Nerve Repair by Means of Tubulization: Past, Present, Future

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Abstract

Peripheral nerve injury may result in injury without gaps or injury with gaps between nerve stumps. In the presence of a nerve defect, the placement of an autologous nerve graft is the current gold standard for nerve restoration. The clinical employment of tubes as an alternative to autogenous nerve grafts is mainly justified by the limited availability of donor tissue for nerve autografts and their related morbidity. The purpose of this review is to present an overview of the literature on the applications of nerve conduits in peripheral nerve repair. Moreover, the different steps that are involved in the design of an ideal nerve conduit for peripheral nerve repair, including the choice of biomaterial, fabrication technique, and the various potential modifications to the common hollow nerve tube, are also discussed.

Keywords

- nerve gap
- nerve repair
- nerve guides
- neurotrophic factors

Although Paulus Aegineta (626–696 AD) is the first physician who postulated the restoration of severed nerves,[1] before the 1700s surgeons were generally afraid to manipulate nerves. Introduction of microsurgical techniques[2] in peripheral nerve surgery and the establishment of the principle of tension-free repair[3] allowed inspired surgeons such as Narakas, Millesi, Allieu, Brunelli, Terzis, Doi, Gu, and others to suggest several new approaches to nerve reconstruction.

With the further accumulation of knowledge and an increasing understanding of nerve anatomy, function, and physiology, a more precise understanding of the process of nerve healing ensued that initiated the establishment of rational strategies for nerve repair, taking it from wild speculation to a more predictable reality. Many factors influence the success of nerve repair and reconstruction. The age of the patient, the timing of nerve repair, the level of injury, the extent of the zone of injury, the technical skill of the surgeon, and the method of repair all contribute to the functional outcome after nerve injury.[4]

Injured nerves do not spontaneously restore their function. Continuity of the nerve has to be reestablished first by microsurgical intervention such as end-to-end repair. When nerve endings cannot be rejoined without tension, interposition nerve grafts are used for nerve reconstruction. The purpose of using a nerve graft is to provide a conduit consisting of a basal lamina scaffold together with their corresponding Schwann cells. However, autologous nerve grafting is associated with morbidity, including potential neuroma formation at the donor site, as well as frequent disappointing functional outcomes.[5] Furthermore, donor nerves are often of small caliber and limited in number.

For these reasons, increasing efforts have been made over the last three decades to seek effective alternatives to autologous nerve grafts. In long nerve defects, nerve allografts may be a suitable alternative when the length of an autologous nerve graft is a limiting factor.[6] Although the use of nerve allografts prevents the possible donor-site morbidity following harvest of an autologous nerve graft, systemic immunosuppression is required for 18 months.[7]

The tubulization technique with nonabsorbable or absorbable tubes has shown promising results experimentally and clinically when used to bridge nerve gaps, or to enclose the nerve suture site.[8–11] A nerve tube is a tubular structure designed to bridge the gap of a sectioned nerve, protect the nerve from the surrounding tissue (e.g., scar formation), and guide the regenerating axons into the distal nerve stump.

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Although their clinical use has been limited mainly to the repair of relatively small defects (less than 3 cm) in small-caliber digital nerves,[12–14] the potential for extending clinical applications to the repair of larger defects and larger mixed or motor nerves[15] has made the development of an ideal nerve tube appealing for both scientists and the medical device industry. The basic design of these tubes is similar, but they are made of different biomaterials using various fabrication techniques. As a result, these nerve tubes also differ in physical properties.

The purpose of this review is to present an overview of the literature on the applications of nerve conduits in peripheral nerve repair. Moreover, the different steps that are involved in the design of an ideal nerve conduit for peripheral nerve repair, including the choice of biomaterial, fabrication technique, and the various potential modifications to the common hollow nerve tube, are also discussed.

Historical Background

The employment of tubulization techniques has seen major advances over the past 30 years, and this approach to peripheral nerve surgery has a long history. Throughout the 19th century scientists had experimentally investigated the possibility of using a non-nervous conduit for bridging a nerve defect.[16–26]

In 1880, Glück[16] first used the central canal of decalcified bone to provide a pathway between the severed stumps of a divided nerve. Based on this study, Vanlair,[17,18] in 1882 used decalcified bone as tubes for bridging a 3-cm gap of the sciatic nerve in the dog. Histological examination showed nerve regeneration, which replaced the resorbed bone distally. Bügner,[19] in 1891, reported the utilization of human arterial grafts to bridge nerve gaps in the dog.

Notthaft,[20] in 1893, attempted to bridge a gap in the sciatic nerve of rabbits using rabbit aorta, but without any sign of regeneration. Willard,[21] in 1894, performed a tubulization procedure using decalcified bone. In 1904, Foramitti,[22] and in 1915, Nageotte[23] observed initial nerve regeneration in an arterial and vein graft followed by subsequent graft disintegration.

Wrede,[24] in 1909, introduced the use of vein conduit to support nerve regeneration across nerve gaps. Weiss and Taylor,[25,26] in the middle of the past century, in an attempt to prove that nerve regeneration was independent of tropic and trophic factors, used biological (from artery, either fresh or freeze-dried and rehydrated) along with artificial conduits from tantalum in their experiments..

The century-old search for the ideal nerve conduit has encompassed the use of autogenous and exogenous biological materials and the use of artificial materials. Since the first attempts, many different materials have been used to fashion nerve guides. The categories of nerve conduits include autogenous biological conduits, nonautogenous biological conduits, and nonbiological conduits.

Mackinnon and Dellon were the first to study nerve regeneration in monkeys to compare the electrophysiologic results of nerve graft versus polyglycolic acid conduit repairs, using bioabsorbable conduits of various lengths.[27,28] Both of their studies demonstrated that the primate peripheral nerve can regenerate across 3-cm nerve gaps when guided by an appropriate nerve conduit.

Contemporary nerve guides are mostly made of biodegradable materials such as aliphatic polyesters or polyurethanes, collagen, chitosan, or excised vein. Nonetheless, silicone has long been the most frequently used material for fabrication of nerve guides, but its nondegradability and relative stiffness have limited its use.

In more recent years, research has been focused mainly on improving single-lumen nerve guides to bridge larger nerve gaps (longer than 3 cm). Different techniques have been applied to make nerve tubes permeable. Nerve tubes have been filled with collagen- and laminin-containing gels, Schwann cells, and growth factors.

