

Abstract

O. O. Potapov,

O. P. Kmyta,

O. O. Tsyndrenko,

*Medical Institute of Sumy State  
University, Sumy, Ukraine*

**MODERN ASPECTS OF THE USE OF NERVE CONDUCTORS  
IN PERIPHERAL NERVOUS SYSTEM INJURY (LITERATURE  
REVIEW)**

Peripheral nerve injuries account for 4 % of all injuries, and the consequences of trauma are a major medical and social problem, since they are characterized by a significant and long-term decline in limb function, and a high level of disability in patients. According to our data, up to 40% of patients sought specialized care for more than 6 months after the injury, and 19.9% were treated conservatively for an unreasonably long period of time. It led to an increase in the portion of unsatisfactory treatment results, since the prognosis of the further functional and useful degree of nerve recovery worsens with increasing time after injury.

The main objective was to select the optimal option of biocompatible material for implementation in practice in case of traumatic peripheral nerve damage.

**Materials and methods.** The analysis of medical literature for 2015–2020 was conducted. First of all, it should be noted that modern non-biological resorbable tubes are made of polyglycolic and polylactic acids. Non-resorbable tubes, including silicone, have shown undesirable effects, including axon compression during regeneration and the reaction of a fibrous foreign body. Hollow cylindrical tubes can be manufactured in several ways, such as electrospinning, crosslinking, physical film rolling, injection molding, melt extrusion, and braiding.

Adequate surgical treatment of peripheral nerve injuries requires that the surgeon, in addition to an accurate knowledge of the anatomical details of the affected area, would also be familiar with microsurgical methods and had necessary equipment to operate. The main procedure in peripheral nerve surgery is the restoration of nerve continuity, which can be obtained by direct coaptation between the two ends of a severed nerve or by the introduction of nerve grafts to replace a defect in nerve tissue.

Polyester is the most common synthetic material used in neural tissue engineering, along with polylactic acid, polycaprolactone, and polyglycolic acid. In combination with mesenchymal stem cells of the bone marrow, polylactic acid showed better results and accelerated the recovery of peripheral nerves. Polylactic acid directed the migration of Schwann's cells and induced the formation of a normal nervous structure. It was proved that the polycaprolactone material had an effect similar to that of autografts in nerve repair, and its characteristics were better than in a polylactic acid tube. Polyglycolic acid also possesses sufficient mechanical properties and can be

used to repair a nerve defect. Artificial synthetic materials have good biocompatibility and biodegradability with minimal toxicity. For the production of high-purity polymer monomers, which are necessary for the manufacture of the frame, much time and financial costs are required. Moreover, the elasticity and hardness of such materials are imperfect.

Three main natural biomaterials are used in tissue repair: collagen, silk, and gelatin. Collagen tube is the most widely used biological material in clinical practice. Silk materials with the protein fibroin, which promote the release of certain substrates, such as nerve growth factor particles, and provide more nutrients and a more favorable microenvironment for nerve repair, are worth noticing. Silk fibroin has good compatibility with the neurons of the dorsal root ganglia and supports cell growth. Gelatin materials are preferred due to the reduction of micromanipulation during nerve recovery. Natural biomaterials are easy to obtain in sufficient quantities; they have good biocompatibility and biodegradability and are easily absorbed by the body. However, each natural biomaterial has its drawbacks. Some of them are brittle or break down in a humid environment. Some natural materials are insoluble in water and traditional organic solvents, which limits their use. One of the most widely used biopolymers of natural origin is chitosan. Chitosan, derived by chitin deacetylation, plays a supporting, protective, and guiding role in the early stage of recovery of peripheral nerves and can provide a relatively stable, localized microenvironment during regeneration. Chitosan is absorbed and gradually decomposed in the late phase of recovery and regeneration of the nervous system.

