Regenerative Medical Care for Peripheral Nerves

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Abstract: In case of a peripheral nerve injury that did not permit instantaneous direct anastomosis, autologous nerve grafting was the only available corrective measure, yet the clinical results were far from satisfactory. Meanwhile, studies on artificial nerve conduits have been pursued from the beginning of the 1980s, and there has been a steady development of artificial nerve conduits capable of meeting clinical needs thanks to progress in tissue engineering. In 2002, PGA-collagen composite nerve conduits filled with collagen sponge were put to clinical use. The therapeutic outcome with the new nerve conduit was far more satisfactory as compared to nerve autografting. Regarding artificial nerve conduit transplantation, further research on technical innovation and development of more improved nerve conduits are essential. Artificial nerve conduit transplantation must be performed in a large number of diverse clinical cases in the future. Important matters remain to be scrutinized in this regard, e.g., multicenter and multidisciplinary collaborative studies to explore the indications for the transplantation in individual cases and their possibilities or to probe their limits and contraindications.

Key words: Peripheral nerve regeneration; Artificial nerve; Collagen; Polyglycolic acid (PGA)

Introduction

Cases of injuries to peripheral nerves of the extremities, fingers, toes or other regions caused by traumas due to traffic accidents or disasters and failing to attain repair have been increasing in recent years. There also exist no few cases where surgical resection of peripheral, i.e. somatic or autonomic, nerves is inevitable in association with such operations as cancer resection. Bridging nerve gaps with venous segments or transplantation of cadaver nerve allografts have been clinically applied in previous years in the event of peripheral nerve severance or surgical resection permitting no instantaneous direct anastomosis. Therapeutic outcomes, however, were not satisfactory. Eventually, autologous nerve grafting was almost the only available corrective measure, yet the clinical results were not very satisfactory.
Under this background, development of clinically usable artificial nerves has been increasingly sought. With the recent rapid progress in tissue engineering, new artificial nerve conduits have been developed and become applied in clinical settings. This article presents a brief review of this aspect of regenerative medical care.

Regeneration of Peripheral Nerves

1. Structure of peripheral nerve

The peripheral nerve consists of the nerve fiber comprised primarily of an axon projecting from a hillock of the nerve cell body in the spinal cord, with covering myelin and Schwann sheaths, and Schwann cells, which constitute a basic unit of the neuron. The axon serves to conduct electrophysiological excitation of the nerve, i.e., nerve impulses, and also has the transporting function to supply various substances required for maintaining nerve functions and structure.

A bundle of nerve fibers constitutes a nerve trunk. An axon coursing peripherad out of a nerve trunk enters an effector organ, where it is branched and transmits function.

2. Tissue reactions at site of nerve trunk injury

In the event of an injury involving nerve trunk severance, a regenerating axon is usually inhibited by associated fibroblast proliferation. The regenerating axon consequently fails to reach the peripheral stump, eventually forms a neuroma and is deprived of its function. A regenerating axon that fortunately has reached the peripheral stump may undergo misdirection if it fails to reach its target organ.

The distal stump of a severed nerve incurs wallerian degeneration due to impaired axonal nutritive flow and loses its function.

3. Approaches to peripheral nerve regeneration

(1) Direct anastomosis

A one-stage direct anastomosis may effectuate functional regeneration of a severed nerve if the nerve gap length is 5 mm or less, provided the anastomosed lesion is completely prevented from tension. Cases in which nerve anastomosis is practicable without any tension applied even if the gap is inconspicuous are rare in reality. Materials and methods to fill up nerve gaps have been sought.

