с признаками апоптоза: Я — ядро с неравномерными и плотными скоплениями гетерохроматина в кариоплазме; МВ — миелиновые волокна (стрелки), ×10 000.

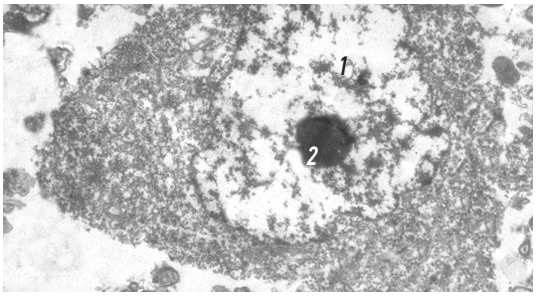


Fig. 4. Normochromic neuron in a treated rat: *1* — nucleus; *2* — nucleolus, ×4,000.
Рис. 4. Нормохромный нейрон крысы после лечения: *1* — ядро, *2* — ядрышко, ×4 000.

organelles, predominantly mitochondria, along with RER cisternae and the Golgi apparatus (Fig. 4). This morphology reflects high functional activity. In addition to these active normochromic neurons, hyperchromic neurons were also detected in the lumbar spinal cord of the treated rats, albeit less frequently than in the controls. These cells exhibited diffusely distributed heterochromatin and prominent nucleoli, suggesting reduced functional capacity. Pale neurons undergoing intracellular repair were also observed in the spinal cords of the experimental group rats. This observation was indicated by the presence of numerous ribosomes; however, a few mitochondria in the cytoplasm, along with the absence of other organelles (Fig. 5).

Notably, axonal growth cones were observed in the spinal cords of the treated rats at this stage. Some were pale and contained vesicles, mitochondria, RER, microtubules, and neurofilaments (Fig. 6), whereas others were hyperchromic and boot-like in shape (Fig. 7).

Similarly, the cytoplasmic changes in the OLs from the experimental group were marked. Some cells contained a full complement of organelles, whereas others displayed marked organelle depletion, indicative of pale-type dystrophic changes.

Certain OLs had nuclei with a normal chromatin organization. Their cytoplasm featured large vacuolated RER cisternae, numerous ribosomes, and occasional phagolysosomes (Fig. 8), reflecting population heterogeneity and partial recovery of functional activity. In some OLs, formation of new myelin sheaths, a marker of normal morphofunctional activity was observed.

By day 14 post-neurotmesis, the lumbar spinal cords from untreated rats showed myelinated fibers with dense, unlaminated myelin. The axonal cylinders of these fibers were either intact or highly condensed, suggesting dark-type dystrophic axonopathy. Fibers with dense myelin but axonal cylinders exhibiting pale-type changes were also identified. In other cases, the axons appeared translucent, and the myelin sheath was significantly thin or partially absent. These findings indicate concurrent myelinopathy and axonopathy (Figs. 1, 3).

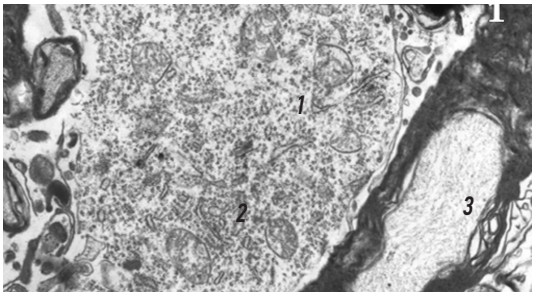


Fig. 5. Neuron rat spinal cord after treatment in the state of intracellular reparation: *1* — cytoplasm; *2* — mitochondria; *3* — axial cylinder of myelin fiber, ×10,000.
Рис. 5. Нейрон спинного мозга крысы после лечения в состоянии внутриклеточной репарации: *1* — цитоплазма; *2* — митохондрии; *3* — осевой цилиндр миелинового волокна, ×10 000.

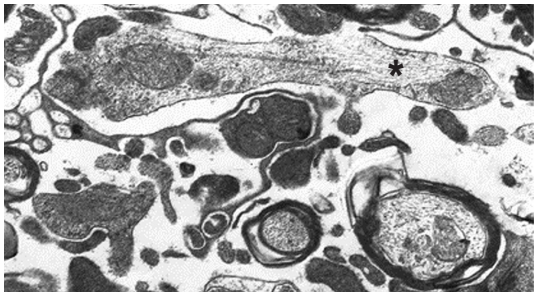


Fig. 6. Growth flask from an axon with light axial cylinder (*), ×5,000.
Рис. 6. Колба роста из аксона со светлым осевым цилиндром (*), ×5 000.