Issues regarding graphene-based nanomaterials use are considered. Graphene is a two-dimensional carbon nanomaterial with good optical, electrical and mechanical properties. It should be noted that when graphene nanoparticles are incorporated into a chitosan or gelatin frame and used to repair peripheral nerve damage in rats, this has contributed to the regeneration of the damaged nerve more quickly. Graphene also reduced the inflammatory response and accelerated the migration of endogenous neuroblasts.

Hence, the use of these materials is not well understood due to the significant duration of recovery of the denervated proximal end of the nerve, so further research is needed to identify the advantages or disadvantages of their use.

**Keywords:** biopolymer, tissue engineering, peripheral nervous system injury.

**Corresponding author:** [Tsyndrenko@ukr.net](mailto:Tsyndrenko@ukr.net)

#### Резюме

Потапов О. О.,

Кмита О. П.,

Циндренко О. О.,

Медичний інститут Сумського державного університету, м. Суми, Україна

#### СУЧАСНІ АСПЕКТИ ЗАСТОСУВАННЯ НЕРВОВИХ ПРОВІДНИКІВ ПРИ ТРАВМІ ПЕРИФЕРИЧНОЇ НЕРВОВОЇ СИСТЕМИ (ОГЛЯД ЛІТЕРАТУРИ)

**Актуальність.** Ушкодження периферичних нервів займають частку 4 % від усіх травм, а наслідки травми мають велику медико-соціальну проблему, оскільки характеризуються значним та тривалим зниженням функції кінцівки, з високим рівнем інвалідизації хворих. За нашими даними до 40 % хворих зверталось за спеціалізованою допомогою в медичні заклади України у терміни понад 6 місяців після травми, 19,9 % - лікувалися консервативно необгрун-

товано тривалий час. Це призводило до збільшення частки незадовільних результатів лікування, оскільки відомо, що із збільшенням термінів після травми погіршується прогноз щодо подальшого функціонально-корисного ступеня відновлення нерва.

**Мета та завдання:** вибір оптимального варіанту біосумісного матеріалу для впровадження в практику при травматичному пошкодженні периферичного нерва шляхом порівняння результатів досліджень.

**Матеріали та методи.** Було проведено аналіз медичної літератури за останні п'ять років, із приділенням уваги дослідженням, що стосувались застосування порожніх циліндричних трубок для забезпечення регенерації пошкоджених периферичних нервів.

Встановлено, що сучасні небіологічні трубки, що розсмоктуються, виготовляються насамперед із полігліколевої та полімолочної кислот, які розкладаються. Трубки, що не розсмоктуються, включаючи силікон, продемонстрували небажані ефекти, такі як стиснення аксонів нервів під час регенерації та реакцію волокнистого стороннього тіла. Основними способами виготовлення порожніх циліндричних трубок є електроспінінг, зшивання, фізична плівкова прокатка, лиття під тиском, екструзія розплавленням і плетіння.

**Ключові слова:** біополімер, тканинна інженерія, травма периферичної нервової системи.

Автор, відповідальний за листування: [Tsyndrenko@ukr.net](mailto:Tsyndrenko@ukr.net)

## Introduction

Adequate surgical treatment of peripheral nerve injuries requires that the surgeon, in addition to an accurate knowledge of the anatomical details of the affected are, would also be familiar with microsurgical methods and had necessary equipment to operate [1]. The main procedure in peripheral nerve surgery is the restoration of nerve continuity, which can be obtained by direct coaptation between the two ends of a severed nerve or by the introduction of nerve grafts [2]. Traumatic peripheral nerve injury that results in significant tissue loss in the injury zone requires the use of a bridge or a frame to regenerate axons from the proximal stump to reach the distal end of the stump. The best results are achieved when the nerve is restored without tension, since the regenerating axons must cross only one part of the joint, which is not possible with large defects. Although, when using a nerve graft, regenerating axons must intersect two recovery sites that may have a clear inflammatory process, resulting in higher axon loss. However, in most cases, with massive damage, the approximation of the nerve stump leads to tension of the suture line. Tension at the recovery site leads to ischemia, connective tissue growth, and scarring that impairs or hinders the progression of

regenerating axons. In these cases, the restoration of nerve continuity is performed by transplantation of autologous nerve grafts, or appropriate biocompatible materials [1].

