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Abstract

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MODERN METHODS OF SURGICAL TREATMENT OF PERIPHERAL NERVOUS SYSTEM INJURIES

Relevance. In Ukraine, 2,500–3,000 people sustain peripheral nerve injuries every year. Often these are young people of working age. In the structure of total injuries, peripheral nerve damage in peacetime makes 1.5–6%, and during military operations (taking into account the situation in the east of Ukraine), this value ranges from 9 to 25% due to gunshot injuries.

Purpose and objectives: selection of the most optimal surgical treatment option for peripheral nerve trauma by comparing the results of studies from literature sources.

Materials and methods. Analysis of medical literature and publications over the past five years was carried out, with due attention to the studies related to modern surgical treatment methods of peripheral nerve traumatic injuries.

The problem of surgical treatment has not been thoroughly studied. Peripheral nerve regeneration is a complex process, and therefore the existing treatment methods are limited due to slow nerve regeneration and insufficient spanning of large post-traumatic nerve defects. To overcome these limitations, a cell therapy has been developed that ensures the presence of supporting cells at the site of the lesion in order to accelerate nerve regeneration. Schwann cells play an important role in many aspects of nerve regeneration. Stem cell transplantation for peripheral nerve regeneration represents alternative cell therapy with several regenerative benefits. Various types of stem cell sources are currently being investigated for use for peripheral nerve regeneration in combination with the most optimal nerve guide conduit.

Key words: autoplasty, nerve grafts, nerve conduits, peripheral nerves, surgical restoration of nerve structure.

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Резюме

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СУЧАСНІ МЕТОДИ ХІРУРГІЧНОГО ЛІКУВАННЯ ТРАВМ ПЕРИФЕРИЧНОЇ НЕРВОВОЇ СИСТЕМИ

Актуальність. В Україні щороку травми периферичних нервів отримують 2,5–3 тис. осіб, частіше це молодий працездатний вік. У структурі загального травматизму ушкодження периферичних нервів у мирний час складає 1,5–6 % , а під час військових дій (беручи до уваги дану ситуацію на Сході України) за рахунок вогнепальних пошкоджень кількість коливається в діапазоні 9–25 %.

Мета та завдання: вибір найоптимальнішого варіанту хірургічного лікування при травматичному ушкодженні периферичного нерва шляхом порівняння результатів досліджень літературних джерел.

Матеріали та методи. Було проведено аналіз медичної літератури та публікацій за останні п’ять років, із приділенням уваги дослідженням, що стосувались сучасних методик хірургічного лікування травматичних ушкоджень периферичних нервів.

Проблема хірургічного лікування є остаточно не вирішеною, регенерація периферичних нервів – складний процес і тому існує обмеження існуючих методів лікування повільною регенерацією нервів та недостатньою наповненістю великих посттравматичних нервових дефектів. Щоб подолати ці обмеження, була розроблена клітинна терапія, що забезпечує наявність підтримуючих клітин в місці ураження з метою прискорення регенерації нервів. Шванівські клітини відіграють важливу роль у багатьох аспектах регенерації нервів. Трансплантація стовбурових клітин для регенерації периферичних нервів пропонує альтернативну клітинну терапію з декількома регенеративними перевагами. В даний час досліджуються різні типи джерел стовбурових клітин на предмет їх застосування для регенерації периферичних нервів в поєднанні з найоптимальнішим нервовим провідником.

Ключові слова: аутопластика, нервові трансплантати, нервові канали, периферичні нерви, хірургічне відновлення структури нервів.

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Introduction

Traumatic injuries of the peripheral nervous system (PNS) are not only a medical, but also an extremely important social problem because they are characterized by a significant prevalence, severity of consequences that lead to disability and require significant effort and technical support for recovery.

The incidence of PNS injuries in advanced countries ranges from 0.3 to 0.5 per 10,000 population. In Ukraine, 2,500–3,000 people sustain peripheral nerve injuries every year. Often these are young people of working age. In the structure of total injuries, peripheral nerve (PN) damage in peacetime makes 1.5–6%, and during military operations (taking into account the situation in the east of Ukraine) this value ranges 9 to 25% due to gunshot injuries.

PN injuries rank high among causes of disability, leading to permanent disability in 28–75% of patients.

