THE NEW ARMENIAN MEDICAL JOURNAL
Vol.13 (2019), No 3, p.49-56

EFFICACY OF COMBINATION NEUROPROTECTIVE DRUGS FOR INFERIOR ALVEOLAR NERVE EXPERIMENTAL TRAUMATIC NEUROPARTHY TREATMENT

Morozova M.N.[1], Demianenko S.A.[1], Kaliberdenko V.B.[2], Marchenko N.V.[1], Shabliy D.N.[1*], Mironova I.V.[1], Kirichenko V.N.[3]

S.I. Georgievsky Medical Academy, Federal State Autonomous Educational Institution of Higher Education "V.I. Vernadsky Crimean Federal University", Simferopol, Russia.

[1] Department of Dentistry and Orthodontics

[2] Department of Internal Diseases No 2

[3] Department of Surgical Dentistry and Maxillofacial Surgery

Received 15.05.2019; accepted for printing 16.01.2019

Abstract

Introductin. *Due to the changed nature of out-patient dental care the inferior alveolar nerve traumatic neuropathy has become a common complication in recent years. This is because of frequent use of the inferior alveolar nerve block with vasoconstrictors, higher use of various techniques for the alveolar ridge osteotomy and dental implants placement.*

Materials and methods. *The experiment was performed in 44 Wistar rats. Inferior alveolar nerve traumatic neuritis was modelled in all the animals. The animals were sacrificed in compliance with the requirements regulating the use of experimental animals at day 1, 3, 10, 30 and 90 by overdosing anesthesia.*

The slides were stained with hematoxylin-eosin and using the van Gieson method. Axis cylinders of nerve fibers and myelin sheaths were defined using E.I. Rasskazova's and Weigart-Pal methods. The succinate dehydrogenase and lactate dehydrogenase activity was assessed using the frozen section method of Nachlas M. and A.Pierse. Specialized microscopes MBI and PEM-100 were used for photographic documentation of the slides.

Results*. At post-surgery days 1, 3 and 10 inflammatory and reactive changes and increased circulatory disorders were found in all the slides. The most marked changes with signs of inflammation and edema in perineural tissues were observed in sub-group 2 during day 30.*

Events of edema became common and developed into dystrophy by day 30 in the second set of the experiment. Milgamma® helped to relieve the disorders. In sub-group 1-"c" the said signs were less pronounced and reversible due to the use of Cocarnit, in sub-group 2-"c" the said signs were not relevantly different.

By post-surgery day 90 in the first set of the experiment reparative processes in the injured tissues were most pronounced in the former suppurative inflammation area (sub-group 2). In group 1-"m" most animals manifested myelin fibers splitting.

By post-surgery day 90 in the second set of the experiment the animals treated with Cocarnit developed compensatory and regenerative disorders with signs of hardening along with dystrophy. Morphological changes suggestive of less pronounced tissue hypoxia as compared to the first set of the experiment were observed in subgroups 1-"m" and 2-"m" animals by day 90. Milgamma ® helped relieve dystrophic and destructive changes.

Conclusion. *The proposed combination therapy of traumatic neuritis facilitated the progress of reparative processes. It is found that Cocarnit is effective for regeneration of all types of fiber while Milgamma has positive effect on regeneration of only injured thin myelin and naked fibers.*

Keywords: *traumatic neuritis, morphological analysis, combination therapy, neuroactive agents.*

Introduction

One of the most common problems with the trigeminal nerve is inferior alveolar nerve (IAN) traumatic neuritis (TN) [*Goriansky Y et al., 2009; Morozova M et al., 2012*]. The TN incidence rate [*Kryzhanovsky G, 1997; Avdeyeva E., Pechursky A., 2007*) is 85% of all CNV3 neuropathy cases. Rising TN incidence is significantly associated with increased use of nerve block anesthesia for painless teeth preparation, increased out-patient surgical interventions in the regions in the vicinity of the man-

Address for Correspondence:
Dmytro M. Shabliy, PhD
Federal State Autonomous Educational Institution of Higher Education "V.I. Vernadsky Crimean Federal University", S.I. Georgievsky Medical Academy
Lenin boulevard 5/7, Simferopol 295000, Russia
Tel.: +7 978 857 59 99
E-mail: shabliy@bk.ru

dibular canal (wisdom teeth removal for orthodontic causes, dental implants placement, etc.) [*Grigoriants A et al., 2002; 2013; Piradov M et al., 2017*].