(2) Objectives of reconstruction with the use of bridging materials

The purpose of the use of a joining device is to prevent intrusion of connective tissues from outside during the process of nerve bundle elongation or regeneration, to facilitate substance exchanges in and out of the joining device and capillary neovascularization on the joining device wall, and thereby to serve as a scaffold or to retain substances constituting a scaffold adequate for growth of the axon and Schwann cells within it. The following joining devices have been clinically applied.

i. Reconstruction with venous segment

A method of bridging nerve gaps by means of autologous venous segments has been applied for a long while but the regenerated nerves reported have been few because of poor vascular lumen retainability.

ii. Nerve autografting

The method is to transplant an autologous sensory nerve segment with relatively minor function into the lesion. In many of the cases treated by this technique, nevertheless, a fairly long period is required to recover nerve function and sensory nerve regeneration is sluggish, occasionally causing sensations of coldness and pain. Motor functional regeneration rates are often disappointing. New development of disorders at the site of an autologous sensory nerve graft presents another problem.

iii. Nerve allografting

In Europe and the United States, nerve grafts obtained from human cadavers are preserved frozen and used in clinical settings. With the progress in development of immunosuppressants since the 1990s, there have been considerable improvements in therapeutic out-
Peripheral Nerve Regeneration Using Artificial Nerve Conduits

1. Historical changes of artificial nerve tube

Attempts to regenerate severed peripheral nerves by bridging nerve gaps using nerve tubes made of artificial materials have been made for several decades. These devices have been changed and developed step by step. Significant improvement of artificial nerve tube has led to their current use in Japan.

2. Artificial nerve conduits made of nonabsorbable artificial materials

Beginning in the early 1980s, replacement surgery using artificial nerve conduits made of nonabsorbable materials such as silicone has been in practice for the treatment of severed nerves, and there are reports documenting partial recoveries with the technique. All these reports, however, are of studies demonstrating recovery in morphological continuity of a nerve with a gap as extremely small as about 10 mm in small laboratory animals such as rats, and recovery in motor function has rarely been achieved. The outcome was in no way superior to that of nerve autografting in any of the reported studies.

3. Artificial nerve conduits made of absorbable artificial materials

It became recognized from the latter half of the 1980s that degradable-absorbable materials in the body after attaining nerve regeneration are preferable. With the progress in material synthesis and bridging techniques, artificial nerve conduits made of absorbable synthetic materials have been developed. Substances such as polyglycolic acid (PGA) and polylactic acid are under investigation as biodegradable-absorbable synthetic materials.

4. Artificial nerve conduits made of absorbable natural materials

Since the beginning of the 1990s a number of reports describing that natural biomaterial collagen is satisfactory as a material for regeneration of various tissues/ organs and is useful also for peripheral nerve regeneration. Thus, comparative experiments with artificial nerve conduits prepared comprising collagen extract alone versus autologous nerve grafting were performed. The results of the study with the conduits were comparable with those of nerve autografting, however, and the regenerated nerves were found much inferior to intact nerves.

PGA-Collagen Composite Nerve Conduits

1. Hollow PGA-collagen composite nerve tube

Collagen is rich in active radicals that promote tissue regeneration but is so rapidly absorbed in vivo as to be unable by itself to retain its shape, tubular in this case, over a certain length of time. Therefore, novel artificial nerve tubes comprising collagen compounded with PGA, which is inferior to collagen in affinity with body tissues but capable of retaining its shape in the body for not less than 3 months, was developed to serve as a barrier against connective tissues in the mid-90s.

The tube applied for repairing the sciatic nerve in a cat proved to afford much improvement in surgical outcome, as compared with previous methods in terms of postoperative motor function and electrophysiological tests, along with the evidence of axonal transport beyond a nerve gap. However, the gap length was approximately 25 mm, which is insufficient for clinical application.

These experiments were carried out using...
hollow tubes. As it takes a long time for a regenerating nerve to bridge a lengthy gap through a hollow tube lumen without footholds for reconstruction, the artificial nerve conduit may be biodegraded-absorbed in place and permit intrusion/growth of cicatrization tissue from outside before completing the bridging.