Open injuries account for the majority of PN injuries (80–85%), stab and cut wounds account for about 70–75%. Closed PN injuries are characterized by compression-ischemic and traction mechanism of damage. Upper limb injuries account for 77% of PN damage cases, and lower limb injuries account for 23% of cases [1].

The purpose and objectives: to determine the most optimal surgical treatment option for peripheral nerve trauma by comparing the results of studies from literature sources.

Materials and methods. Analysis of medical literature and publications over the past five years was carried out, with due attention to the studies related to modern methods of surgical treatment of peripheral nerve traumatic injuries.

The problem of surgical treatment has not been thoroughly studied. Peripheral nerve regeneration is a complex process, and therefore the existing treatment methods are limited due to slow nerve regeneration and insufficient spanning of large post-traumatic nerve defects – nerve gaps [2].

To overcome these limitations, a cell therapy has been developed that ensures the presence of supporting cells at the site of the lesion in order to accelerate nerve regeneration. Schwann cells play an important role in many aspects of nerve regeneration. Stem cell transplantation for peripheral nerve regeneration represents alternative cell therapy with several regenerative benefits. Various types of stem cell sources are currently being investigated for use for peripheral nerve regeneration in combination with the most optimal nerve guide conduit.

Methods of peripheral nerve suturing.

Perineural suturing is a method of joining peripheral nerves, with suturing performed through the perineurium of individual nerve fascicles.

Interfascial suturing is a method of joining peripheral nerves, with adjacent nerve fascicles sutured together via connective tissue.

Epineural suturing (end-to-end suturing) is a method of joining peripheral nerves, with epineural suturing of two disjoined nerve ends and the fascicles joined in a chaotic order. Such suturing leads to excessive nerve tension. Techniques that can help reduce nerve gaps, thereby reducing tension at the repair site: general nerve mobilization, nerve transposition, limb flexion. Nerve transposition provides an additional length of several centimeters. Limb flexion can also provide additional length, while the limb has to be immobilized for some time, and then it is necessary to extend it gradually [13].

End-to-side suturing.

Principle of method: joining of the distal fascicles of the damaged nerve with the lateral fascicles of a healthy nerve by means of perineural sutures; before suturing, epineuria has to be removed on both nerves at the sites of the future joining.

During surgical intervention:

1) reliable signs of the complete destruction of the proximal nerve as a result of injury are identified; cross-section of the distal part within the intact fascicles is performed;

2) registration of the size, number, localization and sections of nerve fascicles is carried out; the fascicles at the end of the nerve are disconnected to allow access by removing external epineurium;

3) for future suturing the site is determined on a healthy nerve: in the determined area, the external epineurium is removed to expose the appropriate number of fascicles required for cross-linking with the damaged nerve fascicles;

4) PN has a cable-like structure, where epineurium is the outer coating that surrounds a set of fascicles running parallel to the long axis of the "cable", with each fascicle covered with perineurium;

5) when removing epineurium, the number of exposed fascicles is usually less than the number of fascicles in the distal part of the damaged nerve because manipulations are possible only on the surface fascicles; this factor leads to decreased nerve recovery level;

6) in order to involve all the fascicles of a healthy nerve that are necessary before suturing, a thread is passed through the epineurium on both sides of the site; the ends of the thread are strained, thereby reducing the distance between the punctures of the epineurium, and as a result, the superficial fascicles take the form of an outward arc and provide access to fascicles that are located deeper [14].

Side-to-side suturing. The first step is to find a trunk of a donor nerve with a similar function located close to the damaged nerve. Then place the donor nerve close to the damaged nerve. For example, if the lower trunk of the brachial plexus is damaged, the ulnar and median nerves are sutured "side-to-side". Depending on the thickness of the nerves, the epineurium and partially the perineurium are longitudinally dissected. The length of the dissection is 1–2 cm.

Stages of suturing:

1 - longitudinal dissection of epineurium of the nerves being sutured;

2 - interrupted suture of the epineurium of the posterior wall of anastomosis;

3 - dissection of the perineurium on adjacent fascicles of sutured nerves;

4 - posterior wall perineurium suture;

5 - anterior wall perineurium suture;

6 - interrupted suture of the epineurium of the anterior wall of anastomosis;

Side-to-side nerve suturing has only one limitation – no donor nerve in close proximity [15].