Pathomorphological changes emerging in the injured nerve fiber, clinical presentation and pathogenesis of the IAN TN have been covered widely enough. However, authors in their studies mainly focused on the processes resulting from complete rupture of the neurovascular bundle or caused by rough cicatricial neurothlipsia (including as a result of fracture consolidation) [*Shulesheva N, Vishnevsky AA, 2006; Timofeyev A, Vesova E, 2007; Kryukov K et al., 2008; Goriansky Y et al., 2009; Korobkeyev A et al., 2010*].

At the same time changes caused by a weak force insult (most unique to out-patient dental interventions) have not been studied enough [*Morozova M et al, 2013*].

Up to now scholarly literature lacks a clear view of the IAN TN clinical progression forms and respective drug therapy. There are known cases of mild traumatic neuritis with short-term transitory impaired sensitivity in the innervation region resolved without targeted treatment [*Shulesheva N, Vishnevsky A, 2006*]. Cases of traumatic neuritis with impaired sensitivity of the IAN-innervated tissues and pain component are described. This form of the IAN TN clinical progression is a problem for differential diagnosis (particularly in the setting of post-surgical course of a disease preceding traumatic neuritis) and requires the use of special approaches to the examination and treatment [*Turbina L 2002, Piradov V et al., 2017*].

The existing recommendations provide for the treatment of acute neuritis with anti-inflammatory, dehydration, sedative, antihistaminic and neuroactive drugs including B neurotropic vitamins. Moreover, a patient may take antibacterial and desensitizing drugs (subject to the cause of TN), thus combination therapy of 4-8 agents is required [*Nedzved M et al., 2013*].

If this is the case the patient may develop adverse reactions caused by the drugs interaction and experience significant discomfort. This is particularly so with out-patient clients. The recent studies show that the existing IAN TN treatment modalities need to be improved in the context of the newly discovered mechanisms of the disease pathogenesis and the latest achievements in pharmacotherapy [*Kril J, 2005; Ivanitskaya O, 2007; Timofeyev A, Vesova E, 2007*].

We see a possible solution to the problem in early (from day 1) use of the latest generation nonsteroidal anti-inflammatory drugs (NSAID) and combination neuroactive agents containing therapeutically effective doses of neurotropic drugs mutually potentiating one another with minimum frequency of drug administration. Many methods and modalities have been proposed to restore and recover the damaged structure and function of the nerve. Combination neuroprotective agents Milgamma and Cocarnit are highly recommended in the specialist literature [*Lutsky I, 2007, Matvienko Y, 2008*]. The difference between the drugs is that Cocarnit contains a complex of metabolic agents and neuroprotective vitamins while Milgamma includes B neurotropic vitamins only. However, a comparative experimental or clinical analysis of their efficacy [*Shabliy D, et al., 2013*] has not yet been covered enough in the newer specialist literature.

The study is meant to carry out a comparative assessment of the morphological changes in the nerve fiber resulting from the use of combination neurotropic drugs Milgamma and Cocarnit for the treatment of experimental inferior alveolar nerve.

Material and methods

Solution to the problems raised in this work to be found the experiment was performed in 48 white male Wistar rats. In our articles published earlier we described the ways of modelling IAN TN specific to dental practice [*Morozova M et al., 2012; 2013*]. The most severe nerve and nerve sheath damage was registered in two models we used in this work. In 24 animals (set 1 of the experiment) anesthetized intramuscularly with Ketamine (Moscow Endocrine Plant, Russia) (0.15-0.2 *ml*) a 10-12 *mm* long linear incision was made in the mandibular buccal cavity and a mucoperiosteal flap was detached in a blunt manner to reach the foramen and the neurovascular bundle. Then the sub-group 1 animals underwent the needling of the neurovascular bundle with a needle 0.3 *mm* in diameter and injection of Ultracainin DC forte, 0.1 *ml* (Aventis Pharma, Deutschland HmbH, Germany); in the sub-group 2 animals the neurovascular bundle was short-termly constricted with a hemostatic clamp. The mucoperiosteal flap

was placed back and fixed with surgical gut. No drug therapy was administered. The animals were sacrificed at day 1, 3, 10, 30 and 90 by overdosing anesthesia.

At stage two of the study (set II) the rats, upon modeling similar damages, were treated during the first two post-surgery days with Nimesil suspension (Laboratori GUIDOTTI S.p.A., Italy), 0,2 *ml* BID. From day 3 they were administered combination neuroactive agents Milgamma® (Solupharm Pharmazeutische Erzeugnisse GmbH, Germany) and Cocarnit (World Medicine Limited, Great Britain), 0,25 *mg*, IM during 6 days with subsequent comparative study of the reparative processes morphology. Subject to the drug tested the sub-groups in the set were marked "c" for Cocarnit and "m" for Milgamma. The animals were sacrificed at days 10, 30 and 90.