The Problem

A nerve injury differs from most other types of tissue injury in the body, since not only a local repair process is required. Transection of axons has implications for the whole length of the neuron, and the repair process involves outgrowth of axons over very long distances. Following peripheral nerve injury, morphologic and metabolic changes occur. End organs also undergo changes after nerve injury.

Within the first few hours to days, morphologic changes occur in the corresponding neurons, including swelling of the cell body, displacement of the nucleus to the periphery, and disappearance of basophilic material from the cytoplasm, a phenomenon termed chromatolysis.

Within 2 to 3 days of injury, edema forms in the distal axonal stump. This degenerative process is called Wallerian degeneration after Augustus Volney Waller, who first characterized morphological changes in sectioned frog glossopharyngeal and hypoglossal nerves 160 years ago.[29] The proximal portion retracts, and the neuron, now deprived of its normal synaptic targets, is vulnerable to retrograde death by apoptosis.

During Wallerian degeneration, Schwann cells from the distal stump proliferate, help inflammatory infiltrating cells to eliminate debris, and upregulate the synthesis of trophic and tropic factors. The Schwann cells close to the site of transection go through the same type of changes as the Schwann cells in the distal nerve segment.

After 3 to 6 weeks, endoneurial tubes are left behind that consist of basement membranes lined with Schwann cells, which proliferate and organize into columns, guiding the regenerating axonal sprouts within the basement membranes to their targets. Metabolic changes within the neuronal cell body involve switching the machinery normally set up to transmit nerve impulses to manufacturing structural components needed for reconstruction and repair of the damaged nerve.

When axons remain without connection to their target tissue over significant periods of time they lose the ability to regenerate, and the possibility for functional recovery is lost. Complete atrophy occurs within 2 to 6 weeks of denervation.

Fibrosis occurs in motor fibers at 1 to 2 years and fragmentation and disintegration occur by 2 years. It is generally agreed that functional recovery is diminished if the nerve does not reach the motor end plate by 12 months.

In contrast, it has been long known that although axons in the peripheral nervous system (PNS) are able to regenerate after being severed, this does not hold true for injured central nervous system (CNS) axons. Studies in the early 1980s[30–35] suggested that the environmental milieu available to injured PNS axons might be more favorable than that encountered by injured CNS axons. Moreover, these studies demonstrated that when injured CNS axons are provided with a supportive substratum, such as a segment of peripheral nerve, they are capable of regenerating for long distances and of being directed toward a specific targeted area.

After traumatic injury to the spinal cord, two events take place that have been associated with impaired neurological function and ineffective attempts at axon regeneration: the acute primary mechanical insult and the chronic secondary reactive damage, the hallmark of which is molecular inhibitors.[36] Attempts of CNS axons to regenerate after axon injury are partially suppressed by inhibitory signals in the injured axon tip.

Molecular inhibitors of axon growth have been particularly linked to three main components of the lesion: the fibrotic scar, the glial scar tissue, and the damaged myelin.[37] The two major classes of CNS regeneration inhibitors are the myelin-associated inhibitors (MAIs) and the chondroitin sulfate proteoglycans (CSPGs). These molecules limit axon regeneration, and, by interfering with their function, achieve some degree of growth in the adult CNS.[38] Thus, the lack of neurotrophic support contributes to the absence of spontaneous regeneration in the CNS.

When a nerve gap is incurred that cannot be repaired by end-to-end suture without tension, the current repair method is a sutured autologous graft from another nerve of lesser functional importance. However, the use of autologous grafts has some disadvantages such as the need of a second surgical site, loss of the donor nerve function, a limited supply of donor nerves, and the mismatch between nerve and graft dimensions.

Development of alternative treatments, especially for larger defects, is necessary to bridge the gap between the proximal and the distal nerve stumps. Tubulization, which involves enclosure of the ends of a severed nerve by a tube, offers a guide to regenerating axons to the distal stump.[39] The tube concept is based on the following principles: (1) nerve regeneration will be favored if the surgical trauma is minimized; (2) a short gap between the nerve ends inside the tube will increase the possibilities for neurotrophic and neurotropic mechanisms to act; and (3) a closed tube system will allow accumulation of neurotrophic factors that are normally synthesized in a nerve trunk after trauma (and prevent interference from the surrounding milieu).[40]

Many attempts have been made to bridge peripheral nerve gaps by various nerve conduits. Most studies have used short-gap models of less than 25 mm.[41–46] The few studies of longer gaps[8,28,47–54] resulted in poor outcomes similar to allografts. There has been only one report of functionally successful artificial conduit applied to a gap of 80 mm in dogs.[48] In this study, Matsumoto et al[48] reported successful nerve regeneration, using a polyglycolic acid (PGA)-collagen tube filled with laminin-coated collagen fibers, across an 80-mm nerve gap in the dog peroneal nerve after 12-month follow-up.

Successful regeneration after tubulization depends on the formation of a new extracellular matrix scaffold, over which blood vessels, fibroblasts, and Schwann cells migrate and form a new nerve structure.[55] Regeneration fails through long gaps (longer than 3 cm) most likely because the regenerative capabilities of the nerve stumps have been exceeded and Schwann cells are not able to provide a permissive environment for axonal elongation.[56]

By using a nerve guide, guidance of regenerating axons is not only achieved by a mechanical effect (the wall and lumen of the nerve guide), but also by a chemical effect (accumulation of neurotrophic and neurotropic factors). This combination of chemical, physical, and biological factors has made the development of a nerve tube into a complex process that requires close collaboration of bioengineers, neuroscientists, and peripheral nerve surgeons. Engineering the ideal tube for bridging large nerve defects remains a challenge.

Designing the Ideal Nerve Tube

Hudson et al[57] listed several important properties that nerve conduits should possess: easily fabricated with the desired dimensions and topography, implanted with relative ease, and sterilizable. The ideal nerve tube should also be nonimmunogenic, causing neither local tissue irritation nor allergic response.[58]

The categories of nerve conduits include autogenous biological conduits, nonautogenous biological conduits, and nonbiological conduits. Several materials, either of biologic origin[28] or synthetically-fabricated,[50] have been used for designing nerve tubes.