Neurolysis is a surgical intervention, which aims to release the nerve from the scar tissue that causes its compression. Most often, it is a blunt injury of a nerve or a bone fracture located next to the nerve. Surgery is performed under the microscope. Cicatricial adhesions and tissue compressing the nerve are dissected with a scalpel in accordance with the nerve projection. Abnormal tissue is removed in its entirety. Anatomical conditions that promote nerve regeneration are created [13].

Autoneuroplasty is a type of restoration of a damaged nerve, when the ends of the peripheral nerve are joined with excessive tension and are used as interposition autologous nerve grafts.

Nerve grafts can be single, cable, trunk, interfascicular, or vascularized.

A single graft is used to join the damaged nerve with a segment of a donor nerve of a similar diameter.

Cable grafts are used to span gaps between large diameter nerves, comprising multiple lengths of a smaller diameter donor nerve to approximate the diameter of the injured nerve.

Interfascicular nerve graft: strands of the grafted nerves are interposed between carefully dissected groups of fascicles in the damaged nerve, creating direct pathways between fascicles for regeneration.

A vascularized nerve graft is a donor nerve that is transposed with its arterial and venous supply into the graft site. Vascularisation allows a nerve graft to avoid the initial period of ischaemia and ensures continuous nutrition of the graft. Intraneural fibrosis is avoided, and axonal regeneration and target connectivity is enhanced.

An autologous nerve graft, that is, a nerve of one's own body, fulfill the criteria for an ideal nerve conduit because they provide a permissive and stimulating scaffold including Schwann cell basal laminae, neurotrophic factors, and adhesion molecules.

An autograft is a functioning nerve (sensory) used to replace a defect of a more important damaged nerve (usually motor). Donor nerve grafts are harvested from expendable sensory nerves, including the sural and medial antebrachial nerves [1].

Disadvantages of autotransplantation: sensory loss and scarring at the donor site and potential for neuroma formation [3].

Cellular therapy serves for the restoration of a PNS defect using the Schwann cells.

Restoration in the peripheral nervous system (PNS) depends on the plasticity of myelinating cells, the Schwann cells, and their ability to differentiate, create axon growth, remyelinate, and restore damaged nerve function.

Schwann cells are PNS glial cells that fall into highly specialized myelinating and non-myelinating cells. When a nerve is damaged, they retain the ability to return to an undifferentiated phenotype. Schwann cells fill the empty endoneurial tubes in organized longitudinal columns called bands of Bungner. The Schwann cells phagocytose axonal and myelin debris until empty endoneurial tubes remain. Macrophages are recruited to the area releasing growth factors, which stimulate Schwann cell and fibroblast proliferation. Plasticity of the Schwann cells is regulated by a complex array of signaling pathways and transcription factors that are activated within Schwann cells in response to injury. They are extracellular-regulated kinase 1/2 (ERK1/2), p38 mitogen-activated protein kinase (MAPK) pathways, and transcription factors c-Jun and Sox2 as regulators of Schwann cell plasticity and PNS repair [3].

Role of p38 mitogen-activated protein kinase (MAPK) and extracellular-regulated kinase 1/2 (ERK1/2)

Mechanical insult to the peripheral nerve initiates a cascade of molecular events in the distal nerve stump that results in myelin degeneration followed by differentiation and proliferation of the Schwann cells. The Schwann cell injury response is accompanied by rapid and sustained activation of the ERK1/2 and p38MAPK pathways.

ERK1/2 (extracellular signal-regulated protein kinase) pathway is activated in the distal stump of the damaged nerve within minutes after damage. Inhibition of this kinase activity using a pharmacological inhibitor blocked injury-induced Schwann cell differentiation and delayed downregulation of the myelin proteins. A study by Napoli et al. demonstrated that the ectopic ERK1/2 activation was sufficient to trigger myelin breakdown, differentiation, and proliferation of Schwann cells in the absence of nerve injury. ERK1/2 activation was sufficient to induce other responses associated with nerve injury and repair. This study strongly indicates that the Schwann cell ERK1/2 activation serves as the signal that initiates the Schwann cell injury response and places the Schwann cell as the key orchestrator of the repair

process in the adult PNS. In addition, another possible upstream activator of ERK1/2 is the Notch receptor on the Schwann cell surface.

