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Recent Medical Techniques for Peripheral Nerve Repair: Clinico-Physiological Advantages of Artificial Nerve Guidance Conduits

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Abstract—This review outlines advanced methods for reconstructing injured peripheral nerve fibers, applying a technology of nerve tubulization with nerve guidance conduits (NGCs), and discusses fundamental and applied prospects for further development of clinical and technological studies to solve this medical problem in young and elderly patients. The current neurosurgical practice includes manipulations on nerve fibers, matching and suturing nerve fiber ends (however, it is important to avoid any tension in the zone of diastasis for a successful nerve regeneration), as well as on allo/autologous nerve grafts. Unfortunately, these therapies are not always implementable in some clinical situations due to certain limitations and their association with a potential risk of postoperative complications. Implanting artificial nerve conduits is an alternative reconstructive technique to promote physiological nerve regeneration. The article describes different engineering constructions derived from various materials, which are now either commercially available or undergoing preclinical and clinical studies. The review underlines the necessity of a further scientific search for new materials and polymers, as well as for novel technologies for fabricating artificial nerve conduits suitable for clinical medicine and rehabilitation.

Keywords: nerve guidance conduits, peripheral nerve injury, nerve regeneration, biomaterials, electrospinning

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INTRODUCTION

Peripheral nerve injuries generate a complex of serious medical and social problems for both young and elderly categories of population at a rate of one case per 1000 patients. Apart from bringing disability to patients themselves, the posttraumatic consequences raise health sector costs, reduce productivity, and force companies to bear losses.

A series of standard methods are currently employed for the management of peripheral nerve injuries. For example, damaged nerve fragments can be matched and sutured in the end-to-end way to repair nerve fiber injuries with small gaps. This method is frequently inapplicable to large diastases, since it leads to a considerable increase in the tension along the nerve tissue repair, reducing an adequate blood supply to the site of injury and negatively interfering, in general, with the process of physiological regeneration and the treatment outcome as a whole.

According to different studies, a disturbance in the physiological process of regeneration emerges when nerve fibers are stretched to 10% of their pretraumatic length. If a gap exceeds 4 mm, the matching of nerves is hardly probable without overstretches with a direct impact on both the clinical outcome and the treatment strategy. The primary strategy to recover the nerve fiber integrity in expressed diastases is the application of autologous nerve grafts. Nevertheless, this method has some limitations, such as, the availability of a donor tissue, disturbances in functional properties of a nerve fiber during the recovery of its anatomical integrity, and probable posttraumatic neuroma formation.

Neurorrhaphy is applicable in gaps not exceeding 20 mm in the majority of clinical cases (best results are reached for gaps of not more than 5 mm). Whereas the application of nonvascularized autonerve grafts is recommended in gaps not exceeding 70 mm, and vascularized autonerve grafts are indicated in gaps exceeding 70 mm, in large gaps (≥120 mm) or in the presence of an expressed denervation process, reconstructive surgeries on the nerve stem are considered inexpedient and musculotendinous plastic surgery is indicated. We should note that the use of autotissue grafts may cause negative consequences, such as defects to the zone of sampling nervous tissue, while the use of donor nerve tissue grafts is complicated by incompatibility between immune responses. Thus, a search for highly efficient innovative technological and, at the same time, accessible techniques for the reconstruction and regeneration stimulation of injured nerve fibers is an important goal in rehabilitation medicine, basic and clinical physiology, and bioengineering [12, 15, 18].

TUBULIZATION OF NERVE FIBERS IN THE AREA OF THEIR INJURY

An alternative approach to the reconstruction of peripheral nerve injuries of a relatively short-length is the nerve fiber tubulization technology—utilization of nerve guidance conduits (NGCs). Such artificial nerve conduits are used not only for the orientation of a regenerating nerve end, but they also allow the properties of intrinsic environment to be additionally modulated and the indicators of natural reconstruction to be improved in general. The assortment of the currently applied nerve conduits is very limited, but, however, we should note that they have demonstrated a high level of clinical postoperative efficacy in the majority of nerve defects with lengths not exceeding 20 mm, compared with the surgical management using autografts. The application of tubulization technology is significantly limited in more expressed defects, due to a possible association with the relatively simple structural configuration of nerve conduits as empty tubes.