Upon dissection the block of tissues was immersed in 10% neutral formalin solution, desiccated in high-proof alcohol, clarified in benzol, embedded in paraffin and sliced. The slides were stained histologically with hematoxylin-eosin and using the van Gieson method. Axis cylinders of nerve fibers and myelin sheaths were defined using E.I. Rasskazova's impregnation method and stained using Weigart-Pal method.

The respiratory enzyme activity to be assessed frozen sections were sliced immediately upon the animals sacrifice. The succinate dehydrogenase (SDG) and lactate dehydrogenase (LDG) activity was assessed using the methods of Nachlas M et al., (1960) and A.Pierse (1962) respectively. Specialized microscope MBI -15-2 was used for photographic documentation of the slides.

Material for electronic microscopy was prepared using the generally accepted techniques. Ultrathin sections were stained with uranyl acetate and lead citrate using Reynolds' method. The sections were photographed in transmission electronic microscope PEM-100 (Quasi-S Pte Ltd, Singapure).

Results

The experimental animals were kept in a vivarium on routine feed, no fatal cases were registered, the surgical incisions healed by primary intention.

Next day after the surgery in set 1 of the experiment the morphological pattern of structural and functional changes evidenced pronounced edema and serofibrous upswelling. Necrobiosis and disorganized cells structure associated hemorrhage foci were observed. Circulatory disorders as well as damaged nerves and perineural tissues marginal traumatic degeneration were pronounced in the damaged tissues. Increased LDG activity anaerobic glycolysis was observed in all the slides.

By day 3 after the operation inflammatory and reactive changes and increased circulatory disorders were observed directly in the nerve and perineural tissues in all the slides. Round-cell and segmented leucocytes and free macrophages content in the transudate raced up. The most pronounced inflammatory and reactive changes were observed in the sub-group 2 animals. Signs of acute suppurative inflammation with leucocytes and macrophages at complete phagocytosis stage as well as necrobiotic changes in perineural tissues were observed in the trauma area. Paralytic dilatation and the nerve sheath vascular congestion with a stasis and hemagglutination component were detected in the distal section from the damage site. Transcapillary transport disorders associated with disorganized intracellular organelles of endotheliocytes, basal membrane and pericytes as well as emergence of multiple macropinocytotic vesicles were found.

Decreased activity of the aerobic cellular respiration enzymes in all perineural structures, muscular and connective tissues as well as in the vascular walls with morphological signs of misperfusion was highly pronounced. In both the sub-groups the transverse sections of the nerve fiber myelin sheaths were relatively intact in terms of their structure.

In the slides stained for myelin the nerve stem sheath changes manifested themselves as edema and trachery elements upswelling. The perineural sleeve was significantly dilated suggesting intrastem edema. In sub-group 2 periaxonal edema phenomena including tortuosity, varixes and axoplasm deposits in the axial cylinders were more pronounced (Fig. 1).

At the ultrastructural level in sub-group 2 the endoneurium associated edema phenomena manifested themselves in the separate nerve fibers splitting accompanied by focal sponginess of facia fibrils with their fragmentation and loss of the myelin sheath outer contours sharpness (Fig.2).

By day 10 in sub-group 1 inflammatory edema

and associated circulatory disorders in tissues reduced significantly. Massive fields of granulation tissue with clearly oriented capillaries developed in the trauma site in both the groups. Signs of moderate tissue hypoxia persisted as evidenced by increased LDG activity and reduced SDG activity.

In sub-group 2 these fields were circled by heavy leucocytic infiltrates with pronounced signs of suppurative inflammation. Edema, stasis and diapedetic hemorrhage persisted in some sites of these fields. Microcirculatory disorders were associated with swollen endothelial cells edema, dilatation and sponginess of intercellular structures, loss of the basal membrane contours sharpness and plasmorrhagia of the capillary walls, precapillary and venous blood vessels walls. Upswelling and fragmentation of the nerve stem sheath trachery elements was observed along with the signs of intrastem edema in the form of the perineural sleeve dilatation. Decrease in the succinate dehydrogenase activity continuing until its total disappearance along with significantly increased lactate dehydrogenase activity persisted.