P38 MAPK activity has also been shown to increase in Schwann cells of the distal stump after nerve injury. Inhibition of kinase activation preserves the distal myelin and attenuates differentiation of denervated Schwann cells in culture, whereas ectopic activation is sufficient to drive Schwann cell differentiation in vitro. Transcription factor c-Jun promotes the generation of a repair-competent Schwann cell or Bungner cell after injury. AP-1 transcription factor c-Jun is upregulated after injury and plays a significant role in the regeneration of neurons. Schwann cells lacking c-Jun are unable to take on the repair cell state after the loss of contact with axons.[6].

Sox2 (SRY-Box Transcription Factor 2) is one of the groups of transcription factors that induce pluripotent stem cells (SC) from adult somatic cells. During development, Sox2 is expressed in immature Schwann cells, and the expression decreases as the Schwann cell begin to differentiate and form myelin. In adults, PN expression of Sox2 is reactivated in the Schwann cells after injury. For repair, it is necessary to form a "nerve bridge" across the gap to guide the growth of the proximal axons into the distal stump. Parrinello et al. have shown that this process is mediated by EphrinB-EphB2 signaling between the Schwann cells and nerve fibroblasts that initiate Sox2-dependent Schwann cell sorting via relocalization of N-Cadherin, and collective migration out of the transected nerve stumps. This finding highlights the importance of Sox2 in promoting the nerve repair function of adult Schwann cells.

It has been estimated that only 10% of adult patients with nerve transection injury will recover full function even with the suturing together of the nerve ends. Increasing the repair potential of the Schwann cells by targeting the components of the MAPK pathways may prove useful for facilitating myelin clearance and axon regeneration [4].

Peculiarities of restoring the peripheral nervous system using stem cells

Stem cells can differentiate into Schwann cells, which involve macrophages to remove non-viable cells. They can also secrete neurotrophic factors such as nerve growth factor and neurotrophic factor that promote axon growth and remyelination [5].

Stem cells used to repair nerves include embryonic stem cells (ESC), neural stem cells (NSC), bone marrow stem cells (BMSC), adipose tissue stem cells (ADSC), stem cell originating from skin-derived precursors (SKP-SC), fetal stem cells, hair follicle stem cells (HFSC), dental pulp stem cells (DPSC), muscle-derived stem/progenitor cells (MDSPC), induced pluripotential stem cells (IPSC).

The Schwann cells, bone marrow mesenchymal stem cells (BMSC), ADSC, and pluripotent stem cells are the main cell types used in scientific research. The importance of SC is conditioned by their versatility in the development and regeneration of the nervous system. They play a crucial role in nerve regeneration by producing neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor, platelet growth factor, and neuropeptide Y. In addition to being a source of growth factors, stem cells are capable of proliferation, immunomodulation, remyelination, and migration [6].

Methods of implanting stem cells into the area of damage

Microinjection into a damaged nerve ending can be traumatic for both stem cells and neural architecture, leading to abnormal cell division and neuroma formation. Delivery directly to the neural tube: this method is technically more complex for cell delivery. Three-dimensional printing aims to create tissues with multiple cell types inside the framework to mimic native tissue and is also the most advanced step in the development of methods for restoring damaged PN. Three-dimensional printing technology can provide the desired geometry, such as multi-conduit, branched and personalized structures, allowing adjusting the nerve guide conduit (NGC) that exactly matches the specific defect of the patient's damaged nerve [5].

Aspects of nerve guide conduits.

Nerve conduits serve as a bridge between the proximal and distal stumps of the damaged nerve, and are the framework for axon regeneration. The most important advantage of conduits is the ability to provide an ideal microenvironment for neuronal repair. An ideal nerve conduit should have properties such as biocompatibility, permeability, flexibility, biodegradability, malleability, neuroinductivity, and neuroproductivity.

Nerve guide conduits are divided into two groups depending on their structural materials: biological and synthetic. Biological nerve conduits are divided into autogenic and non-autogenic. These biomaterials are widely used to repair minor (<3 cm) nerve injuries [16].

Autogenic biological conduits include vena cava, arterial vessels, and soft tissues, including muscle and tendon grafts. Venous conduits are the best biological conduits.

The problem with muscle grafts is that regenerating axons are not contained in the graft and can form neuromas.