Neural autografts remain the clinical standard for the treatment of critical and significant defects of large-diameter peripheral nerves. The autograft provides a frame and trophic support in the form of a basal plate, endoneural tubes, and stem cells for regenerating axons that direct nerves to the distal stump. Donor nerves that are used as autografts are usually significant sensitive nerves, such as the calf nerve or the medial cutaneous nerve of the forearm. Thus, the disadvantages of autotransplantation are loss of sensitivity, possible neuroma formation and pain in the donor area, insufficient availability of donor tissue, secondary incisions and suboptimal sizes of the donor nerve to restore the site of damage [7].

Many scientists, in addition to creating an alternative to autograft, wanted to receive a model for studying peripheral nerve regeneration, where the tube could act as a device for monitoring nerve regeneration through a defect. At first, they used a pseudosynovial nerve sheath to overcome a nerve defect in the rat's gluteal nerve, which was soon followed by silicone channels. These materials were later used in the development of a convenient

method for encapsulation of tropical and trophic factors, associated with nerve regeneration, and estimation of its regeneration time. The above mentioned experiments provided the knowledge that the axon nerve that grows into the empty channel was supported by the migration of glial cells into the channel and the subsequent formation of a protein frame. They also demonstrated that nerves are able to produce their own scaffolds (cell matrices) to support axon regeneration at a short distance [11]. And at the beginning of these studies, it was found that the silicone channels cause significant chronic nerve compression and irritation at the site of implantation, which in turn required its removal. It was found that the low compatibility of silicone and the long-term presence of the material make a negative contribution to the chronization of the process and stimulated the research of alternative materials that can act as temporary biodegradable channels [10, 11].

In general, polymer, synthetic and natural materials usually support the regeneration of axons in small defects (up to 3 centimeters), but do not have the qualities of an autograft. It is believed that the absence of cellular support and extracellular matrix during recovery is a factor contributing to limited regeneration. Thus, the use of a neural conductor as a frame for tissue engineering requires the inclusion of an extracellular matrix to stimulate the migration of axons into the channel [3].

Neural allografts, i.e. donor neural tissue, would be an ideal alternative to an autograft. However, their use requires immunosuppression to avoid rejection and impaired regeneration. The use of pharmacological immunosuppression is associated with significant clinical morbidity and limits the use of allografts in restoring peripheral nerve integrity [3, 4].

Polyester is a common synthetic material used in neural tissue engineering, such as polylactic and polyglycolic acids, and polycaprolactone. In combination with mesenchymal stem cells of the bone marrow, polylactic acid showed better results and accelerated the recovery of peripheral nerves [3]. Polylactic acid directed the migration of Schwann's cells and induced the formation of a normal nervous structure. Polycaprolactone material has an effect similar to that of autografts in nerve repair, and its characteristics were better than in a polylactic acid tube [9]. Polyglycolic acid possesses sufficient mechanical properties in nerve defect repair [4].

Artificial synthetic materials have good biocompatibility and biodegradability. It is important that their decomposition does not harm the body. For the production of high-purity polymer monomers, necessary for the manufacture of the frame, a lot of time and financial costs are required. Moreover, the elasticity and hardness of such materials leave room for improvement.

Three main natural biomaterials are used in tissue repair: collagen, silk and gelatin [6]. Collagen tube is the most widely used biological material in clinical practice. Collagen is an important structural protein that is a structural component of most body tissues, for example, in the form of endoneurial fibrils or as a non-fibrillar component of the basal lamina. It supports tissue healing and cell proliferation. Collagen hydrogels are formed from fibrillar collagen layers that are folded into three-dimensional nerve channels. In numerous animal studies, collagen conductors have shown good functional results in nerve regeneration [9]. It has been shown that collagen nerve channels can reduce the severity of symptoms associated with neuropathic pain and accelerate the regeneration of damaged nerves [10].