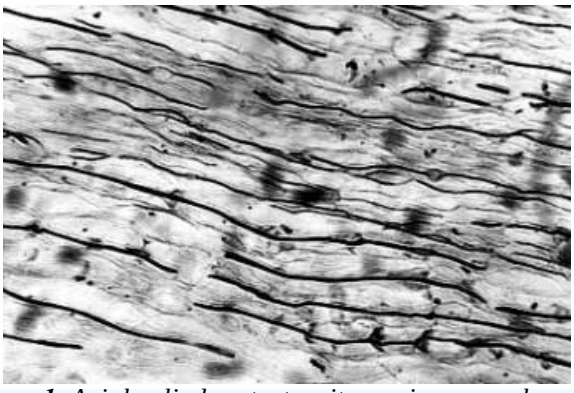

Figure 1. *Axial cylinders tortuosity, varixes, axoplasm deposits. Day 3, set I, sub-group 2. E.I. Rasskazova's impregnation method. Magnification x 200.*

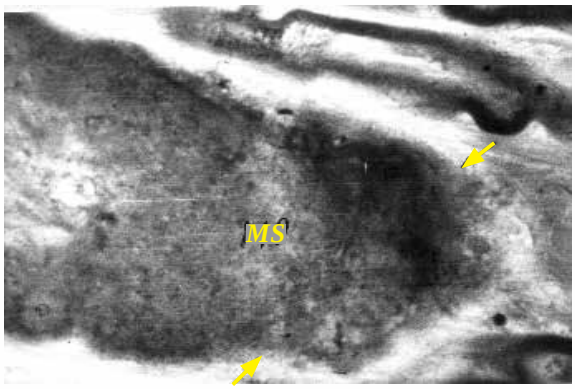

Figure 2. *Endoneurial edema-loss of the nerve myelin sheath (MS) outer contours (arrows)sharpness. Day 3. Set II. Sub-group 2.. Magnification x 30000..*

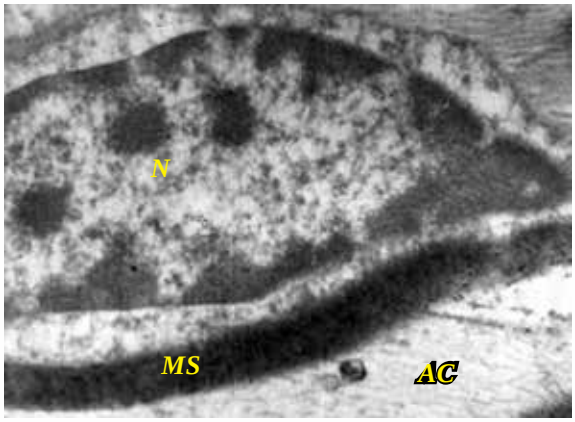

Figure 3. *Myelinated nerve fibers (N – nucleus, MS – myelin sheath, AC – axis cylinder). Set I. Sub-group 2. Day 10. Electronic microphoto. Magnification: 9000.*

Most of the naked fibers retained their structure with total absence of any changes in the peri- and endoneurium. Irritation signs such as uneven impregnation, neuroplasm deposits, tortuosity and Ranvier's nodes dilatation prevailed in axial cylinders (Fig. 3).

Discussion

Due to the pronounced inflammatory and reactive changes in the nerve fiber and perineural tissues found in the sub-group 1 and sub-group 2 animals immediately after the nerve trauma from day 1 after the surgery the set II animals were administered neuroactive drug therapy with Cocarnit and Milgamma ® and a NSAID Nimesulide.

By day 10 after the trauma in the second set of the experiment (sub-groups 1-"m" and 1-"c") moderate edema and fibroblasts proliferation were detected microscopically. Inflammatory cells were absent or singular, mostly round-cell leucocytes. Specifically, the fiber fragmentation and collagen disorder signs observed in set I were next to absent and the serofibrous impregnation zone reduced significantly.

Circulatory disorders were less pronounced, developed focally, mostly in postcapillary vessels and small veins and manifested themselves as vasodilation and plethora. Sludge, diapedetic hemorrhage and clotting were absent or developed focally in the traumatic degeneration areas.

In sub-groups 2-"m" and 2-c" by day 10 inflammatory edema and circulatory disorders in perineural tissues were more pronounced than in subgroups 1-"m" and 1-"c" but less severe that in set I (no treatment). Stasis and diapedesis, edema and

epithelial cells upswelling persisted. Microcirculatory disorders manifested themselves as focal capillary vasodilation, plethora and hemagglutination in dilated postcapillaries and small veins.

Reduced circulatory disorders in the animals under treatment significantly relieved tissue hypoxia in perineural tissues as evidenced by the preserved activity of the aerobic respiration enzyme SDG in both the sub-groups of set II. Complete inactivity of the enzyme was not observed or it occurred in traumatic degeneration regions. Certain mosaicism of the succinate dehydrogenase enzyme pattern testified to a focal nature of tissue hypoxia as evidenced by moderate activation of the lactate dehydrogenase enzyme the content of which increased in perineurium and serous impregnation areas.