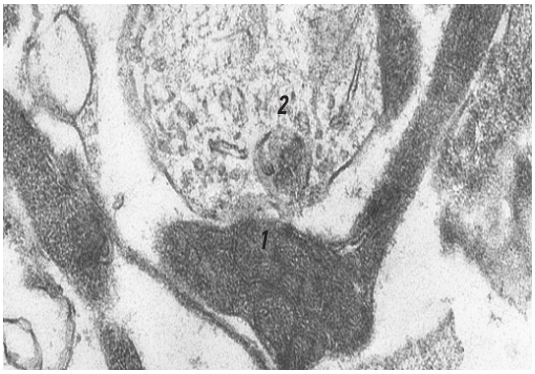


Fig. 7. Growth flask from a hyperchromic axon in the form of a boot (*1*). *2* — process of normal axial cylinder, ×26,000.
Рис. 7. Колба роста из гиперхромного аксона в виде сапога (*1*). *2* — отросток обычного вида, ×26 000.

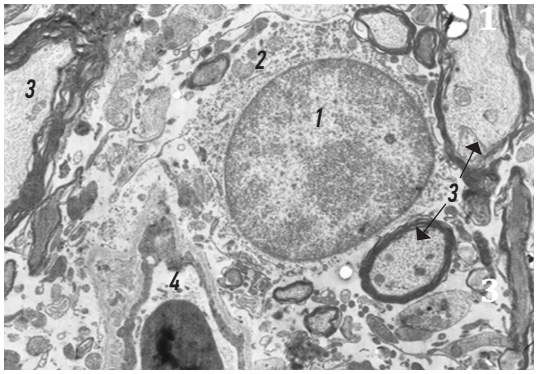


Fig. 8. Oligodendrocyte rat spinal cord after treatment: *1* — nucleus; *2* — cytoplasm; *3* — myelinated fibers; *4* — capillary with an erythrocyte, ×5,000.
Рис. 8. Олигодендроцит спинного мозга крысы после лечения: *1* — ядро; *2* — цитоплазма; *3* — миелиновые волокна; *4* — капилляр с эритроцитом в просвете, ×5 000.

Notably, in the treatment group, 2 weeks after neurotmesis, isolated myelinated fibers in the spinal cord showed a substantial structural restoration of the myelin sheath, accompanied by moderate axonal cylinder dystrophy (axonopathy) and signs of remyelination (Fig. 9, *a*, *b*).

In the control group, the capillaries of the lumbar spinal microcirculatory bed had intact basal membranes. However, erythrocyte aggregation into rouleaux was observed in the vessel lumina, indicating erythrostasis.

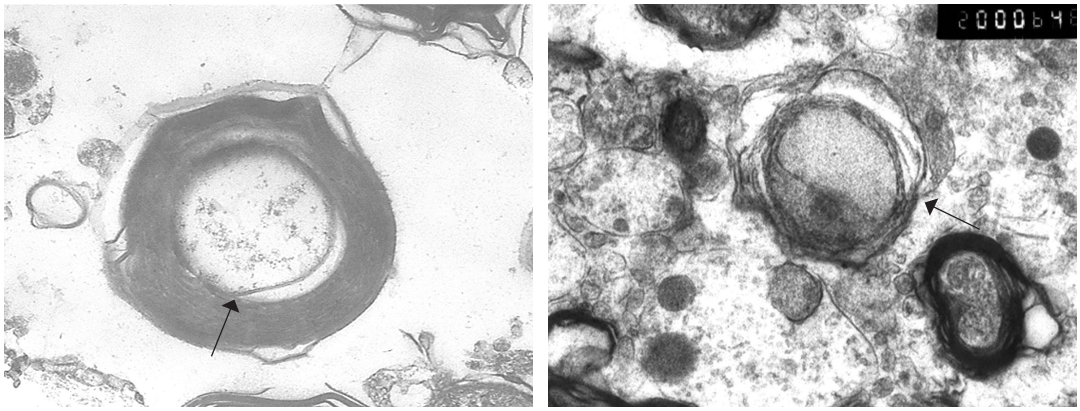
Endothelial cells exhibited dystrophic changes, more frequently of the dark-type than pale-type. Astrocytic end-feet were often absent around the capillaries, with numerous adjacent myelinated fibers showing signs of myelinopathy and axonopathy (Fig. 10). These vascular and perivascular changes reflect moderate microcirculatory impairments.

Seven days after ipidacrine treatment, some capillaries in the examined spinal cord segment contained abnormally shaped erythrocytes that did not form rouleaux. The capillary walls were extensively vacuolated, and the perivascular space appeared clear, lacking astrocytic end-feet, an essential component of the blood–brain barrier (Fig. 11). These findings suggest an incomplete restoration of the microvasculature.

DISCUSSION

The findings on the structural state of the lumbar spinal cord segment following sciatic nerve injury or neurotmesis with or without a subsequent 7-day ipidacrine treatment indicate the onset of structural improvements among all components — neurons, glial cells, myelinated fibers, and the microcirculatory bed — in the experimental (treatment) group.