The choice of biomaterial and fabrication technique is an important first step in the development of a nerve tube. Ideally, the nerve conduit should be porous to allow and control nutrient exchange, and biodegradable to eliminate the need for its removal.[59] Moreover, the tube material must strike a balance between an appropriate rate of degradation and its intrinsic mechanical properties, which should minimize inflammatory responses and prevent nerve compression.

The first nerve conduits used in rodent and human trials were composed of nonresorbable polymers based on silicone and poly-tetrafluoroethylene (Gore-Tex).[60–62] Potential drawbacks of nonresorbable nerve guides are permanent fibrotic encapsulation of the implant and late loss of functional recovery caused by compression of axons within the conduit.

With the evolution of tissue engineering, a second generation of nerve guide conduits has been synthesized from bioresorbable polymers of synthetic or biological origin. Extensively used synthetic polymers, including polylactic

acid (PLA)[32] and poly(D,L-lactide-co-glycolide) (PLGA)[63] are known for their ease of processing, low inflammatory response, and approval by the U.S. Food and Drug Administration (FDA).

Several nerve tubes are currently being marketed, including Neurotube (Synovis Surgical Innovations, Deerfield, Illinois, USA), Neurolac (Ascension Orthopedics, Plainsboro, New Jersey, USA), and NeuraGen (Integra LifeSciences, Plainsboro, New Jersey, USA). A few of these resorbable conduits have been tested in small cohorts of humans with short nerve defects.[11,14,64,65] Currently, these nerve conduits can only be used in cases where the nerve gap is less than 3 cm in length.[66] Additionally, some nerve conduits' designs and regeneration strategies are more successful than others in yielding functional recovery that is similar to the gold standard, the nerve autograft. Thus, current research is focused on strategies for improving nerve conduit design and increasing regeneration potential.

Wall thickness is also an important factor. If the conduit wall is too thick, it will degrade too slowly, thus lengthening the time of possible foreign body reaction. On the other hand, a thin-walled guide could degrade too quickly, resulting in loss of the supportive structure. Empirically, biodegradable nerve guides with an internal diameter of approximately 1.5 mm and a wall thickness of approximately 0.3 mm have given optimal results for peripheral nerve regeneration.

Permeability of a conduit is an important nerve tube property because nutrients and oxygen need to diffuse into the site of regeneration before the tube becomes vascularized. Absorbable tubes, such as poly-glycolic acid conduits, have increased permeability, thus improving the interaction of the nerve ends with the surrounding environment. This interaction has been demonstrated to improve axonal regeneration when compared with impermeable nerve guides.[58,67]

The favorable effects of permeable tubes may be attributed to different reasons, including metabolic exchange across the tube wall; diffusion into the guide lumen of growth promoting factors generated in the external environment; retention of trophic factors secreted by the nerve stumps; or a combination of all these.[67] Hence, the size of the tube wall pores and its stability over time seem to be important factors determining the flow of different constituents that may promote or inhibit regeneration. Permeability depends on the hydrophilic properties of the material and the technique used.[68]

Flexibility is an important nerve tube property, especially in the repair of larger nerve gaps, because the ends may not be in the same plane/line and the gap that needs to be bridged may cross a joint.[69] Nerve conduits should be pliable enough to glide and bend with the limb's movements, yet stiff enough not to collapse in vivo.

Moreover, the ideal nerve tube should remain intact for the time axons need to regenerate across the nerve gap and then degrade gradually with minimal swelling and foreign body reaction.[69] Bioreabsorbable tubes that degrade too quickly may not survive for a long enough time for nerve regeneration and maturation. If the nerve guide breaks down at an early stage, fibrous tissue can be formed inside the tube and impair further maturation of the regenerated nerve.[70]

Surgical Technique

An assessment of the soft tissues at the injury site is a mandatory step to determine whether reconstruction should be performed before, or concomitant with, the nerve repair. Exploration of the injured nerve takes place proximal and distal to the lesion site until normal nerve to inspection and palpation is reached.

The surgeon then trims back the nerve ends to a level where there is neither intraneural hemorrhage for an acute injury nor interfascicular scarring for a subacute injury. The proximal and distal stumps of the nerve are approximated without tension to prevent torsion, which can change the orientation of fascicles in the two nerve stumps.

Commercially available conduits range from 1.5 mm to 10.0 mm in diameter. The chosen conduit should be slightly larger than the diameter of the nerve. The technique for preparing the tube varies considerably in relation to the type of material employed. In general, the tube is soaked in plain or heparinized saline before use.

After the correct-sized conduit is chosen, the nerve tube is stabilized to the neighboring soft tissues with interrupted sutures and sewn in a U-shaped fashion over the tube. Anchoring of the tube facilitates insertion and suturing of the nerve stumps in the tube ends. Both nerve stumps are inserted 2 mm into each end of the tube and fixed by means of two or three interrupted epineurial stitches (9–0 or 10–0 nylon suture) under adequate magnification.

The technique of anchoring the nerve ends to the tube is as follows: the nylon is passed through the wall of the tube, at least 1 mm from its end. The stitch is passed in and out through the epineurium, 2 to 3 mm from the cut end. Then, the suture is passed through the tube wall, close to the point where the suture is first penetrated. Finally, the nerve end is gently inserted into the tube by tension on the nylon and fixed in place by means of a knot on the outside of the tube.

The conduit's lumen is filled with sterile saline to prevent blood products and clot from forming within its lumen. Some studies suggested the use of heparin at this step, instead of saline, to decrease blood clot formation, which can impede axonal regeneration by blocking the axon's advancing growth cone.[18,23] Closure of well-vascularized soft tissues over the tube is critical to achieve uninterrupted wound healing.

Autogenous Biological Conduits

Among the various different types of biological tubes that have been used for bridging a peripheral nerve defect, veins and skeletal muscles are the organs that receive the most attention by researchers.

Artery: The idea of using nerve conduits from vascular origins is not new and has been studied since the end of the 19th century. Conduits made by small segments of artery were first employed by Bünger in 1891,[19] who obtained successful nerve regeneration. Despite the experimental

use of artery as a nerve guide, this technique has not been implemented in clinical practice, likely due to a lack of suitable donor vessels.

