

Progress of nerve bridges in the treatment of peripheral nerve disruptions

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Abstract: Clinical repair of a nerve defect is one of the most challenging surgical problems. Autologous nerve grafting remains the gold standard treatment in addressing peripheral nerve injuries that cannot be bridged by direct epineural suturing. However, the autologous nerve graft is not readily available, and the process of harvesting autologous nerve graft results in several complications. Thus, it is necessary to explore an alternative to autologous nerve graft. In the last few decades, with significant advances in the life sciences and biotechnology, a lot of artificial nerve grafts have been developed to aim at the treatment of peripheral nerve disruptions. Artificial nerve grafts range from biological tubes to synthetic tubes and from nondegradable tubes to degradable tubes. Among them, acellular nerve allografts and artificial nerve repair conduits are two kinds of the most promising substitutes for nerve autografts. The history, research status, and prospect of acellular nerve allografts and artificial nerve repair conduits are described briefly in this review.

Keywords: peripheral nerve injury, repair, acellular nerve graft, nerve conduit

Introduction

Peripheral nerve injuries constitute one of the main problems in trauma centers.^{1,2} Treatment of injuries to peripheral nerves is one of the most challenging surgical problems. In cases of simple peripheral nerve disruption, to some extent, functional recovery can be attained through tension-free, end-to-end coaptation of residual nerve stumps. In contrast, trauma and surgical procedures, such as tumor resection, often result in peripheral nerve defects. When the gap between proximal and distal nerve end is large, autologous nerve grafts (autografts) were often clinically used to repair the nerve defect. Autologous nerve grafting remains the gold standard treatment in addressing peripheral nerve injuries that cannot be bridged by direct epineural suturing.³ However, the autologous nerve graft is very limited and not readily available, and the process of harvesting autologous nerve graft results in morbidity, such as additional operation injury, recipient nerve difficult to match, donor site denervation, and neuroma formation at the site of harvest,⁴⁻⁶ which is like “robbing Peter to pay Paul”. Thus, it is necessary to take an alternative to autologous nerve graft to achieve satisfactory functional recovery with little complications, particularly in patients with extensive peripheral nerve injury and insufficient amount of donor nerve for harvest. As a result, a lot of interest has been placed in the development of effective alternatives to nerve autografts in the treatment of peripheral nerve injuries. In the last few decades, researchers have been working to find substitutes for autologous nerve grafts and have

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made great progress. Among them, the most promising and most possible alternatives to autologous nerve grafts were acellular nerve allografts and artificial nerve repair conduits.

Acellular nerve allograft

Necessity of acellular nerve allograft

Allogenic nerve tissue (allografts) is one of the most promising substitutes for nerve autografts due to its similar structure to the autologous nerve. Unfortunately, transplantation of fresh nerve allografts is limited by the concomitant need for systemic immunosuppression, which predisposes graft recipients to opportunistic infections, neoplasia, and toxicity-induced side effects.^{7,8} Studies have confirmed that the main antigen of allogenic nerve present in Schwann cells (SCs) and myelin sheaths and the collagen composition of nerve epineurium, perineurium, and endoneurium have no immunogenicity; the basement membrane has the function of guiding and promoting axon growth in the process of nerve regeneration.^{9–11}

Processing nerve allografts to remove cellular components offers an attractive means of circumventing these limitations by reducing graft immunogenicity. The acellular nerve allograft remains a natural neural three-dimensional scaffold structure, which has the advantages of low immunogenicity, no donor area damage, and so on, and thus has been widely studied. Many experiments confirmed that allogeneic nerve

graft with appropriate acellular treatment does not cause obvious immune rejection^{12,13}; thus, in recent years, many scholars mainly focus on how to reduce the immunogenicity of allografts and as far as possible to retain its natural support structure. Although different processing techniques were explored, all of them simultaneously aim to 1) remove cellular, myelin, and other components of the antigen to reduce the graft immunogenicity and 2) promote the growth of new nerve fibers in the acellular nerve allograft. However, there is little consensus about which processing technique best preserves the natural regenerative capacity of peripheral nerve tissue and maximizes removal of SCs.