Of note is the higher morphofunctional activity of neurons in the ipidacrine-treated group, as evidenced by the preserved integrity of organelles, particularly the nucleus and mitochondria. The maintained energy status of the spinal cord cells prevents the development of excitotoxicity and oxidative stress — key mechanisms of injury — and thereby inhibits the onset of necrosis and apoptosis [9].



a *b*

Fig. 9. Myelinated fibers with remyelination patterns: *a* — due to the inner mesaxon leaflet. ×15,000; *b* — due to the outer mesaxon leaflet (in the center of the image), ×20,000. The arrow indicates the area of the onset of remyelination in both images.
Рис. 9. Миелиновые волокна с признаками ремиелинизации: *а* — за счет внутреннего листка мезаксона, ×15 000; *b* — за счет наружного листка мезаксона (в центре снимка), ×20 000. Стрелкой обозначен участок начала ремиелинизации на обоих снимках.

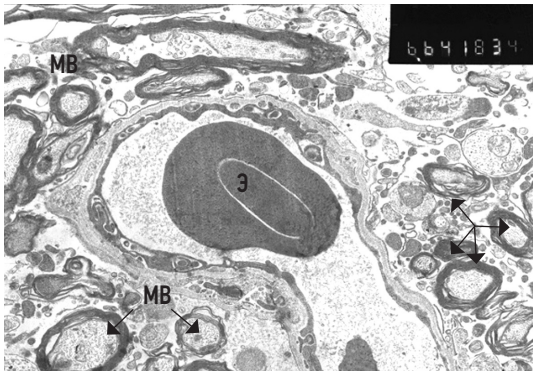


Fig. 10. Capillary with erythrocytes (Э) in the lumen. MB — myelin fibers (arrows), ×6,600.
Рис. 10. Капилляр с эритроцитами (Э) в просвете. МВ — миелиновые волокна (стрелки), ×6 600.

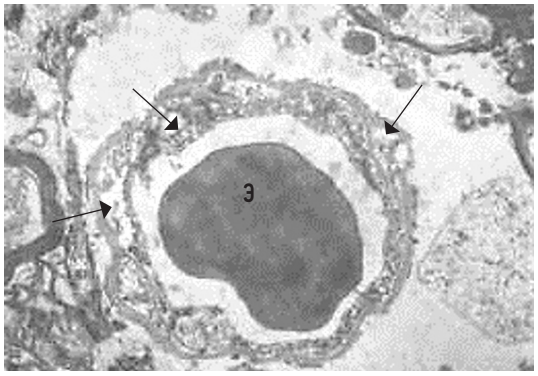


Fig. 11. Capillary with vacuolized wall (arrows) and erythrocyte (Э) irregularly shaped in the lumen, ×5,000.
Рис. 11. Капилляр с вакуолизированной стенкой (стрелки) и эритроцитом (Э) неправильной формы в просвете, ×5 000.

While the morphological changes in the OL were qualitatively similar between the control and experimental groups, the number of affected cells differed. The quantity and quality of the preserved OLs reflect the overall potential for subsequent neural tissue recovery, as these cells not only produce myelin but also provide trophic support to neurons and are involved in regulatory functions [10–14].

The neurons undergoing intracellular repair and the so-called "growth cones" within the spinal cord identified in our study have not been described previously, in the context of nerve injury. Notably, growth cones on day 7 of ipidacrine treatment after nerve injury have been reported by a few studies only in the peripheral nerves [4, 15]. Notably, growth cones were first observed in the early stages of post-transection regeneration as early as the 19th century by Ramon y Cajal. Their presence indicates a directed pattern of regeneration from the center to the periphery and the potential for navigated axonal outgrowth. The preservation of the central spinal structures enables centrifugal axonal extension toward the target organ [16].

The microcirculatory response and early disruption of the blood–brain barrier are critical contributors to neuronal death after neurotmesis [17]. After 7 days of ipidacrine treatment, the condition of the microcirculatory bed improved partially.

The number of myelinated fibers with altered and normal structure differed between the control and experimental groups. Although both groups exhibited various forms of axonopathy and myelinopathy, pathological myelinated fibers were more frequent in the absence of ipidacrine. A key finding supporting the beneficial effects of ipidacrine on myelinated fiber restoration is the occurrence of fiber remyelination in the spinal cord segment studied, consistent with previous reports on peripheral nerve regeneration [4, 15].

One of the major consequences of neurotmesis is the spinal reorganization of neuronal ensembles, primarily driven by changes in synaptic number and structure [5]. Synaptic

plasticity underlies adaptive neuroplasticity [18], a dynamic process regulated by neuronal activity [19]. The pivotal role of acetylcholine in the development and maintenance of adaptive neuroplasticity is well established. Therefore, ipidacrine, which increases acetylcholine levels, enhances the capacity for adaptive neuroplastic responses [20].