Immediately in the trauma region in sets 2-"m" and 2-"c" there was found granulation tissue in which polymorphonuclear leucocytes were identified. Cell elements overweighed fibers. Granulation tissue foci were detected in the trauma region but their size was significantly less than in sun-group 2 at stage 1 of the study. There were no leucocytic infiltrates around these foci. Perineural sleeve dilatation due to the neural trunk edema and upswelling was insignificant.

By day 30 the animals in set I manifested reduced circulatory disorders in traumatic tissues. In both the sub-groups the forming healing tissue consisted of rough, orthochromatically stained collagen fibers with singular fibroblasts and fibrocytes. Around the newly formed granulation tissue in place of the former or persisting suppurative inflammation sites (sub-group 2), mostly in the postcapillary vessels, collagen fibers plethora, stasis, upswelling and disorganization persisted. Prominent vessel wall involution in the healing tissue was observed. Singular capillaries and vessels the wall of which contained 1-2 layers of smooth muscle elements were present. Incomplete fibrillogenesis foci, spongy polymorphocellular infiltrates, postcapillary vessels plethora and perivascular edema were present in the suppurative inflammation sites.

Moreover, by day 30 the animals in both the sub-groups and particularly in sub-group 2 manifested endoneural and perineural thickening as a result of increased collagenosis and fibroblast proliferation often in the shape of a chain (Fig. 4).

At this stage in sub-group 2 nerve fiber degeneration phenomena prevailed. They were present in most axial cylinders and fiber myelin sheaths. Coagulative necrosis, fragmentation and crumbly necrosis were often detected in axial cylinders (Fig. 5).

Destructive changes in the form of partial or complete breakdown of the myelin sheath visible in transverse sections prevailed in the myelin nerve fibers in sub-group 2 (Fig 6).

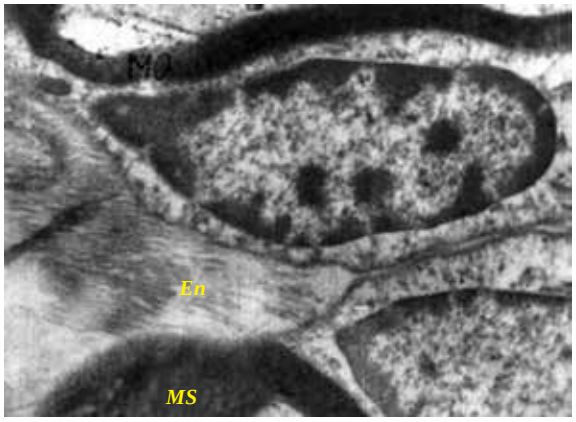

Figure 4. *Changes in perineural cells and endoneurium (MS –myelin sheath, En – endoneurium). Set I. Sub-group 2, day 30. Magnification: 5000.*

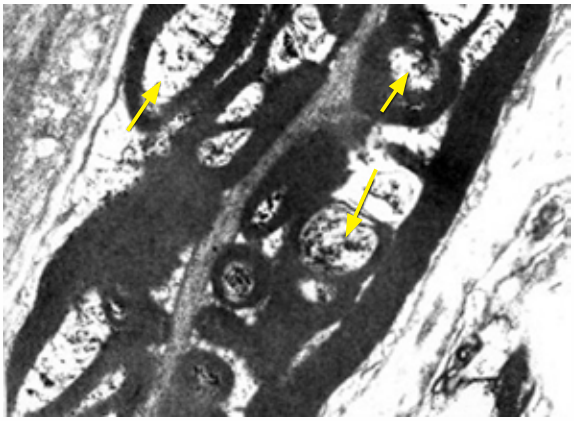

Figure 5. *Clearing islets with separation and fragmentation of myelin fibers (arrows) in the myelin sheath. Set Set I. Sub-group 2. Day 30. Magnification: 10000.*

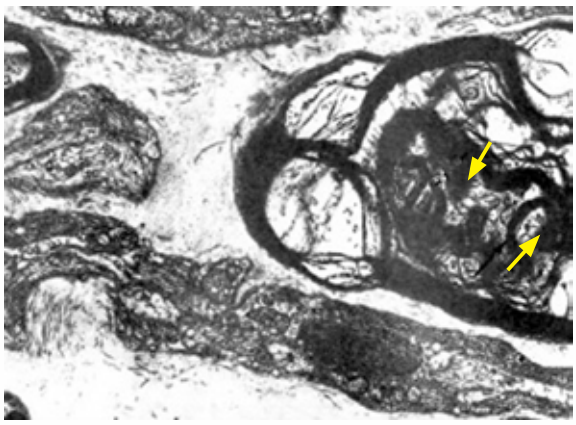

Figure 6. *Newly-formed myelin sheath(arrows) islets in the demyelinated nerve fiber. Set I. Sub-group 2. Day 30. Magnification: 6000.*

The ultrastructure study detected densely packed myelin sheath fibrils, focally split and with lucent spots of various size. Centrally-directed cone-shaped bulges representing one or several myelin fibrils stripped off by the transudate were detected as well. The axial cylinder was found separated from the myelin sheath. Signs of steatosis in the form of rounded homogenous inclusions of moderate electron density were found in fibers.