Processing techniques of acellular nerve allograft

Multiple methods exist for preparing acellular nerve grafts from allogenic donor nerve tissue. The processing technique of acellular nerve allograft is the use of chemical, physical, and biological methods to remove allogeneic nerve SCs and myelin, axons, and other ingredients, so that the remaining main components of basement membrane tubes are without damage to repair peripheral nerve defect. At present, a number of methods for peripheral nerve cell removal have been investigated, which are roughly divided into three kinds: physical, chemical, and biological processing techniques (Table 1).

Table 1 Some processing techniques of acellular nerve allografts

Category	Processing methods	In vitro evaluation	In vivo evaluation	Clinical practice	Shortcomings
Physical methods	Prolonged cold-preservation: allografts in UW solution at 4°C for 3 weeks	Effectively eliminate the antigenicity of peripheral nerve allografts and conserve native SC basal laminae and nerve ECM ^{14–16}	Enable robust axonal regeneration through transplanted acellular allografts ¹⁶	NA	Clinical application of cold preservation techniques has remained limited due to extended processing times (~7 weeks) and poor mechanical properties of these friable acellular grafts ¹⁷
	Freeze-thawing: by quickly repeated freezing and thawing tissue, making cell membranes rupture, and causing cell lysis	By controlling the rate of temperature change, preventing the structure of the basement membrane from destruction by formation of ice crystals within the cells ¹³	Longest distance of neural repair by acellular nerve allograft treated with freeze-thawing is 2–4 cm ^{18,19}	NA	More fractures exist in neural basement membrane by freeze-thawing process, and these broken structures facilitate infiltration of lymphocytes ^{13,20}
	Lyophilization: freeze-drying technique is used to freeze allograft nerve into a solid state at lower temperatures, which is then sublimated directly into gas, and finally cause nerve dehydration	Has a larger porosity and pore diameter, and it is possible that this is conducive to the adhesion and growth of cells ²¹	Although animal experiments confirmed that the freeze-dried nerves could repair peripheral nerve defects, some scholars believe that this kind of allograft could not well promote nerve regeneration ¹⁸	NA	After freeze-drying treatment, SCs of treated nerve still have part of the activity, with somewhat immunogenicity ²¹

(Continued)

Table 1 (Continued)

Category	Processing methods	In vitro evaluation	In vivo evaluation	Clinical practice	Shortcomings
Chemical methods	Detergent processing: early protocols relied heavily on the use of sodium deoxycholate, Triton X-100, and deionized water to decellularize nerve grafts ^{15,22}	Morphological observations demonstrate that all cells and myelin basic structures were cleared, and the nerve basal lamina structure was intact ²³	Its regenerative axon density was significantly higher than the acellular allografts treated with freeze-thaw method	NA	Basement membrane retention methods need to be improved
	Detergent processing: nerve allografts were repeatedly exposed to solutions of deionized water, SB-10, and Triton X-200/SB-16 over a period of 4 days ²⁴	Superior preservation of native ECM and equivalent levels of decellularization compared to previous chemical processing techniques ²⁴	Having been shown to support significantly greater densities of regenerating axons than both thermally decellularized and chemically decellularized nerve allografts when implanted in rat sciatic nerve ^{24,25}	NA	More effectively retain the basal lamina structure
	AxoGen®-processed nerves are known to undergo a combination of treatments, including chemical decellularization (detergent processing), gamma irradiation, and enzymatic digestion of CSPG	Differences in washing time could have differential effects on the integrity of the ECM within donor nerves ¹⁷	AxoGen-processed nerve grafts in rats were unexpectedly observed to facilitate lesser degrees of functional nerve regeneration compared to detergent-processed nerve allografts ¹⁷	Successfully applied in a clinical setting	Reduced regenerative capacity of AxoGen-processed nerve grafts may result from the optimization of the AxoGen decellularization techniques for use with human nerve tissue, rather than rodent ¹⁷
	An hANG as an alternative to autogenous nerve commercially named “Shenqiao”	The scaffolds were cell free and rich in collagen I and laminin, with a microarchitecture similar to the fibrous framework of human peripheral nerves	Results of clinical trials showed that its efficacy in restoring digital nerve function was similar to that of other materials on the market, suggesting that it is both safe and effective	Restoring digital nerve function in clinic	The patients of this study did not receive sensory reeducation, and maximum follow-up time was only 6 months
Biological methods	Enzyme digestion methods: enzymes currently mainly used were trypsin and nuclease	Generally, enzyme digestion was applied using physical or chemical methods, to assist in the destruction of the engagement between the cell membrane and the basement membrane ²⁶	NA	NA	Need to be combined with a physical or chemical method
	Chondroitinase ABC: chondroitinase ABC can degrade nerve CSPGs, which is believed to impede axonal regeneration ^{27,28}	NA	Experiments confirmed that nerve allografts treated by chondroitinase ABC could promote the regeneration of peripheral nerve and reduce the generation of scar ²⁹⁻³¹	NA	Need to be combined with a physical or chemical method