Vein: The first employment of veins as nerve conduits was reported by Wrede in 1909,[24] who successfully repaired the median nerve of a male by means of a 45-mm-long vein tube. Strauch et al,[71] in an experimental rabbit model, determined that good axonal regrowth occurred in a vein nerve conduit of 3 cm in length. For lengths between 3.5 and 5.25 cm, rare regrowth was evident, whereas with gaps measuring 6 cm, nerve regeneration was found for a length of only 1.45 cm.

Chiu and Strauch, in 1990, validated the clinical application of autogenous venous nerve conduits.[72] They reported 15 secondary reconstructions after resection of symptomatic neuromas in the hand and forearm using either a vein graft or a conventional nerve graft. Although superior results were obtained from nerve grafting, in vein conduit patients there was successful return of two-point discrimination. Although Chiu[73] demonstrated the efficacy of autogenous venous nerve conduits in both acute and delayed nerve repairs of digital nerves, Walton et al[74] suggested that veins were not successful as nerve guides in delayed nerve repairs.

Tang et al,[75] in 1993, used autologous vein grafts to bridge 18 digital nerves during tendon surgery in zone II. Interestingly, the vein lumen was seeded with nerve slices. Recovery of sensibility was evaluated as good or excellent in 11 digital nerves. Two years later, the same author[76] reported another series of 16 patients with the same method. This clinical study suggested that vein conduits with the interposition of nerve tissue is a practical and reliable procedure for nerve defects between 2.0 cm and 4.5 cm.

In general, vein conduits have not been recommended for clinical use, as there is always the possibility of collapsing because their thin walls can be constricted from surrounding tissues. However, Tseng et al[77] have demonstrated in the rat that hematoma and thrombin within the vein can conversely keep the conduit patent.

Muscle: The rationale for the use of skeletal muscle as a nerve conduit is the availability of a longitudinally oriented basal lamina and extracellular matrix components that direct and enhance regenerating nerve fibers.[78,79] These factors are not available in vein grafts or in degradable or nondegradable nerve conduits when used for bridging. Also, donor sites for muscle grafts are numerous. The main disadvantages of this technique are the risk that nerve fibers can grow out of the muscle tissue during nerve regeneration and that a donor site is necessary to harvest the muscle tissue.[80]

The use of skeletal muscle autografts for nerve repair was first reported in 1940.[81] Studies in animals and humans have demonstrated that both fresh and denatured muscle conduits can lead to successful regeneration and even lead to superior results when compared with end-to-end sutures.[82–85] Most studies suggest an upper limit of 5 cm for the largest animal models (sheep femoral nerve) and 2 cm in rat sciatic nerve. However, in longer nerve defects, the effectiveness of skeletal muscle autografts may be progressively reduced.

Pereira et al[84,85] in two studies used denatured muscle grafts for nerve defect reconstruction. In a series of 12 patients with leprosy,[84] they bridged defects between 25 to 60 mm in nine posterior tibial and three median nerves. They reported encouraging results. In the second study,[85] they described 24 digital nerve defects between 15 to 28 mm. They reported better results than with nerve grafting.

Tendon: Brandt et al,[86] using the rat sciatic nerve model, suggested that tendon grafts can be used as nerve conduits for bridging defects of 10 mm. The extracellular matrix components of the rat tail tendon, along with the longitudinal arrangement of the collagen bundles in the graft, constitute a favorable substrate for regenerating axons and other cellular elements involved in the regeneration process. Furthermore, Brandt et al[87,88] suggested that based on functional and morphometric evaluation, the tendon autograft does not differ from the freeze-thawed muscle graft in supporting axonal regeneration across an extended defect. Nishiura et al[89] suggested that the main advantage of this technique is that there is abundant graft material with limited loss of function.

Nonautogenous Biological Conduits

Collagen: Collagen is the major component of the extracellular matrix and is known to promote cellular proliferation and tissue healing.[90–92] It has been described that extracellular matrix components (mainly collagen, laminin, and fibronectin) localized in the endoneurium and basal membranes are presumptive trophic factors that guide the growth cones.[93]

Archibald et al[92] have demonstrated the effectiveness of nerve guides constructed from purified type I bovine collagen in the regeneration of a 5-mm nerve gap in the nonhuman primate. Keilhoff et al,[94] using the rat sciatic nerve model, tested collagen type I/III tubes as a potential nerve guiding matrix. They suggested that collagen-type I/III can serve as template to design "living" nerve conduits, which may be able to ensure nerve regeneration through extended nerve gaps.

Ashley et al[95] used collagen matrix tubes (Neurogen) instead of autologous nerve graft material in five patients with obstetrical brachial plexus palsy. They used the collagen tubes for gaps smaller than 2 cm and diameters less than 5 mm. According to their results, four out of the five patients made a good recovery and were functional by 2 years postoperatively.

Nerve allografts: The earliest report of clinical nerve allografting was in 1885 by Albert.[96] However, the results were disappointing. Renewed interest in this technique was not seen until investigators began to understand the immunological responses to nerve allografts and developed techniques to combat antigenicity, such as pretreatment with irradiation and lyophilization.[97]

Allografts have been broadly studied as a potential alternative reconstructive material. This tissue has met with moderate success in its clinical application[98] serving as a temporary scaffold for regenerating fibers. Allograft can provide an abundant supply of donor nerves. However, significant potential side effects of necessary immunosuppression[99,100] and the risk of disease transmission[101] limit their application to only the most severe injuries.

In contrast to autografts, the use of nerve allografts relies upon the viability of both host and donor Schwann cells. The donor Schwann cells act as support cells for remyelination and as facultative antigen-presenting cells. This dual role prohibits a complete removal of these presumed primary sources of major histocompatibility complex (MHC) II molecules and simultaneously maintains the requirement for systemic immunosuppression.[102,103]

Multiple studies in rat and primate models have analyzed the short nerve allograft response with and without systemic immunosuppression.[104–108] MacKinnon et al[109] suggested that the immunosuppressed allograft functions as a structural scaffold for regenerating host nerve fibers. As regeneration proceeds, donor Schwann cells are lost and replaced by host Schwann cells. On the contrary, a nonimmunosuppressed allograft undergoes scarring and fibrosis, providing a mechanical barrier to regenerating host fibers.