Silk fibroin materials can promote the release of certain factors, such as nerve growth factor particles, and provide more nutrients and a more favorable microenvironment for nerve repair. Silk fibroin has good compatibility with the neurons of the dorsal root ganglia and supports cell growth [5]. The silk protein, N-fibroin, is first produced in the form of soluble protein in the glands of silk worms, and then formed into fibrous structures during the spinning process. N-fibroin has been thoroughly studied, which proved its excellent biocompatibility and low immunogenicity. To restore the nerve, it must be embedded in a tubular structure to provide a guide channel for axon growth and protect nerve fibers and their neurotrophic factors from fibrous tissue infiltration [7]. Several recent studies have demonstrated the good potential of N-fibroin and other silk proteins in peripheral nerve reconstruction. It is proved that the recently developed silk-and gold-based nanocomposite channel with Schwann's cells has shown good results in terms of structural and functional regeneration of damaged gluteal nerves in vivo [10]. This discovery confirms earlier studies that prove enhanced interaction of cellular material, such as cell adhesion, proliferation, and differentiation, by chemically modified silk

nanofibers with gold nanoparticles [10]. It is thought that gold nanoparticles immobilize certain nanofiber molecules without significant cytotoxicity. In addition, increased cell adhesion and propagation on the modified surface can be achieved. Animals were even able to perform complex motor functions with a positive sciatic nerve index. Subsequently, several studies were published in which excellent results were demonstrated using fibroin silk conductors, with the addition of nerve growth factors. Despite the auspicious results of using N-fibroin conductors, neither the US Food and Drug Administration nor any other organization has approved any silk conductors [8, 9].

Gelatin is a denatured collagen that is widely used in tissue engineering after being combined with various chemical substances. Genipin in this case acts as a cross-linking agent with low cytotoxicity. Gamez et al. used gelatin-based photofabricated nerve tubes and implanted them between the proximal and distal end of the dissected sciatic nerve (10 mm) in adult male rats for up to 1 year. As a result, there was a restoration of functional, morphological and electrophysiological response. In another study, genipin-crosslinked gelatin channels were evaluated as a guiding channel for peripheral nerve regeneration, and successful functional recovery of a 10 mm gap was tested on a gluteal rat model. Liu et al. made a proanthocyanidin cross-linked gelatin channel with a rough outer surface. The pipeline was used to regenerate a 10 mm defect in a rat sciatic nerve model, and regenerated nerve fibers that cross the gap site and exit from it were shown after 8 weeks. Nie et al. tested gelatin and chitosan nerve tubes with transforming growth factor  $\beta 1$  in a 10 mm sciatic nerve defect in rats. After implantation, the inner surface of the nerve conduits remained intact for a long time of regeneration; thus, it can prevent connective tissue ingrowth [12, 13].

The above mentioned natural biomaterials are sufficient and they are easy to obtain. Natural biomaterials also have good biocompatibility and biodegradability and are easily absorbed by the body. However, each natural biomaterial has its drawbacks. Some of them are easily broken or destroyed in a humid environment. Some natural materials are insoluble in water and traditional organic solvents, which limits the range of their application [7].

Chitosan derived by chitin deacetylation plays a supporting, protective and guiding role in the early stage of recovery of peripheral nerves and can provide a relatively stable, localized microenvironment during regeneration. Chitosan is absorbed and gradually decomposed in the late phase of recovery and regeneration of the nervous tissue [8].