Non-autogenic biological conduits made of type I, III or IV collagens and available for clinical use. Animal studies with collagen "tubes" have shown equivalent efficacy compared to an autograft, but there are no clinical studies [7].

Synthetic nerve conduits include degradable and non-degradable conduits. Non-degradable nerve conduit materials include silicone, elastomeric hydrogel, and porous stainless steel. Degradable materials for nerve conduits are made of collagen, complex polyesters (such as polyglycolic acid (PGA)), chitosan, polylactic acid (PLA), and hydrogel. Collagen nerve tubes are most commonly used [6].

A nerve conduit has the form of a hollow cylinder with smooth edges containing a central part and two terminal cuffs. The tube wall is made of silicone 0.5–2 mm thick. Inside the central part of the cylinder, three rectangular plates are located longitudinally, motionlessly connected to the cylinder wall and converging to the cylinder axis at an angle of 120^0. Along the edges of the cuff circumference, there are 6–12 holes in the cylinder wall. The diameter and length of the cylinder depend on the thickness of the damaged nerve and the size of the defect [17].

The use of conduit promotes the germination of nerve fibers in a certain direction; due to the anti-adhesive properties of silicone, it prevents the growth of fibroblasts in the defect area, which reduces the likelihood of neuroma formation [8]. Conduit implantation is performed as follows:

1 - under anesthesia (under aseptic conditions), the proximal and distal parts of the affected nerve are exposed.

2 - epineurium (perineurium) is removed by 1–2 mm, depending on the nerve diameter, from both ends of the defect;

3 - the size of the conduit is selected depending on the size of the defect;

4 - the conduit is placed in the area of the defect;

5 - the distal part of the damaged nerve is placed in the terminal cuff until it is secure with the longitudinal plates of the central part of the conduit;

6 - the distal epineurium of the nerve with conduit is fixed by stay sutures through the holes of the terminal cuff;

7 - similar actions are performed with the proximal part of the nerve, while adhering to the appropriate direction of the nerve fascicles [8].

In the early postoperative period, the conduit cavity is filled with intercellular fluid containing fibrin, neurotrophic and growth factors. By the end of the 1st week of observations, fibrin matrix is formed. During the 2nd week, fibroblasts, lemocytes (Schwann cells), macrophages, and endotheliocytes enter the formed matrix [9].

The advantages of conduits are: peculiarities of structure prevent scar tissue from entering its cavity; flexibility, elasticity, biocompatibility and biodegradability [10].

However, complications may develop, such as rejection of foreign material. Due to the fact that the tube wall is made of thin elastic material, compression of the regenerating nerve by surrounding tissues is possible, and, as a result, compression syndrome occurs, as well as associated increased risk of violation of the integrity of the nerve suture. For this reason, with the advent of implants based on synthetic resorbing biomaterials, the clinical use of silicone conduits is mostly abandoned [9].

It is advisable to use silicone nerve conduits only if the nerve defect is not more than 5 mm. Despite the fact that the silicone tube promotes the regeneration of nerve fibers in a certain direction, disorientation of regenerating nerve fibers inside the conduit itself is possible, which undoubtedly reduces the effectiveness of treatment and the result as a whole.

As for collagen nerve conduits, it is known that the rate of biodegradation of the conduit can be controlled. This depends on the method of its manufacture and additional composition, so the dissolution period can range from 1 month to 3-4 years. Early non-clinical studies have shown that collagen-based conduits can enhance the growth and differentiation of stem cells needed for regeneration. Attention should also be paid to the fact that such conduits are flexible and robust.

Collagen-based nerve conduits based on type 1 collagen, known as NeuraGen®, NeuroMatrix® and Neuroflex®, are commercially available in medical and pharmaceutical domains [8].

NeuroGen® is a collagen-based neural tube with a satisfactory recovery rate in 43% of treated

patients with expected peripheral nerve defects 2.5–20.0 mm long.

Neuoflex® is manufactured by Stryker Corporation (Kalamazoo, Michigan, USA), the only nerve conduit indicated for the treatment of symptomatic neuromas, and has corrugated walls that allow bending by approximately 60 degrees without occlusion. It is designed to interact between the nerve and surrounding tissue to prevent the ingrowing of scar tissue [8].