In some cases, the internal membrane was found devoid of its integrity with partially fragmented split osmiophil fibrillous structures inside lacunae.

Due to the rupture of released osmiophil myelin membranes the transudate penetrated into the axial cylinder and caused sponginess and disintegration of neurofilaments and emergence of electrooptically transparent irregular spots with blurred outlines.

In set two of the experiment by day 30 following the damage perineural fibrosis in the nerve sheath as a result of the fibroblasts proliferation was observed in sub-group 1-"m" (under treatment with Milgamma®) (Fig. 7)

Neurofibrils splitting and sponginess accompanied by mitochondrial edema and upswelling with focal lucent spots in their matrix, mitochondrial cristae reduction and decompensation was observed in the inferior alveolar nerve naked fibers (Fig. 8). Phenomena of edema proliferate and gradually give way to dystrophic changes.

With the use of Cocarnit in sub-group 1-"c" the aforesaid changes grew less prominent and were detected against the background of the mitochondria with retained ultrastructural organization. Most of the naked nerve fibers retained their structure with virtually total absence of any changes in peri- or endoneurium. These facts may evidence particular increased resistance of nerve fibers to damaging factors as far as the changes described are reversible and mostly reactive.

With the use of Cocarnit in sub-group 2-"c" the ultrastructural changes did not differ relevantly from the outcomes in the control group.

The use of Milgamma® in sub-group 2-"m" resulted in significantly reduced manifestations of hydropic dystrophy on the background of insignificant changes in the lemmocyte nucleus, fine-focal changes in the cytoplasm were few.

By day 90 after the surgery in set I of the experiment reparative processes in the traumatic tissues manifested themselves as further induration, blood vessels involution and fibrous and sclerotic changes. The latter were most prominent in the former suppurative inflammation sites (sub-group 2). Rough collagen fibers get partially homogenized and undergo hyaline degeneration. Fibroblastic cells and polymorphonuclear leucocytes grow in number in a distal direction. Specifically, the healing tissue proliferated to the adjacent muscles. Large sclerotic fields with split and dystrophic muscle bundles as well as thick intermuscular connective septum developed in the muscles.

Animals in both the sub-groups developed increased edema of myelin nerve fibers associated with neurofibrils sponginess, mitochondrial upswelling with focal lucent spots in their matrix, mitochondrial cristae reduction and decompensation. Variably sized lacuna- and vacuole-shaped buildups emerged between neurofibrils apparently as a result of intraneural edema.

The manifestations described may be treated as

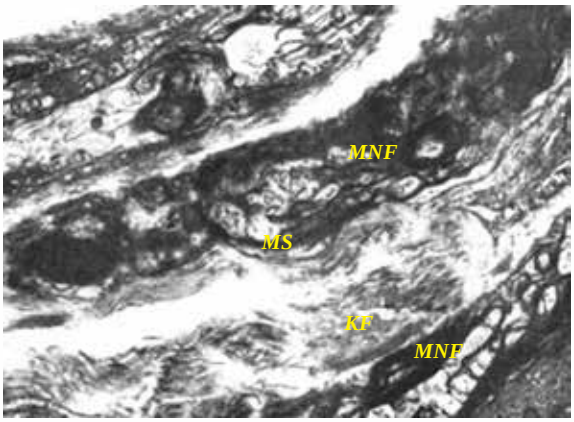

Figure 7. *Proliferation of the endoneurial collagen fibers (KF) between myelin nerve fibers (MNF). MS – myelin sheath. Set II. Sub-group 1. Day 30. Magnification: 6000.*

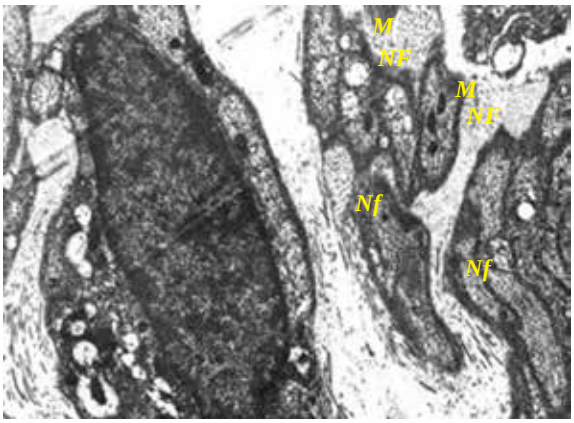

Figure 8. *Neurofibrils (Nf) sponginess and mitochondrial (M) edema in naked nerve fibers (BM). Set II. Sub-group 1-"m". Day 30. Magnification x 6000.*