Abbreviations: UW, University of Wisconsin; SC, Schwann cell; ECM, extracellular matrix; NA, not applicable; SB-10, sulfobetaine-10; SB-16, sulfobetaine-16; CSPG, chondroitin sulfate proteoglycan; hANG, human acellular nerve graft.

Artificial nerve repair conduits

Advantages of nerve repair conduits

Nerve repair conduit is another alternative to nerve autograft. In nerve conduit bridging technique, proximal and distal nerve stumps are inserted into the two ends of a nerve

conduit, and axons regenerating from the proximal stump grow through the conduit and selectively grow into their original pathways in the distal stump. The conduit provides trophic support for both stumps and prevents the invasion of the surrounding tissues into the gap between the two stumps.

Moreover, nerve conduits enrich the neurotrophic factors within the chamber and build a microenvironment, which enhances axonal regeneration after injury.³²

The ideal nerve repair conduits should possess the following features: 1) the diameter could be adjusted to accommodate repairing nerves of different diameters; 2) the length should be adjusted freely, to avoid anastomotic tension and ensure simple operation; 3) preventing the invasion of scar tissue outside and guide axonal growth in orientation; 4) ensuring that endogenous neuroactive molecules aggregate and exclude exogenous inhibitory molecules outside the conduits; and 5) the most important is they should avoid the suffering from nerve autograft.

Material research of nerve repair conduit

Nerve repair conduits can be divided into biological and synthetic nerve conduits.

Biological conduits

Biological conduits such as autologous arteries, veins, muscles,³³ and umbilical cord vessels have been widely used to repair relatively short nerve defects. These materials can provide support for the nerve in the short term and degrade to innocuous products after complete nerve regeneration. Some authors have used autogenetic epineurium,^{34,35} autogenic veins and autogenic small arteries, and even muscle fibers^{36–40} to repair peripheral nerve injury and reported satisfying results.

Synthetic nerve conduits

Synthetic nerve conduits include nondegradable and degradable nerve conduits.

Nondegradable nerve conduits

Nondegradable nerve conduits include silicone, plastic, and polytetrafluoroethylene tubes. The silica gel canal was the earliest artificial conduit.^{41,42} Lundborg et al⁴¹ used silicon tubes to repair nerve defects.¹ Hollow silicon tubes have been used to repair <1 cm long nerve defects in rat sciatic nerve,⁴³ and silicone tubes filled with SCs have been used to repair a 1.5 cm defect in rat sciatic nerve.⁴⁴ Although nondegradable nerve conduits eliminated the need to harvest autologous nerves, they always cause inflammation of the surrounding tissues and compression of nerve that could affect the regeneration of nerve axons.⁴⁵ Another disadvantage of these conduits is that they require a second surgery for removal, which could cause pain and more injury to the patient.

Degradable nerve conduits

The commonly used degradable materials include collagen,^{46,47} chitin,^{48,49} polyglycolic acid (PGA), polylactic acid (PLA), glycolide, trimethylene carbonate,⁵⁰ etc.