In 1992, Mackinnon et al[109] reported the clinical outcome of seven patients who underwent reconstruction of long upper- and lower-extremity peripheral nerve gaps with interposition peripheral nerve allografts. Six patients demonstrated return of motor function and sensation in the affected limb, and one patient experienced rejection of the allograft secondary to subtherapeutic immunosuppression.

Elkwood et al[110] reported a series of eight patients with multilevel brachial plexus injuries that were selected for transplantation using either cadaveric allografts or living-related donors. Seven patients showed signs of regeneration, demonstrated by return of sensory and motor function and/or a migrating Tinel sign. One patient was noncompliant with the postoperative regimen and experienced minimal return of function despite a reduction in pain.

Nonbiological Conduits

Several reports on the employment of nonbiological materials for tubulization were published during the 20th century.[111] Garrity,[112] in 1955, reported on the unsuccessful employment of polyethylene, polyvinyl, and rubber in three patients with very long (>7 cm) nerve defects. Also, the widespread use of tantalum metal cuffs on soldiers during World War II led to unsatisfactory clinical results.[113]

Nonbiological conduits are divided in nonabsorbable and absorbable ones. Both have been proven to permit nerve regeneration through the conduit. However, nonabsorbable nerve guides have the disadvantage that they remain in situ as foreign bodies with subsequent scar tissue formation, which results in compression of the newly formatted nerve.[114]

Nonabsorbable Nerve Conduits

Silicone: Merle et al[115] were the first to use silicone nerve guides clinically and reported successful nerve regeneration in three patients. Silicone is not biodegradable, nor is it permeable to large molecules. Chen et al[116] showed that silicone nerve guides filled with a collagen-, laminin-, and fibronectin-based gel resulted in a more mature organization of regenerating axons when compared with controls.

Lundborg et al[10,61,117] presented three prospective studies with successful regeneration through silicone guides in short gaps of less than 5 mm. Long-term follow-up of patients treated for median and ulnar nerve deficits demonstrated that the use of a silicone tube was at least as good as direct suture repair. However, some of the patients in these studies required removal of the silicone because of irritation.

In 1999, Braga-Silva[118] described the use of silicone tubes for late repair of median and ulnar nerves in 26 patients. He suggested that silicone tubes were effective in the repair of peripheral nerve injuries with gaps of up to 3 cm, with better results in the ulnar nerves than in the median nerves. However, the silicone tubes had to be removed in seven patients because of irritation at the implantation site as well as loss of nerve function.

Other materials: Stanec et al[119] evaluated the effectiveness of the expanded polytetrafluoroethylene (ePTFE) tube in clinical repair of median and ulnar nerves in 43 patients. According to them, the ePTFE conduit is a reliable and successful surgical procedure for nerve repair in reconstruction of nerve gaps up to 4 cm between the ends of median and ulnar nerves at various levels of the upper extremity.

Pitta et al[120] evaluated regeneration associated with the use of Gore-Tex (GT; WL Gore & Associates, Flagstaff, Arizona, USA) vein graft tubes for repair of the inferior alveolar nerve and lingual nerves lesions in seven patients. The nerve defects were all smaller than 3 mm. Only two patients had any return of sensation. The authors suggested that Gore-Tex tubes are not recommended for nerve reconstruction of the inferior alveolar nerve and lingual nerve lesions.

Absorbable Nerve Conduits

Polyglycolic acid: PGA conduits are the most commonly used guides, both experimentally and clinically. PGA is a bioabsorbable substance that is currently used as a commonly chosen suture material for wound closure.[50,121] It is absorbed in the body by hydrolysis within 90 days of implantation.[122] The PGA conduit unfortunately has two drawbacks. First, these tubes cost more than the suture used in a standard repair. Second, it is reported that extrusion of the tube can be encountered due to the poor quality of the skin overlying the tube. In 1999, the U.S. Food and Drug Administration approved the use of PGA tubes (Neurotube; Neuroregen LLC, Bel Air, Maryland, USA) in humans in the United States.

Early support for the PGA tube was provided by Dellon et al,[8] who compared the regeneration achieved after 1 year in a 3-cm ulnar nerve gap in monkeys using a PGA conduit compared with an interfascicular sural nerve graft. The results suggest that PGA conduits are a good alternative to short nerve grafts.

Matsumoto et al[48] reported successful nerve regeneration, using a PGA-collagen tube filled with laminin-coated collagen fibers, across an 80-mm nerve gap in the dog peroneal nerve after 12-month follow-up. The tube was made of cylindrically woven PGA mesh and its outer and inner surface were coated with amorphous collagen layers. The conduit was reinforced with PGA mesh, as it was believed that if the outer tube was made from collagen alone, it might degrade too quickly to

maintain enough space for good axonal outgrowth and the ingrowth of scar tissue might prevent nerve regeneration in the case of a long gap. The authors provided evidence that this conduit effectively guided peripheral nerve elongation with good function recovery across a wider gap than previously reported for artificial nerve conduits.

Weber et al[14] described a prospective, randomized, multicenter study of the use of PGA tubes versus standard repair. They studied 136 nerve transections in the hand in 96 patients and found that repair with PGA conduit produced superior results for short gaps of less than 4 mm when compared with end-to-end repair. For longer defects of up to 30 mm, they demonstrated superior results when compared with nerve autografts.

Polyesters: PLGA and poly(caprolactone) (PCL) are FDA-approved biodegradable polymers that are currently being examined as matrices for tissue-engineered applications.[50,123] Copolymerization has been used to obtain these materials with characteristics tailored to degradation behavior, mechanical performance, thermal properties, and wettability.

Polymer crystallinity affects permeability and biodegradation of nerve guides. The crystalline phase is inaccessible to water and other permeable molecules. Biodegradation and permeation decrease with an increase in crystallinity.[124] Crystalline debris formed during degradation may cause an inflammatory response, which may jeopardize the regeneration process and the recovery of nerve function.

Pêgo et al[125] investigated the physicochemical properties of synthetized copolymers of trimethylene carbonate (TMC) and e-caprolactone with the aim of assessing their potential in the development of flexible and slowly degrading artificial nerve guides. They suggested that poly(trimethylene carbonate) and poly(trimethylene carbonate-co-epsilon-caprolactone) copolymers with high epsilon-caprolactone content possess good physical properties that make them suitable for the preparation of porous artificial nerve guides.