The applicable materials should be approved by different medical, ethical, and technical commissions (such as, the US Food and Drug Administration, FDA), and, therefore, the materials need to be not only physically flexible and soft, but also semipenetrable, in particular, for trophic factors and oxygen necessary for the nerve growth physiology. The direct effects projected from the tubulization of severed nerves include growth, increased number and length of regenerating fibers. To provide a higher efficacy in neuroregeneration and neuroprotection, an implanted biomatrix based on synthetic and other materials should be compatible with neurotrophic factors, pharmacological preparations with a neuroprotective activity, and stimulators of neurogenesis [9, 17].

The first reports about a comparably successful application of nerve conductors (from the area of decalcified bone) date back to the end of the 19th century (T. Gluck, 1880). An ideal nerve conduit for creating artificial nerve tunnels should possess the following properties: relatively available production, biocompatibility between materials, creation of best conditions for axonal growth, correspondence to the sizes of the injury (length and diameter), physiological semipenetrability to prevent the penetration of fibroblasts and anti-inflammatory cells and, at the same time, to secure passage for oxygen, chemotaxis and trophic factors necessary for nerve growth. It is also necessary that the reconstructed nerve not be subjected to compression and damage by surrounding tissues and, therefore, an artificial nerve conduit should equally be properly flexible and elastic [13, 19].

Clinical trials have shown that there is a direct dependence between the thickness of the conduit wall and the final result of the nerve fiber regeneration process, including the neurin formation. Based on numerous data, it has, in particular, been established that nerve conduits with a wall thickness exceeding 0.81 mm, on average, significantly reduce the axonal growth efficacy, which is most probably associated with difficulties in the delivery of nutrients and growth factors necessary for the physiological regeneration process. Furthermore, the structural thickness of a conduit is a dynamic value, since the formation of a local inflammatory process and edema in the surrounding tissues is not excludable. On the whole, the optimal structural parameters of nerve conduits should include the wall thickness of around 0.6 mm with a 80% relative porosity and pores varying within 10–40 μm [23].

The problem of nerve tubulization, using conduits with the indicated "ideal" parameters, remains unsolved so far, and, therefore, a scientific search for the improvement of the quality, structure, and availability of materials continues.

MAJOR MATERIALS FOR CONDUITS

Neurosurgery now utilizes technical and engineering constructions from various materials, including natural biomaterials (collagen, fibrin, fibronectin, eggshell, chitosan, and natural silk) which have already been tested or undergoing preclinical or clinical tests, as well as biocompatible biodegradable synthetic materials, including those obtained through a bacterial fermentation process (polyethylene glycol, polyacrylates, copolymers based on lactic and glycolic acids, copolymers based on glycolic acid and caprolactone, and polyhydroxyalconates).

Silicon. The main nerve regeneration stages, using a silicon-based artificial nerve conduit, were demonstrated by L. Williams et al. in 1983. For example, the conduit lumen was already filled with the intercellular fluid containing fibrin, neurotrophic and growth factors during the initial postoperative period. A fibrin matrix was formed by the end of the first week of observations. During the second week, fibroblasts, lemmocytes (Schwann cells), macrophages, and endotheliocytes were entering the formed matrix. The axons of the proximal segment of the injured nerve simultaneously formed a nerve cone which extended to10 mm, on average, by the fourth week of observations.