Chitosan (poly(1,4)-b-D-aminoglucose) is a linear polysaccharide consisting of randomly distributed D-glucosamine molecules (acetylated part). The material is derived from crustacean chitin and is widely used for biomedical purposes. Chitosan demonstrates properties of a biocompatible, non-toxic and non-antigenic material that can be broken down by lysozyme. It supports the growth of neutral cells and regeneration of nerve fibers and is used to create nerve conduits, including an environment for neuroactive substances [11].

Reaxon plus® (Medovent GmbH, Mainz, Germany) is made from chitosan biopolymer. Chitosan is made from chitin, a biopolymer found naturally in the exoskeleton of crustaceans and in the cell membranes of fungi, yeast, and other microorganisms. Reaxon plus® has certain advantages: it prevents nerve compression, it is transparent, thus facilitates nerve implantation and fixation [9].

Polyglycolic acid (PGA) is initially used in medical practice to produce suture material and surgical meshes. On average, biological development takes 90 days. Nerve conduits with PGA, such as Neurotube (Synovis Micro Companies Alliance, Birmingham, Alabama) are dense mesh tubes (2–4 cm long and 2–8 mm in diameter) of a porous structure, permeable to nutrients and neurotrophic factors, but preventing penetration into the fibroblast growth area. It has the only drawback associated with the risk of extrusion of polyglycol conduits before their complete resorption [10].

Manufacture of the above-mentioned nerve conduits is more expensive as compared to the classic suture material. Clinical randomized trials show equally effective results in restoring peripheral nerve motor disorders using both nerve tissue autotransplantation and PGC-based conduits. At the same time, positive results in reconstruction by PGC conduits were achieved even with a larger nerve defect. Moreover, for nerve diastases of less than 4 mm and more than 8 mm, even better rates of restoration of sensory conduction were noted compared to the data obtained using autologous nerve grafts. Comparison of the effectiveness of PGA therapy with venous-muscle grafts also demonstrated high rates of restoration of motor and sensory function of damaged fibers [8].

Neurotube® (Neuroregen LCC, Bel Air, Maryland, USA) and Neurolac® (Polyganics BV, Rosenburglan, Netherlands) are nerve cuffs made of polyDL-lactide-ε-caprolactone, approved for surgical reconstruction of nerve defects of up to 3.0 cm long. Neurotube® demonstrated successful facial nerve regeneration in several cases with a defect size of 1.0 to 3.0 cm. During restoration of the human facial nerve, there were no signs of tissue rejection or inflammatory processes. Neurolac® is a product competing with Neurotube®, and one report suggests improved regeneration compared to autologous nerve grafts on peripheral nerve defects up to 1.0 cm in rodents [11].

AxoGen Avance® (AxoGen, Alachua, Florida, USA) is the only FDA-approved human nerve allograft. Several animal model studies have demonstrated the effectiveness of nerve regeneration using decellularized allografts, but it is still inferior to isografts. Clinical trials have shown that 87% of 132 nerve injuries using Axogen Avance® (AxoGen, Alachua, Florida, USA) restored sensory and motor functions with peripheral nerve defect sizes ranging from 5.0 to 50.0 mm. According to the results of Brooks et al., nerve regeneration with restoration of sensory function was observed in 86% of the included cases [11].

All FDA-approved nerve grafts available on the market show a satisfactory recovery result with a defect length of about 3.0 cm with minimal side effects [12].

Discussion. The results of our research are based on the literature sources analyzed during the work on the paper. It should be noted that extensive biomedical and technical research is ultimately needed to fully understand the effectiveness of these methods. It was found that for significant traumatic nerve defects, the best option is to use the nerve conduits of combined composition and appropriate design in combination with cell cultures and growth factors (NGF, ciliary neurotrophic factor, neuropeptide Y).

Conclusions

Selection of management scheme for the injured peripheral nerve has not been definitively determined. Peripheral nerve regeneration is a complex process, and therefore the existing treatment methods are limited due to slow nerve regeneration and insufficient use of integrated approaches to repair damaged nerves. Timely nerve reconstruction using microsurgical techniques and the most optimal modern biologically compatible materials, such as chitosan, graphene, collagen significantly improves functional recovery.

Prospects for future research

In the field of peripheral nerve surgery, consideration should be given to meeting the requirements of an autograft and to understanding factors that stimulate and prevent nerve regeneration. It is important to use nerve conduits in combination with cell cultures and growth factors.

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