demyeliniation and hydropic dystrophy. Similar changes occurred in lemmocytes while ultrastructural changes in the neucleus were relatively insignificant, pronounced changes developed in the cytoplasm. Fine- and large-focal lucent sports including in the form of vacuoles were accompanied by mitochondrial edema and upswelling, mitochondrial cristae reduction and highly pronounced lucency of their matrix, endoplasmic reticulum tubules dilatation and emergence of multivesicular formations.

Naked fibers showed steatosis manifested as rounded homogenous inclusions of moderate electron density (Fig.9). No signs of neurilemma cells proliferation. Collagen fiber proliferation as well as pronounced perineural and perivascular sclerosis were observed along the nerve and in the adjacent cellular tissue.

At day 90 of the experiment in sub-group 1-"m" of the experimental set there was noted multiple separation of densely located highly osmiophilic myelin fibers accompanied by formation of round islets with fragmented and partially homogenized fibers contained in the center.

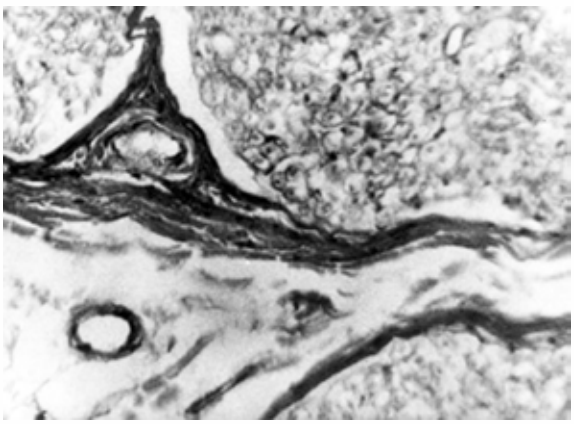

Figure 9. *Perivascular proliferation of connective tissue. Set I. Sub-group 2. Day 90. Van Gieson's stain. Magnification: 200.*

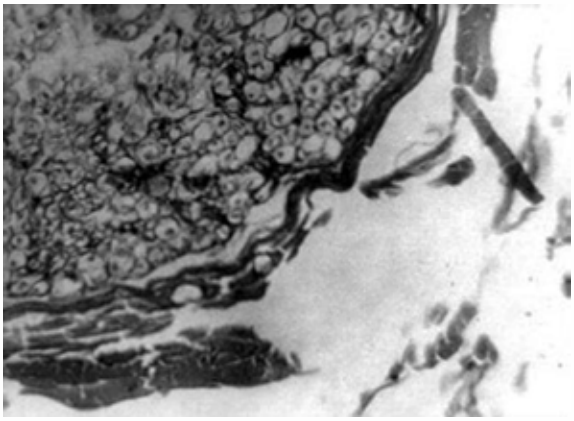

Figure 10. *Perineurium thickening due to fibroblasts proliferation and increase in collagen fibers. Set II. Sub-group 1. Van Gieson's stain. Magnification: 160.*

By day 90 in the second set of the experiment animals in sub-group 1-"c" developed compensatory and regenerative changes along with the above described dystrophic and destructive ones in fibers. Signs of remyelination evidenced by the emergence of newly-formed myelin sheath were observed.

In sub-group 1-"m" by day 90 the animals manifested morphological changes evidencing the presence of chronic tissue hypoxia (though less pronounced as compared to set 1 animals). Fibrosis of various intensity was found in epi-, peri- and endoneurium in next to all cases as manifested in proliferation of reticular and collagen fibers (Fig.10).

In sub-group 2 by day 90 the use of Milgamma® resulted in substantial decrease of hydropic dystrophy manifestations on the background of insignificant changes in the lemmocytes nuclei, fine-focal changes in the cytoplasm were few. Along with dystrophic and destructive changes there were regions of newly-formed myelin sheath (remyelination) in a number of fibers.

In sub-group 2-"c" (under treatment with Cocarnit) by day 90 manifestations of the axial cylinder sclerosing in myelin nerve fibers were observed. Endo- and perineurium thickening occurred as well.

Thus, comparative study of microstructural aspects of the inferior alveolar nerve inflammation and regeneration in the context of early post-surgery administration of nonsteroidal anti-inflammatory drugs and neuroactive agents has proven their efficacy. It has also been found out that the use of Cocarnit is most effective for regeneration of all types of fiber while Milgamma manifests pronounced positive effect on regeneration of traumatic thin myelin and naked fibers.