Chitin, a component of the cytoskeleton in the external skeleton of insects and in the exoskeleton of crustaceans, is the main source of chitosan, and after starch, it is the second most common polysaccharide on Earth. Chitosan is a linear polysaccharide consisting of glucosamine and N-acetylglucosamine linked by  $\beta$ -1,4-glycosidic bonds. Chitosan is a deacetylated form of chitin that is dissolved in a slightly acidic medium. Chitosan-based building frames are appropriate for use in tissue engineering due to their ability to form interconnected porous structures (sponges). Zheng Cui used a chitosan channel in combination with mesenchymal bone marrow stem cells to stimulate peripheral nerve regeneration. It was found that stromal bone marrow cells can differentiate into neural stem cells in vivo in rats, and can overcome an 8 mm defect after their differentiation [11]. Prof. K. Haastert-Talini used chitosan tubes to regenerate 10 mm nerve defects in adult rats. Chitosan tubes were made from low, medium, or high grade of deacetylation chitosan, and, therefore, represented different levels and rates of degradation. However, chitosan tubes had certain limitations, such as high decomposition rates and low mechanical stability. In another study, conducted with chitosan nanofibers for peripheral nerve repair, it was concluded that the non-toxic nature of chitosan fibers is justified for applications in peripheral nerve regeneration [13].

Micro-pattern surface and inclusions of extracellular matrix proteins are new methods that allow providing the most necessary topography of the nanostructure for adequate growth of peripheral nerves and simulation of topographic dimensions similar to the extracellular nerve matrix [12].

One of the most promising methods of nerve conductor manufacturing is electrospinning. This method provides a larger area-to-volume ratio in the channel compared to frames with a smooth surface. A higher area-to-volume ratio leads to significantly greater adhesion of molecules, which leads to increased cell fixation. In addition, by controlling the architecture of the pore size in the



wall of the neural frame, a microporous inner layer and a macroporous outer layer can be developed, resulting in two-way permeability. Another advance in this field is the combination of extracellular matrix proteins (such as fibronectin, laminin, and collagen) with degradable biological polymers. This gives the usually hydrophobic frame a hydrophilic surface that is best for controlled cell signal transmission. Due to the risk of infection and rejection, peptides that mimic the active binding domains of various extracellular matrix molecules have been developed. For example, arginine-glycine-aspartic acid promotes the secretion of neurotrophic factors and cell attachment [12,13].

Graphene is a two-dimensional carbon nanomaterial with good optical, electrical and mechanical properties. Graphene is one of the most versatile nanomaterials due to its exceptional physical and chemical properties. In addition, graphene can interact with other biomolecules such as DNA, enzymes, proteins, or peptides, which is important in regenerative medicine and tissue engineering. In recent years, after the discovery of many interesting properties and biocompatibility, graphene and its chemical derivatives have become a new class of nanomaterials and are widely used in the biomedical industry [14]. In addition, good mechanical strength, rigidity, and electrical conductivity make graphene-based materials a good candidate for neural tissue engineering [14].

The use of unique surface and electrical properties of graphene to simulate signals in vivo and enhance the differentiation of stem cells into neurons is an extremely attractive strategy in treatment of neural damage and diseases of the peripheral nervous system. Reports have shown that graphene-based materials promote differentiation of stem cells into neurons, as well as improve the rate of their proliferation [15].

The attractiveness of graphene use for the manufacture of nanofibers instead of traditional advanced materials such as carbon nanotubes and poly-3,4-ethylenedioxythiophene is due to graphene's excellent electrical properties and mechanical strength. The fibers are covered with a strong graphene film with a thickness of 1-3 nm, and showed no stratification in ionic media, that is, they could be used to form nanofiber frames with significantly higher dimensions and strength. Mechanical tests showed that the fibers remained completely intact after 5.000 twisting cycles when twisting 2.5 circles, and had acceptable rigidity and

maximum conductivity. By using this frame to cultivate nerve cells by means of electrical stimulation, the proliferation and differentiation of primary motor neurons was accelerated. This has shown that graphene nanofiber frames can provide excellent stability, electroactivity, and strength for neural engineering purposes [12, 13, 14].

It should be noted that when graphene nanoparticles are incorporated into a chitosan or gelatin frame and used to repair peripheral nerve damage in rats, this has contributed to the regeneration of the damaged nerve more quickly. Graphene reduced the inflammatory response and accelerated the migration of endogenous neuroblasts [10]. Hence, the use of these materials is not well understood, so further research is needed to identify the advantages or disadvantages of their use.