Silicon belongs to nonresorbable, nonporous, biologically inert materials with almost universal application in medical practice. According to some clinic trials, the recovery of the posttraumatic nerve conduction in the median and ulnar nerves, using silicon conduits, contributes to an insignificant improvement of the motor and sensory function, negatively correlating with the value of a nerve defect. Since silicon is not a biodegradable material, silicon-based conduits may cause compression in the regenerating nerve with a decrease in the axonal conduction, and, therefore, silicon conduits are to be surgically removed. Silicon

conduits have been withdrawn from clinics for this reason with the appearance of commercial grafts based on resorbable synthetic biomaterials [5, 13].

Foamed polytetrafluoroethylene (PTPE) is another commercially available nonresorbable biologically inert material. New reports about the application of PTPE in medical practice and clinical trials were also very scarce in recent years. There were opinions during the period of PTPE application that clinical results of reconstructive tubulization with this material showed improvement if the size of a nerve defect was comparably small (according to S. Stanec, 78.6% against 13.3% of nerve function recovery, respectively, for gaps not exceeding and exceeding 4 cm) [6, 13].

Autogenous venous grafts. Vein grafts (as well as vein-muscle grafts) were among one of the first conduits based on biomaterials applied for the peripheral nerve repair. All conduits of this type shared the same drawback that significantly affected the clinical treatment outcome, i.e., vein grafts were at a high risk of flexion and compression by surrounding tissues during the regenerative period. In the early 20th century, L. Wrede (1909) and H. Platt (1919) were among the first authors reporting official data about a clinically efficient application of autogenous venous vessels as conduits for the posttraumatic nerve tissue regeneration. The available regeneration results recorded over more than a century history of vein grafting were characterized by favorable outcomes in the recovery of gaps not exceeding 3–4 cm [14, 30].

Collagen. In contrast to silicon and PTPE, collagen is a natural resorbable material of protein structure. Nerve conduits based on a purified bovine collagen demonstrate low immunogenicity. The biological decomposition rate of a collagen-based conduit depends on its fabrication technology, is controllable and ranges from one month to three or four years. The early preclinical tests have shown that collagen-based conduits can enhance the growth and differentiation of many cell types required for regeneration. Furthermore, these conduits have proven to be flexible with durability properties, while their semipenetrability promotes the diffusion of chemotaxis and neurotrophic factors, serving as an auxiliary recommendation for their further use. The collagen-based nerve conduits I type include trademarks, such as NeuraGen, NeuroMatrix, and Neuroflex, which are commercially available on the market of medical and pharmaceutical products [10].

A multitude of well-grounded clinical data have already been accumulated about the efficient reconstructive application of collagen-based conduits in the therapy of injured peripheral nerves, in particular, in the median, ulnar, digital, and lingual nerves. Positive results expressed in the improved sensory and motor nerve functions and reduced posttraumatic painful sensations have been obtained in more than two-thirds of reconstructive treatment cases by all available studies during three, six, and twelve months of observations and even longer (we should note here that the data are referred to gaps extending to not more than 20 mm, on average).

D. Kuffler et al. described an individual case with more than their three-year observation over the reconstruction of a12-cm-long ulnar nerve gap [24]. The authors filled the designed collagen-based conduit with the autologous thrombocyte-rich fibrin matrix. The neuropathic pain became less intensive after two years of observations. A withdrawal from analgesic drugs became possible after two years, as well as a recovery in the motor function was noted. This fact is hopeful for an applied use of the nerve tissue tunneling method, utilizing, in particular, collagen-based conduits for the recovery of large gaps.

Decellularized nerve allografts. The application of nerve allografts is an alternative to autologous grafts, but this additionally requires a prolonged (up to 18 months) prescription of immunosuppressive drugs. The production technology for decellularized nerve allografts allows excluding immunosuppression with its negative consequences for a recipient's body and preserving the same structural properties, as in collagen-based conduits, for the formation of conduits. The latter simultaneously contribute to the oriented growth of the injured nerve, cell migration into the zone of reconstruction, and selective diffusion of the needed growth factors, and, in addition, the axonal growth cone formation is facilitated due to the presence of adhesive glycoproteins, in particular, laminine-8. The available decellularized allografts (Avance) allow surgeons to reconstruct peripheral nerve gaps of up to 70 mm long and 5 mm in diameter [25, 31].