2. PGA-collagen composite nerve tubes filled with collagen fibers

For the above reason, the possibility of providing a scaffold comprising collagen for reconstruction through the hollow tube lumen was explored. A collagen fiber-filled, PGA-collagen composite artificial nerve conduit was prepared at the end of the 1990s and assessed by trying it in bridging an 80-mm gap by replacement neuroplasty of the fibular nerve in a dog.7)

The regenerated nerve was proven electrophysiologically to be virtually comparable with the intact nerves in both motor and sensory functions. Light and electron microscopic examination demonstrated morphologic evidence of regenerated thick nerve fibers and nerve trunk, and there was recovery in gait and jumping capacity.

3. PGA-collagen composite nerve tube filled with collagen sponge

In recent years, many published articles have stressed the importance of three-dimensional matrices.8) The present author and his coworkers developed a PGA-collagen composite nerve conduit filled with collagen sponge (Fig. 1) in 2000 on the rationale that three-dimensional structures would be superior to unidimensional structures such as fibers to serve as scaffolds for axonal elongation and Schwann cell proliferation.9) This nerve conduit has proven to be remarkably superior not only because of greater foothold and surface areas but also in industrial reproductivity.

In a canine peroneal nerve 80-mm gap bridging experimental study, the author and his associates assessed the sponge-filled conduit in comparison with the fiber-filled conduit, with the results demonstrating superiority of the sponge-filled conduit.9) Assessments of the regenerated nerve in various respects have shown highly potential clinical applicability of this new artificial nerve conduit.10)

Present Status of Medical Care for Peripheral Nerve Regeneration

1. Controlled release of growth factors, etc.

In the event of a local injury, growth factors are released spontaneously at the site of the injury. Artificially added growth factors may accelerate tissue regeneration at the injury site. The author and his associates make it a rule to intraoperatively add laminin from the
human placenta.\textsuperscript{7,9,10} Further investigation will be needed for administration of appropriate factors at appropriate periods.

2. Clinical application in humans

PGA-collagen composite nerve conduits filled with collagen sponge have been clinically used in several different specialties such as surgery, orthopedics, etc. primarily at university hospitals in the Kansai Area since the spring of 2000 in this country, with satisfactory results (Fig. 2).\textsuperscript{11} Further, in the Netherlands and certain other European countries, cooperative multicenter clinical trials of the device have been in progress since last year.\textsuperscript{12}

3. Topics for future investigation

Of the studies on peripheral nerves, there has been no data published concerning regenerative treatment for autonomic nerves. In clinical application, indications of the techniques for long-standing lesions, chronic degenerative disorders, and acute phase lesions remain to be evaluated.

Conclusion

After the early 1980s, reports began appearing in the literature of animal experiments demonstrating peripheral nerve regeneration across and beyond gaps, though only a few mm in length, bridged by artificial nerve conduits after nerve severing.

With the subsequent rapid progress in tissue engineering, development of artificial nerve conduits capable of meeting clinical needs followed. PGA-collagen composite nerve conduit filled with collagen sponge was put into clinical use in surgical cases in 2002 in Japan, and a lot of satisfactory therapeutic outcomes have been reported. It may thus be said that the era of practical application of peripheral nerve regeneration with artificial nerve conduits has come true.

As artificial nerve regeneration has been just realized in its clinical application, further technological innovation including the use of growth factors and development of more improved artificial nerve conduits are now considered to be growing importance.

There has been no study data published concerning regenerative treatment for autonomic nerves bearing importance in the function after visceral surgical intervention, though being likewise peripheral nerves. This, as well as clinical

Fig. 2 An operation performed on a 53-year-old man (Courtesy of Dr. Inada, Lecturer, Nara Medical University) (a) The patient incurred an injury involving a crushed heel and severance of the posterior tibial nerve three years before. A neuroma (↓) formed in due course. (b) Upon resection of the tumor, the severed nerve lesion was replaced with an artificial nerve conduit about 3 cm in length (↓). One month after the operation, the patient’s nerve recovered both sensory and motor functions almost to normal, and the patient was completely free from tumor-associated pain.
indications of the techniques and their potential, remain as problems that need to be resolved.

REFERENCES