Rosen et al compared autologous nerve graft and PGA conduit to bridge 5 mm defects in rat femoral nerve. After 11 months, autologous nerve graft was found to be superior to PGA grafting only by means of axonal diameter, but having no difference by means of axonal count or electrophysiologic or functional characteristics between the techniques.⁵¹ den Dunnen et al used poly(DL-lactide-epsilon-caprolactone) nerve guides and autologous nerve grafts to repair rat sciatic nerve defects. Application of biodegradable nerve conduits resulted in faster and qualitatively better nerve regeneration across a short nerve gap (1 cm) than with the autologous nerve grafting method.⁵²

Techniques and methods for processing nerve conduits

Physical structures of nerve conduits significantly affect their performance. Processing methods of the nerve conduits mainly include solution casting – impregnated particles filtered out technology, melt injection – particles filtered out technology, solvent evaporation technique, physical roll film technology, weaving techniques, and the electrospinning technology. However, hollow biodegradable materials can be used to repair only relatively short nerve defects, and the functional recovery is still not satisfying. The combined use of fibronectin mats,⁵³ allogeneic SCs,^{54,55} ectogenous neurotrophic factors, and bridging tubes was proved to enhance neural regeneration after the injury.⁵⁶ Thus, the aim should be to mimic the natural repair process after nerve injury using a variety of techniques and methods to build complex nerve conduit that will integrate several factors to promote nerve regeneration within the conduit.⁵⁷ The methods of biomedical nanotechnology, electrospinning technology, and tissue engineering are able to develop new ways for these new conduits possessing good electrical, mechanical, and biological characteristics, which are beneficial to the axon guidance and the promotion of nerve regeneration.

Clinical application of nerve repair conduits

In the last several decades, nerve conduits have been used in clinical practice and have successfully improved the functional recovery after peripheral nerve injury.^{58–61} The current clinical applications of such materials are thus

Table 2 Nerve repair conduits approved by the FDA

Product name	Material	Diameter × length	Degradation time	Company
Neurotube™	PGA	2–8 mm × 4 cm	3 months	Synovis Micro Companies Alliance, Birmingham, AL, USA
NeuroMatrix™, Neuroflex™	Type I collagen	2–6 mm × 2.5 cm	7 months	Collagen Matrix Inc., Franklin Lakes, NJ, USA
Neurolac®	Poly(DL-lactide-caprolactone)	1.5–10 mm × 3 cm	16 months	Polyganics BV, Groningen, the Netherlands
Neuragen®	Type I collagen	2–7 mm × 2 cm	4 years	Integra Neuroscience, Plainsboro, NJ, USA
SaluBridge®	Polyvinyl alcohol hydrogel	2–10 mm × 6.35 cm	No degradation	SaluMedica LLC, Atlanta, GA, USA

Abbreviations: FDA, US Food and Drug Administration; PGA, polyglycolic acid.

mainly limited to treating small peripheral sensory nerve defects. These applications primarily use the type I collagen conduit Neuragen®, the PGA and PLA conduit Neurotube™, and the PCL copolymer conduit Neurolac® for nerve defects of £20 mm,⁶² and both types of tubes (biological and synthetic) have led to good clinical results,⁶³ even if they could not reach the effect level of autologous nerve repair. On the other hand, treatment of large-diameter, long-distance nerve regeneration remains the biggest challenge faced by the researchers in this field. Table 2 lists some nerve repair conduits approved by the US Food and Drug Administration (FDA) in the world.

Conclusion

Acellular nerve allografts and artificial nerve repair conduits are two kinds of the most promising substitutes for nerve autografts, and some products of both of them were approved by the FDA (US and China). The functionality of acellular nerve allografts was better than the artificial nerve repair conduits, due to the natural basal lamina structure of the former, which displays much more efficiency in the repair of longer nerve defects. However, nerve repair conduits possess some merits, eg, easy operation, readily available, low cost, and especially suitable for the repair of small gaps of nerve defects. Although significant progress was achieved in both kinds of the products, they could only repair a shorter length of nerve defect, comparing with autologous nerve graft, and the repair functionality needs to be improved. With technological advances in the life sciences and biotechnology, it is believed that better nerve repair products will come out in the near future.

Disclosure

The author reports no conflicts of interest in this work.

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