In 2012, D. Brooks et al. published results of a multicenter prospective study on the utilization of a commercially available decellularized nerve allograft to reconstruct peripheral nerve injuries. Positive clinical outcomes were demonstrated in all groups of observations both in the functional sphere and depending on the size of nerve diastases. In particular, the functional reconstructions of sensory, mixed, and motor nerves reached 88.6, 77, and 85.7%, respectively. The structural and functional recovery was reached in 100% of cases in the recovery of small nerve gaps (up to 15 mm), in 76.2% of cases for medium gaps (up to 3 cm), and large defects (up to 5 cm) were repaired in more than 90% of observations [7].

Polyglycolic acid (PGA). This acid was initially utilized in medical practice and associated with the production of suture material and surgical meshes. The average time of biological resorption was 90 days. The commercially available devices of PGA for nerve tissue reconstruction (Neurotube) are dense mesh tubes (2–4 cm long and 2–8 mm in diameter) with a porous structure, which is penetrable for nutrients and neurotrophic factors, but which prevents the penetration of

fibroblasts into the zone of growth. There is a certain risk of extrusion for polyglycolic conduits before their complete resorption. It should be noted that the commercial production of these conduits is more expensive, compared with the classical suture material. Clinical randomized studies have shown equally efficient outcomes in the recovery of functional motor disorders in peripheral nerves, using both autologous nerve tissue and PGA-based conduits. Positive reconstructive results were reached by PGA-based conduits even in nerve gaps of larger sizes. Furthermore, even better indicators for the sensory conduction recovery were recorded in nerve diastases not reaching 4 mm and exceeding 8 mm, compared with the data shown by autologous nerve grafts. The compared efficacy between the PGA-based conduit therapy and vein-muscle grafts also demonstrated high indicators for the recovery of motor and sensory functions of injured fibers and no significant differences were shown. There are literature data about a successful therapy of a plantar neuroma (Morton's neuralgia) with a complete arrest of the pain syndrome and the reconstruction of sensitivity less than one year after the reconstruction, using materials from PGA [28, 29].

Composites of polyglycolic acid and collagen. Conduits based on composites of polyglycolic acid and collagen are at the stage of clinical trials and not yet available for commercial use. They are polyglycolic conduits covered with 1% collagen solution and filled with a collagen matrix, while nerve fibers were presutured to prevent their too-quick resorption. Japanese researchers have a worldwide priority in the clinical studies of PGA-collagen conduits. High indicators have been demonstrated in the repair of physiological functions in the reconstruction of chorda tympani nerve, superficial fibular and digital nerves, branches of the facial nerve, as well as in the repair of the complex regional pain syndrome (causalgia type 2) [20, 35].

Composites of lactic acid and caprolacton. The copolymer of lactic acid and caprolacton (PLAC) also belongs to synthetic biocompatible materials with a resorption period of nearly one year. A positive property of commercially available PLAC conduits is their transparency, which facilitates the manual matching of severed nerve ends. The increased wall thickness in the initially created conduits based on this polymer caused an edema in the surrounding tissues at the site of reconstruction, while structures with a smaller wall thickness had a high risk of falloff. Furthermore, their softening in water was required prior to use, due to their pronounced stiffness. A change in the ratio between the copolymer components, in particular, an increase in the share of polylactide, reduces negative edema-generated consequences, but leads, after several weeks, to the loss of mechanical firmness by the graft. On the whole, the results of clinical trials in PLAC tunneling have not shown reliable comparative data on the PLAC efficacy in patients, unlike other biodegradable biocompatible materials or grafting [21, 22, 32, 34].