Thus, the potential conductor should be immunologically inert, have the mechanical properties of a normal nerve. Polymer channels are more advanced because their range of decomposition, mechanical stability, and piezoelectric property can be modulated to improve nerve regeneration. Natural materials such as collagen, fibronectin, and fibroin, are biodegradable, possess biocompatible advantages over polymers, but the ability to regulate their mechanical and degenerative properties is limited [12].

The main objective and task was to select the optimal option of biocompatible material for implementation in practice in case of traumatic peripheral nerve damage.

**Materials and methods.** The analysis of medical literature for 2015-2020 was conducted. First of all, it should be noted that modern non-biological resorbable tubes are made of polyglycolic acid, polylactic acid. Non-resorbable tubes, including silicone, have shown undesirable effects, including axon compression during regeneration and the reaction of a fibrous foreign body. Hollow cylindrical tubes can be manufactured in several ways, such as electrospinning, crosslinking, physical film rolling, injection molding, melt extrusion, and braiding.

**Discussion of the results.** The results of our study are consistent with the data, contained in literature, which we analyzed when planning the work. The main procedure in peripheral nerve surgery is the restoration of nerve continuity, which can be obtained by direct coaptation between the two ends of a severed nerve or by the introduction

of nerve grafts. The best results are achieved when the nerve is restored without tension. Alternatively, when using a nerve graft, regenerating axons must intersect two recovery sites that may have a clear inflammatory process, resulting in higher axon loss. However, in many cases, the approximation of the nerve stump leads to a tightening of the suture line. Tension at the recovery site leads to ischemia, connective tissue growth, and scarring that impairs or hinders the progression of regenerating axons. In these cases, the restoration of nerve continuity is performed by transplantation of autologous nerve

### Conclusions

It should be noted that the cost of traumatic injury of peripheral nerves treatment is significant, since they are more common in young, previously healthy and economically active people. Rapid and adequate treatment of these injuries may lead to the restoration of at least partially lost function. Timely

### Prospects for future research

It should be noted that functional recovery as a result, even of an ideal surgical intervention using an autograft or nerve conductor, is not complete and often leads to limited regeneration. In the field

grafts, or appropriate biocompatible materials. Ideally, this nerve defect substitute should consist of a skeleton component that mimics the extracellular matrix of the peripheral nerve, and a cellular component for stimulation and support of the regeneration of peripheral nerve axons. Although substantial biomedical research is ultimately needed to fully understand the effectiveness of these methods, there is a great promise for tissue engineering in the future, as it may influence the acceleration of peripheral nerve regeneration.

nerve reconstruction, performed using appropriate microsurgical techniques with the use of non-optimal modern biocompatible material, such as chitosan, graphene, silk fibroin or their combination, significantly improves the functional recovery of this disabling condition.

of tissue engineering, one should consider not only meeting the "gold standard" of autograft, but also understanding what stimulates and hinders nerve regeneration. An important aspect is the use of cell cultures and growth factors in combination with the nerve conductor.

### Conflict of interest

The authors declare no conflict of interest.

### Відомості про авторів

**Потапов Олександр Олександрович**, завідувач кафедри нейрохірургії та неврології медичного інституту Сумського державного університету, доктор медичних наук, професор; вул. Троїцька, 48, м. Суми, 40003 (potapov.neiro@gmail.com).

**Кмита Олексій Петрович**, асистент кафедри нейрохірургії та неврології медичного інституту Сумського державного університету, кандидат медичних наук; вул. Троїцька, 48, м. Суми, 40003 (alex\_kmyta@ukr.net).

**Циндренко Олександр Олександрович**, аспірант кафедри нейрохірургії та неврології медичного інституту Сумського державного університету, вул. Санаторна, 31, м. Суми, 40000 (e-mail: Tsyndrenko@ukr.net, тел.: +380508629913).

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(received 04.05.2020, published online 29.06.2020)

(одержано 04.05.2020, опубліковано 29.06.2020)