Den Dunnen et al[70,126,127] evaluated poly(D,L-lactide)-E-caprolactone (DLLA-E-CL) nerve guides to bridge a 10-mm nerve gap. The conduit was composed of 50% DL-lactide and 50% E-caprolactone, with the lactide component containing 85% L-lactide (LLA) and 15% D-lactide (DLA). The authors reported that nerve regeneration through DLLA-E-CL guide was faster and qualitatively better when compared with an autologous nerve graft.

Meek et al[128] evaluated, using the rat sciatic nerve model, nerve regeneration after bridging a 15-mm gap with either a DLLA-E-CL nerve guide or an autologous nerve graft. They suggested that return of motor function is better after bridging the gap with a DLLA-E-CL nerve guide, compared with autologous nerve grafts.

Chitosan: Chitosan is a polysaccharide obtained from N-deacetylation of chitin and is a copolymer of D-glucosamine and N-acetyl-D-glucosamine. Hsu et al[129] suggested that gene expression for neurotrophic factors in Schwann cells is upregulated on chitosan substrate compared with that on polylactide. Various researchers[130–133] demonstrated that chitosan has a good affinity for nerve cells and promotes the survival and neurite outgrowth of nerve cells in vitro, which suggests that chitosan might be applicable as a scaffold for axonal regeneration in peripheral nerves.

Wang et al[134] used chitosan as a dual-component nerve graft for bridging a 30-mm gap in the sciatic nerve of beagles. In this application, the external part of graft consisted of chitosan, and the internal part consisted of PGA. According to their results, in the chitosan/PGA graft group, the dog sciatic nerve trunk had been reconstructed with restoration of nerve continuity and functional recovery, and its target skeletal muscle had been re-innervated, improving locomotion activities of the operated limb.

Chávez-Delgado et al[135] evaluated nerve regeneration in chitosan prostheses used as in situ delivery vehicles for progesterone in bridging a 10-mm gap defects in the facial nerves of rabbits. The lack of inflammation, wound infection, or local destruction at the implantation site showed that chitosan prostheses were promising for nerve regeneration. Progesterone-releasing chitosan scaffolds positively affected the regenerative response of rabbit facial nerves, significantly increasing the number of myelinated fibers and the regenerated area when compared with chitosan scaffolds alone.

Zhang et al[136] investigated, using the rat sciatic nerve model, nerve regeneration following application of de-acetyl chitin conduits for bridging a 10-mm gap. According to their results, the combination of chitin conduits with nerve fibers inside can be successfully used for bridging nerve defects of 10 mm. Moreover, using the above-mentioned combination, nerve regeneration is better than using either chitin conduits alone or autologous nerve grafts.

Combined Tubes and Tissue Engineering

Tissue engineering has focused on developing alternative treatments to the autologous nerve graft, especially for larger defects, and improving recovery rates and functional outcome. The application of tissue engineering techniques in the field of nerve tubulization is based on the belief that conduits can be manipulated in the laboratory to mimic important biological features in the nerve microenvironment. Moreover, using these advanced techniques can produce tubes, whether biological or synthetic, enriched with various elements promoting regeneration of the peripheral nerve that previously were not possible in nonautogenous conduits.

When considering substrate materials, it is imperative to choose one that exhibits good biocompatibility. The materials must be strong enough that they will not collapse during the patient's normal activities. Moreover, they must also contain a biodegradable and porous channel wall, be able to deliver bioactive factors, enable the incorporation of support cells, have an internal oriented matrix to support cell migration, and intraluminal channels to mimic the structure of nerve fascicles and electrical activities.

Two bioengineered grafts that have been successful in human and animal studies are the nerve/vein combined graft and the muscle/vein combined graft. Tang[76,137] evaluated, in humans, nerve regeneration by means of autogenous vein

graft with slices of normal nerve graft in the lumen. According to these studies, the nerve/vein combined graft may be a promising alternative to group fascicular nerve grafting for nerve defects between 20 and 45 mm.

Meek et al,[138–140] using the rat sciatic nerve model, evaluated nerve regeneration by means of a thin-walled biodegradable nerve guide with denatured muscle tissue inside the lumen. The placement of modified denatured skeletal muscle inside the nerve guide prevented the collapse of the conduits and led to good, and faster, sciatic nerve fiber regeneration and functional recovery in a rat as compared with conduit without denatured muscle.

Brunelli et al[141] compared nerve regeneration in nerve grafts, free fresh muscle grafts, vein conduits filled with muscle, and empty vein grafts for bridging nerve gaps of 1.0 and 2.0 cm. They suggested that vein filled with muscle might serve as a grafting conduit for the repair of peripheral nerve injuries and could give better results than traditional nerve grafting.

Battiston et al[142,143] used the muscle-vein-combined grafts for bridging both sensory and mixed nerve defects in 21 patients. The nerve defects ranged from 0.5 to 6 cm in length. They suggested that muscle-vein-combined grafts seem to be superior to other kinds of artificial or biological conduits.

Recently, tissue engineering has started to use polymeric biomaterials with or without living precursor cells for nerve regeneration. Polymers can be used as scaffold to promote cell adhesion and maintenance of differentiated cell function without hindering proliferation. They also serve as template for organizing and directing the growth of cells, and they assist in the function of an extracellular matrix.[144] Some disadvantages of these polymers in tissue engineering applications are their poor biocompatibility, release of acidic degradation products, poor processing characteristics, and loss of mechanical properties very early during degradation. For this reason, these materials must be modified to become more "cell-friendly."[145]

The tissue engineering approach for nerve regeneration includes scaffolds for axonal proliferation, support cells such as Schwann cells, growth factors, and an extracellular matrix. Variations of artificial material properties allow alterations in geometric configuration, biocompatibility, porosity, degradation, electrical conductivity, and mechanical strength. These variations in the aforementioned parameters can dramatically alter the ability of axons to proliferate. Moreover, porosity and pore size are often dependent on the method of scaffold fabrication.[146]

The physical structure of conduit channels also dramatically affects the quality of nerve regeneration. Because the total surface area of an oriented intraluminal framework or filament is larger than that of an empty tube, there is a common belief that fiber-filled devices or intraluminal scaffolds may improve nerve regeneration.[147,148] McCaig[149] suggested that the use of an applied electric field in conjunction with pharmacological agents (such as dimethyl sulfoxide, forskolin, and ganglioside GM_1) might enhance nerve regeneration in vivo.