ELECTROSPINNING TECHNIQUE FOR THE FABRICATION OF ARTIFICIAL NERVE CONDUITS

The application of a variety of products manufactured using the technique of electrostatic shaping (electrospinning) is an advanced technology in the field of tissue engineering, cell transplantology, and creating pharmaceuticals and controlled drug delivery systems. Each specific biomedical task, in particular, the fabrication of conduits for nerve tissue repair, requires a selection of polymers to provide the necessary physical and mechanical properties, biocompatibility, structural specificities, and optimal biodegradation efficiency of materials.

The technique of electrospinning is intended for obtaining nanofibers of random lengths from polymer solutions, which can be used as an artificial stroma for a tissue to be grown. The cells of a biological tissue are either placed onto or premixed with the polymer. The process of electrospinning includes the electrical field that allows experimenters to move a charged polymer molten or solution from a portioner to a collector, which helps to pull out ultrafine fibers from a liquid medium. The result includes the complete evaporation of the solvent with the subsequent shaping of nanofibers with a possible diameter from several nanometers/microns and an almost unlimited length. Using electrostatic shaping, we can obtain superfine fibers, tubes from polymers, composites, and even semiconductors and metals, and we can modulate the structure of the created products by changing the parameters of electrospinning.

At the same time, the morphology of the surface, the diameter and length of fibers, semipenetrability and physical and chemical properties of nerve conduits fabricated through electrospinning affect the adhesion, proliferation, differentiation and growth of cells in both the nerve fibers themselves and their auxiliary structures. Different polymeric materials manufactured by electrospinning are now tested for criteria of biocompatibility, the ability to recover a tissue from a defect, serve as cell carriers, or scaffolds, and drug delivery systems and the necessary nerve growth factors. The known polymers, such as polylactides, polyglycolides, and their copolymers, polyoxyalkanoates, polycaprolacton, collagen, chitosan, spidroin, fibrinogen, their mixtures, etc., are now already used for creating nanofibers under laboratory conditions [21, 33, 34].

FURTHER DEVELOPMENT PROSPECTS

The currently used engineering methods for the fabrication of nerve conduits have technical limitations to the creation of a certain microstructure in the

lumen of the conduit itself. Therefore, the contemporary conduits are technically simple in the majority of cases, looking like empty tubes from a variety of natural and synthetic materials and do not consider the unique microstructural specificities in the organization of a nerve fiber in the lumen of the channel. The use of the microstereolithography technique (MSL) allows researchers to design devices with a sophisticated ultrastructure, orienting researchers in this field towards engineering improvements in the nerve tissue tubulization technique. According to the experimental data, the use of the 3D-prototyping techniques for the fabrication of artificial nerve microconduits from biocompatible biodegradable materials in the area of diastasis has demonstrated improvement in the results of controlled nerve fiber growth in gaps exceeding 20 mm. The method is based on the technology of additive production of micromodels from liquid photopolymer resins, and the solidification of the material occurs due to irradiation by ultraviolet laser with a wavelength of 360 nm or by another similar energy source. At the present time, the technology for the fabrication of nerve conduits using microstereolithography is limited by a small number of biocompatible materials.

A possible utilization of artificial nerve conduits from liquid metal alloys saturated with growth factors to stimulate neuroregeneration is studied in other experiments. Alloys of liquid metals are analyzed for the presence of physical characteristics enabling researchers not only to technically regenerate/match the severed nerve ends, but also preserving electrophysiological properties of nerve conduction. Constructions based on GaInSn alloy (67% gallium, 20.5% indium, and 12.5% tin) demonstrate some useful properties, including specific electroconductivity, which are much higher than in other nonliquid metal and/or natural materials.

Simultaneously with the development of nerve fiber tubulization techniques, studies are being carried out on a controlled stimulation of the natural physiological process in nerve cell reconstruction, using weak laser irradiation in the growth cone area. An "optical trap" (or "laser tweezers") with a wavelength of 800 nm coming from a titanium-sapphire laser is used in the so-called laser-controlled growth of peripheral nerve fibers. The power of optic exposure cannot damage the axon growth area, but it is sufficient to facilitate the polarization of new actin filaments and the controlled lamellipodia lengthening and growth (on the leading edge) of the nerve cell in the growth cone area [4, 8, 11, 16, 26, 27].