In this study, ipidacrine administration resulted in morphological changes across all components of the segmental spinal apparatus, including neurons, neuroglia, nerve fibers, and the microcirculatory bed. Such a detailed electron microscopy-based analysis provides a comprehensive understanding of the reactive spinal cord changes following neurotmesis. It further supports the rationale for using anticholinesterase agents in treating peripheral nerve injuries.

CONCLUSION

Thus, the findings of this study indicate similar microscopic features comprising early retrograde pathomorphological changes in the segmental apparatus of the spinal cord in both groups.

However, a comparative analysis revealed distinct characteristics in animals treated with ipidacrine: preservation of neuronal organelles, presence of axonal growth cones, signs of active remyelination in the myelinated fibers, a relatively greater number of OLs, and an improved state of the blood–brain barrier.

Given the effects of early ipidacrine administration on the spinal cord segment following sciatic nerve injury, these findings indicate an improvement in regenerative potential due to better preservation of the spinal structures.

This, in turn, may promote a more favorable therapeutic outcome and prognosis in patients with this condition.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: I.V. Litvinenko, article design, data analysis, manuscript preparation; S.A. Zhivolupov, article design, data analysis, manuscript preparation; L.S. Onishchenko, material collection and processing, electron microscopy data analysis and interpretation, manuscript preparation; A.V. Klimkin, manuscript preparation; E.N. Gnevyshev, data interpretation, manuscript preparation; K.R. Magomedov, literature collection, manuscript preparation.

Funding source. The study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

Ethical expertise. The conducted study was approved by the local ethics committee of the S.M. Kirov Military Medical Academy in 2008.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Участие авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Вклад каждого автора. И.В. Литвиненко — дизайн статьи, анализ полученных данных, подготовка рукописи; С.А. Живолупов — дизайн статьи, анализ полученных данных, подготовка рукописи; Л.С. Онищенко — сбор и обработка материала, анализ и интерпретация данных электронной микроскопии, подготовка рукописи; А.В. Климкин — подготовка рукописи; Е.Н. Гневышев — интерпретация данных, подготовка рукописи; К.Р. Магомедов — сбор литературы, подготовка рукописи.

Финансирование. Поисково-аналитическая работа проведена на личные средства авторского коллектива.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Этическая экспертиза. Проведенное исследование одобрено локальным этическим комитетом ФГБВОУ ВО «Военно-медицинская академия им. С.М. Кирова» в 2008 г.

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AUTHORS' INFO

Igor' V. Litvinenko, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0001-8988-3011; eLibrary SPIN: 6112-2792

Sergey A. Zhivolupov, MD Dr Sci (Medicine), Professor;
ORCID: 0000-0003-0363-102X; eLibrary SPIN: 4627-8290

Lyudmila S. Onishchenko, Cand. Sci. (Biology);
ORCID: 0000-0003-3562-1029; eLibrary SPIN: 4985-7683

Andrei V. Klimkin, MD Cand. Sci (Medicine);
ORCID: 0000-0002-6180-4403; eLibrary SPIN: 6309-3260;
e-mail: klinkinpark@mail.ru

Evgeny N. Gnevyshev, MD Cand. Sci (Medicine), Associated Professor; ORCID: 0000-0001-9671-462X; eLibrary SPIN: 9885-0260;
e-mail: evg-gnevyshev@yandex.ru

***Kamil' R. Magomedov**, MD doctor neurologist;
ORCID: 0009-0000-5649-2321; eLibrary SPIN: 8555-9957;
e-mail: Kamagomedov@gmail.com

ОБ АВТОРАХ

Игорь Вячеславович Литвиненко, докт. мед. наук, профессор; ORCID: 0000-0001-8988-3011; eLibrary SPIN: 6112-2792

Сергей Анатольевич Живолупов, докт. мед. наук, профессор;
ORCID: 0000-0003-0363-102X; eLibrary SPIN: 4627-8290

Людмила Семеновна Онищенко, канд. биол. наук;
ORCID: 0000-0003-3562-1029; eLibrary SPIN: 4985-7683

Андрей Васильевич Климкин, канд. мед. наук;
ORCID: 0000-0002-6180-4403; eLibrary SPIN: 6309-3260;
e-mail: klinkinpark@mail.ru

Евгений Николаевич Гневышев, канд. мед. наук, доцент,
ORCID: 0000-0001-9671-462X; eLibrary SPIN: 9885-0260;
e-mail: evg-gnevyshev@yandex.ru

***Камиль Рабазанович Магомедов**, врач-невролог;
ORCID: 0009-0000-5649-2321; eLibrary SPIN: 8555-9957;
e-mail: Kmagomedov@gmail.com

* Corresponding author / Автор, ответственный за переписку