Various studies[150–152] support the concept that Schwann cells offer a highly preferred substrate for axon migration and release bioactive factors that further enhance nerve migration. Moreover, Schwann cells synthesize and secrete a cocktail of neurotrophic molecules such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and ciliary neurotrophic factor (CNTF), which enhance nerve regeneration.

Enrichment of conduits of various origins with Schwann cells has proved to significantly improve the morphological and functional restoration of the injured nerve. Zhang et al[153] and Strauch et al[154] suggested that a vein conduit filled with Schwann cells allowed successful bridging of rabbit nerve defects up to 40 and 60 mm, respectively.

The influence of neurotrophic factors in neural development, survival, outgrowth, and branching was explored at various levels, from molecular interactions to macroscopic tissue responses.[155] Controlled release is one means of supplying factors to enhance nerve regeneration. Biodegradable nerve guidance channels serve as a vehicle for delivery of bioactive factors to manipulate cellular processes within the scaffold microenvironment. They can be made to release growth or trophic factors trapped in or adsorbed to the polymer.[156] There are several delivery devices used in neural applications, including polymer matrices,[157] microspheres,[158,159] viral vectors,[160,161] and liposomes.[162] Rich et al,[163] using the rat sciatic nerve model, studied the effect of exogenous NGF on axonal growth across a gap that was bridged with silicone chambers. They demonstrated that the myelinated axons in the chamber approximately doubled and that the myelin sheath doubled in size.

Insoluble extracellular matrix molecules, including laminin, fibronectin, and some forms of collagen, promote axonal extension and, therefore, are excellent candidates for incorporation into the lumen of guidance channels.[164] Alternatively, these molecules could be placed on natural biological conduits through adhesion molecules or similar processes. Components of the extracellular matrix and matrix analogues have also demonstrated promise in nerve replacement.[165] Labrador et al,[166] using the mouse sciatic nerve model, assessed the usefulness of nerve chambers prefilled with collagen and laminin gels to enhance nerve regeneration. They found that both matrices allowed for higher levels of recovery and for successful regeneration in a higher proportion of mice than saline solution. Furthermore, the laminin gel performed slightly better than the collagen gel.

Nerve Growth Factors

Nerve growth factors are molecules that are naturally released in the process of nerve regeneration.[167] They are released from the nerve ending especially following a nerve injury and have an effect on nerve growth, differentiation, and surveillance.[168,169] This knowledge has led to studies related to the application of factors that increase nerve regeneration through the conduit lumen.

The basic neurotrophic factor concept is defined by the hypothesis that trophic proteins are synthesized in the target

tissues and delivered to the neuronal soma via retrograde transport, where they exert a trophic and survival effect.[170–172] The influence of growth factors is exerted via their binding to particular classes of tyrosine kinase receptors present on the surface of the responsive cells.[40]

Different growth factors, including NGF, glia cell-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3), and fibroblast neurotrophic factor (FGF) have been added to single-lumen nerve tubes.[173–176] They can be incorporated directly (in solution) into the tube's lumen or through a delivery system. Due to the fact that the effect of growth factors is often dose-dependent and requires their release over extended periods of time, delivery systems are generally preferred. Besides, solutions may leak from the nerve tube. Different carriers and delivery systems have been used, including absorption to fibronectin mats, collagen matrices, bovine serum albumin (BSA), and microspheres.[173,175–177]

Nerve growth factor: NGF is present at low concentrations in healthy nerves. Following nerve injury, NGF is upregulated in the distal nerve stump[178] and plays an important role in the survival of sensory neurons and outgrowth of their neurites. Moreover, the concentration of NGF receptors is increased in the Schwann cells in the distal nerve segment.[179] Conversely, NGF has little or no influence on motor neurons and their neurite outgrowth.[180]

He et al[181] suggested that the mere inclusion of NGF–saline solution into plain silicone nerve guides can enhance the magnitude of motor nerve conduction velocities in rats 6 weeks after a 5-mm sciatic nerve injury. Rich et al[182] reported that a silicone tube filled with NGF and implanted in a rat sciatic nerve gap yielded significantly more myelinated axons in the distal part of the defect at 4 weeks after surgery than a NGF-free control silicone tube.

Lee et al[174] used heparin to immobilize NGF and slow its diffusion from a fibrin matrix inside a conduit bridging a 13-mm rat sciatic nerve defect to produce similar numbers of nerve fibers to isografts. They demonstrated that the delivery system used in their study revealed a marked dose-dependent effect and also enhanced peripheral nerve regeneration.

One of the few studies that compared NGF-loaded tubes against an autograft found significantly more myelinated fibers in the autograft than in the NGF-tube group after 5 weeks.[183] Although the number of regenerating myelinated axons within the nerve grafts was greater than that of axons within silicone tube implants, functional recovery of autologous nerve graft repairs may not be superior to that of tube repairs.

Glial growth factor (GGF): GGF is a trophic factor specific for Schwann cells rather than neurons, but it has a significant role in the interaction of the two cell types.[184] Mahanthappa et al[185] suggested that GGF increases Schwann cell motility and proliferation, and these two effects are dependent on the concentration of growth factor available to the glial cells.

Mohanna et al,[186] using the rabbit common peroneal nerve transection model, demonstrated that the presence of GGF in poly-3-hydroxybutyrate (PHB) conduits produced a progressive and sustainable increase in the distance and quantity of Schwann cells and axonal regeneration for up to 63 days. When the GGF is applied into PHB conduits for bridging nerve gaps of 2 to 4 cm in rabbit peroneal nerves, it increased the number of Schwann cells and improved the axonal regeneration, whereas it decreased the muscle mass lost in comparison with the control group.[187]

Fibroblast growth factor: FGFs are a family of at least 23 cytokines that are involved in cell growth and regeneration and are naturally secreted by damaged nerve ends after injury.[188] The earliest published study showing the regenerative effect of FGF was in 1992, in which it was demonstrated that addition of FGF is a successful method of salvaging penile erectile function after division of the cavernous nerves.[189]

Walter et al,[190] using the rat sciatic nerve model, studied the effect of recombinant acidic FGF into a synthetic conduit bridging a 15-mm nerve gap. They observed that functional motor return, nerve amplitude, and muscle action potential increased in the FGF group in comparison with the control group. Midha et al,[191] using poly (2-hydroxyethyl methacrylate-co-methyl methacrylate) (PHEMA-MMA) porous tubes filled with 10 µg/mL of acidic FGF (dispersed within a collagen matrix) to bridge a 10-mm rat sciatic nerve gap and demonstrated enhanced nerve regeneration at 8 weeks postsurgery.