Conclusions: 1. It is prudent and advantageous to administer Cocarnit to reduce consequences of a fine-needle traumatic injury with further injection of Ultracainini forte solution (Articaine + vasoconstrictor) into the neurovascular bundle, interventions made for severe dystrophic and cicatrical changes treatment and prevention.

2. In the experimental set of animals exposed to short-term compression of the neurovascular bundle in treatment and prevention of severe dystrophic and cicatrical changes Milgamma showed the best effect.

REFERENCES

1. *Avdeyeva EA, Pechursky AI.* [Cause-specific trigeminal traumatic neuritis incidence] [Published in Russian]. Materials of the III Congress of Maxillofacial Surgeons of the Republic of Belarus-Vitebsk: VSMU. 2007; 91-93.
2. *Goriansky YI, Son VE, Stoyanov AN.* [Revisiting Diagnosis and Treatment of Facial Pain] [Published in Russian]. International Neurological Journal. 2009; 5: 61-63.
3. *Grigoriants AA, Badalian VA, Tomazov MV.* [Medical tactics upon pain syndrome caused by the stopping material filling in the inferior dental canal] [Published in Russian]. Essence. 2002; 2(1-2): 15-18.
4. *Ivanitskaya OS.* [Facial nerve peripheral injury treatment with embryofetoplacental complex products] [Published in Russian]. Extended abstract of Cand. Sci. (Medicine) Dissertation: Major 14.01.22 "Dentistry". Poltava. 2007; 20.
5. *Korobkeyev AA, Sirak SV, Kopylova IA.* [Study of the lower jaw anatomic and topographic structure features for planning endodontic and implantological treatment] [Published in Russian]. Medical Bulletin of the North Caucasus. 2010; 1: 7-22.
6. *Kril JJ.* Neuropathology of thiamine deficiency disorders. Metabolic Brain Disease. 2005; 11(1): 9-17.
7. *Kryukov KI, Reva GV, Edranov SS, Kotsyurbiy EA.* [Dynamics of the trigeminal ganglion neurons structural changes caused by the maxillary nerve compression trauma in rats] [Published in Russian]. Experimental Biology and Medicine Bulletin. 2008; 145(5): 597-600.
8. *Kryzhanovsky GN.* [General pathophysiology of the nervous system] [Published in Russian]. M.: Medicine. 1997; 345.
9. *Lutsky IS.* [B vitamins in clinical practice] [Published in Russian]. International Neurological Journal. 2007; 2(12): 115-122.
10. *Matvienko YO, Bozhenko NL.* [Facial nerve neuropathy: View of the problem [Published in Russian]. World Medicine. 2008; 2: 53-61.
11. *Morozova MN, Kaliberdenko VB, Shabliy DN.* [Morphological changes in the modelled inferior alveolar nerve trauma of various severity] [Published in Russian]. Tavria Medical and Biological Bulletin. 2012; 2(15): 154-157.
12. *Morozova MN, Shabliy DN, Kaliberdenko BV.* [Ultrastructural changes in the nerve fiber studied on the experimental model of acute inferior alveolar nerve trauma] [Published in Russian]. Tavria Medical and Biological Bulletin. 2013; 3(16): 87-91.
13. *Nedzved MK, Pokhodenko-Chudakova IO, Vilkitskaya KV.* [Morphological changes and laboratory test values in case of distal n. trigeminus traumatic toxic damage] [Published in Russian]. Medical Journal. 2013; 4(46): 27-31.
14. *Piradov MA, Maksimova MY, Sineva NA.* [Herpes zoster-induced painful trigeminal neuropathy] [Published in Russian]. Case study. 2017; 11(1): 62-64.
15. *Shabliy DN, Morozova MN, Kaliberdenko VB.* [Experimental morphological assessment of combination neuroprotective drugs' efficacy for inferior alveolar nerve traumatic neuritis treatment in the long term] [Published in Russian]. Current topics of the present-day medicine: Ukrainian Medical and Dental Academy. 2013; 4(44): 196-200.
16. *Shulesheva NV, Vishnevsky AA.* [Brain stem: clinical presentation and pathophysiological comparison] [Published in Russian]. Saint Petersburg. 2006; 220.
17. Timofeyev A.A., Vesova E.P. [Integrity-sparing surgical treatment of CNV3 peripheral neuralgia] [Published in Russian]. Modern Dentistry. 2007; 1: 80-82.
18. *Turbina LG.* [Revisiting facial pains classification] [Published in Russian]. Russian Dental Journal. 2002; 3: 44-45.