We should note that the use of artificial nerve conduits in the country's healthcare system is not widely practiced and remains at the level of scientific search and at the stages of basic (under experiments on animals) and clinical studies in methodology. In Russian clinics and in the near abroad, surgeons use conventional neurosurgical methods of treatment, in particular, neurorrhaphy with a clinically approachable tension of nerve ends, as well as in combination with the limb soft tissue tunneling and allografting. The applied methods allow us to achieve necessary clinical effects, although the outcome of surgical treatment directly depends on an adequate, qualified presurgical (including premedical) aid to a patient immediately after the injury, as well as on the length of interval after the trauma. However, prospects for applying the nerve conduit method by domestic clinicians in the near and more distant future are apparent. This is confirmed in the recent years by the appearance of a series of patents in the scientific domestic press on inventions of constructions by the type of nerve conduits, as well as on the methods for nerve regeneration stimulation, and original articles, describing an experimental implantation of artificial nerve conduits filled with a neurotrophic and angiogenic matrix, as well as in combination with the local delivery of genetic material for the promotion of nerve growth.

CONCLUSIONS

Further progress in a scientific search for new materials and polymers for fabricating nerve conduits with their subsequent preclinical tests and clinical trials is expedient and even necessary. The accumulated knowledge about the efficacy of already applied and commercially available materials are mainly based on a comparably small series of clinical applications, the results of which may significantly vary. Furthermore, the type of nerve fiber and the nature of injuries, the etiology of trauma, the size of a defect, a patient's general condition and other factors not only immediately influence the clinical outcome, but also create technical complications during the adequate comparison of the results obtained utilizing different materials and reconstructive methods. At the same time, we should note that a long-term clinical effect in the reconstruction of nerve injuries, using any of the techniques reviewed by this article, can be achieved through subsequent long-term rehabilitation during the entire rehabilitation period [1, 2]. In addition to the abovementioned materials that are clinically tested, a certain number of materials are still undergoing preclinical tests, such as, natural biodegradable polymers of nonmammalian origin, artificial biocompatible polymers, including those fabricated through electrospinning, as well as combinations of such materials with stem cells (lemmocytes, mesenchymal stem cells) for improving the indicators and regeneration rate.

Today, the foreign and domestic scientific literature does not offer any extensive volume of experimental and clinical data on the application of technology for the tubulization of severed nerves with advanced biomaterials separately in elderly and old patients. The main causes for peripheral nerve injuries include anthropogenic catastrophes and occupational

traumatism as a result of industrial development and intensive automation of technical systems, road traffic accidents, as well as household traumatism. Therefore, the frequency of peripheral nerve injuries in young patients significantly exceeds this in elderly and old persons and, according to official statistics, constitutes 1.5–10% of all traumas, while disability due to this pathology reaches 70%. At the same time, budget losses significantly increase with the incapacity of the country's working-age population. Therefore, the accumulated basic and clinical statistics represents generalized data, mainly obtained from young patients. At the same time, the authors of this article are convinced that it is now equally necessary to accentuate researchers' additional attention at the tubulization of injured nerve fibers with advanced biomaterials in patients of senior age groups. For example, considering the long-term neuroregeneration periods in elderly and old patients, compared with young people, the studies in this area are of a specific interest in the aspect of obtaining new basic scientific knowledge and new data of comparative clinico-functional analyses.

On the whole, all the above-mentioned considerations remain very important for further studies in the outlined research area. Despite the technical and economic difficulties in the development and introduction of new devices, we may already conclude that the tubulization technology for peripheral nerve injuries has broad prospects in the clinical application of commercially available materials, as well as in the scientific development of methods. This is confirmed by most accomplished studies demonstrating good results in physiological reconstruction, especially in peripheral nerve gaps not exceeding 3 cm, which is comparable (or even more advantageous) with the results shown by nerve and other biological grafts.

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