Similarly, the efficacy of basic FGF in enhancing peripheral nerve regeneration has also been demonstrated. Wang et al[192] used poly (D,L-lactide) (PDLLA) tubes containing basic FGF to repair a 15-mm gap in the rat sciatic nerve. They concluded that basic FGF enhances the regeneration of peripheral nerves, retains its bioactivity after being embedded in PDLLA matrix, and can be released continuously from the polymeric matrix for a prolonged time.

Glial cell-derived neurotrophic factor: GDNF is a neurotrophic factor secreted by Schwann cells after nerve injury, which is known to improve motor/sensory neuron survival, neurite outgrowth, Schwann cell migration and, in particular, the survival of dopaminergic neurons.[193] GDNF has a beneficial effect on axonal regeneration, as assessed by the nerve pinch test.[194] GDNF also improves the conduction velocity of motoneurons following regeneration,[195] and that of small-diameter sensory neurons.[196]

Fine et al[173] demonstrated enhanced motor and sensory neuronal regeneration across a 15-mm synthetic nerve tube in the rat sciatic nerve defect gap using GDNF, as compared with the inclusion of NGF, at 7 weeks postimplantation. Chew et al[197] reported, by using a copolymer of caprolactone and ethyl ethylene phosphate (PCLEEP) tubes with GDNF encapsulated within electrospun polymer fibers, enhanced nerve regeneration and functional recovery at 3 months postimplantation across a 15-mm critical defect gap in rats as compared with nerve guides without GDNF inclusion. From the comparative studies performed thus far, it appears that GDNF is a potent candidate for inclusion into tubes for enhancing nerve regeneration.

Neurotrophin-3: Following nerve injury, continuous infusion of NT-3 has proved to be effective in restoring sensory and motor conduction velocity in a dose-dependent manner,[194] consistent with the neuroprotective role of NT-3 in sensory neuropathy.[197] The strong trophic effect on muscle

sensory afferent fibers is evident following exogenous administration of NT-3, even in the absence of the target organ.[198]

The exogenous administration of NT-3 restores muscle mass and is selectively beneficial for the reinnervation of type 2b fast muscle fibers.[199,200] Sterne et al,[201] by using the rat sciatic nerve model, investigated the effect of NT-3 delivered via fibronectin mats, which were grafted into 1-cm sciatic nerve defects. In the presence of NT-3, axonal regeneration was significantly increased at day 15 as compared with the control group (comprised of plain fibronectin mats). By 8 months after surgery, although both NT-3 and control groups resulted in the formation of axons of similar diameters, the presence of NT-3 supported a significantly greater number of myelinated axons.

Other factors: Several other growth and neurotrophic factors, although less commonly used in peripheral nerves, also have demonstrated efficacy in enhancing peripheral nerve regeneration. Such factors include CNTF,[202] vascular endothelial growth factor (VEGF),[203] leukemia inhibitory factor (LIF),[204] insulin-like growth factor I (IGF-I)[205] and platelet-derived growth factor (PDGF).[206] In general, these proteins are either injected directly into the lumen of nerve conduits, or embedded within a hydrogel as nerve guide lumen fillers. Moreover, the combination of two or more growth factors may offer additional benefits. It is apparent that more detailed understanding of neurotrophic factor dose response and their combinations on nerve regeneration is necessary for optimal scaffold designs.

The Future

Today, tubulization represents, in selected clinical situations, a possible alternative to autogenous nerve grafts for peripheral nerve repair. Although research efforts in nerve regeneration have been extensive, we are still hindered by a lack of knowledge of the underlying mechanism for axonal proliferation.

Clinical data indicate that simple monotissue biological conduits such as veins or skeletal muscle hold a good chance of succeeding if they are used for short gaps. This is also true for silicone tubes. If longer defects require bridging, combined biologic tubes (vein plus muscle or vein plus nerve) can be employed.

The era of molecular nerve repair holds much promise for the future of peripheral nerve surgery. The expanding knowledge and advances in nerve biology will lead us to more insights in the specificity of nerve fiber growth toward their target organs. Despite the multiple studies describing the utilization of growth-promoting factors inside the lumens of nerve conduits, they have not been introduced to clinical practice.

Utilizing biodegradable synthetic and natural polymers could be good options for nerve regeneration, and for the design and engineering of hollow tubes filled with different materials, thus achieving optimal porosity, pore size, morphology, and strength. The most important developmental field from a future perspective will be tissue-engineering conduits enriched with either neurotrophic factors and/or support cells of nerve regeneration (e.g., Schwann cells). The increased understanding of the underlying mechanisms of peripheral nerve regeneration will allow scientists to devise more appropriate nerve conduits with integrated growth factor delivery systems and/or cellular components. The potential to release growth or trophic factors inside the conduit lumen, to reduce nerve cell death, and to improve the outgrowth of axons after nerve injury, is an area in which considerable achievement will be expected.

The combination of two or more growth factors will likely exert a synergistic effect on nerve regeneration, especially when the growth factors belong to different families and act via different mechanisms. Combinations of growth factors can be expected to enhance further nerve regeneration, particularly when each of them is delivered at individually tailored kinetics. The combination of Schwann cells with growth factors may further improve nerve regeneration. Such a system may be engineered from longitudinally aligned fibers that contain and deliver the growth factor(s) and act as support for Schwann cells.

Experiments have demonstrated that tissue-engineered tubes are effective in nerve repair for gaps longer than 4 cm. These results were previously thought to be possible only with autogenous nerve grafts. Thus, in selected clinic situations, tubulization represents a viable alternative to autogenous nerve grafts. Future studies need to provide us with information regarding the effectiveness of different tubulization techniques.

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