REGENERATION AND REPAIR OF PERIPHERAL NERVES WITH DIFFERENT BIOMATERIALS: REVIEW

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Peripheral nerve injury may cause gaps between the nerve stumps. Axonal proliferation in nerve conduits is limited to 10–15 mm. Most of the supportive research has been done on rat or mouse models which are different from humans. Herein we review autografts and biomaterials which are commonly used for nerve gap repair and their respective outcomes. Nerve autografting has been the first choice for repairing peripheral nerve gaps. However, it has been demonstrated experimentally that tissue engineered tubes can also permit lead to effective nerve repair over gaps longer than 4 cm repair that was previously thought to be restorable by means of nerve graft only. All of the discoveries in the nerve armamentarium are making their way into the clinic, where they are, showing great potential for improving both the extent and rate of functional recovery compared with alternative nerve guides. © 2010 Wiley-Liss, Inc. Microsurgery 30:574–588, 2010.

Peripheral nerve injuries are encountered frequently in clinical practice.[1–3] Until the late 18 century, it was believed that peripheral nerves did not regenerate after injury.[4–6] Since that time, tremendous advances have been made in our understanding of peripheral nerve injury and repair. Nerve regeneration, and target reinnervation are complex processes, involving multiple factors. Because of their complexity, the repair and reconstruction of the damaged nerves with sufficient function remains a clinical challenge.[7–9]

In nerve repair end to end suture is the preferable choice of treatment when the gap is short, as in simple injuries. Unfortunately inelastic recoil occurs in, nerve stumps. If the operation is performed within a day of injury it is much easier to overcome this problem without undue tension on the nerve. However, the longer the delay, the more likely it is that nerve grafts will be required. Moreover, in delayed repair, the nerve stumps become embedded in scar tissue, resulting in increased collagenization within the nerve stumps.[10–12]

Peripheral nerve injury may result in injury without gaps or injury with gaps between the nerve stumps. Under the appropriate conditions axon extensions can regenerate over gaps reconnecting with the distal stump. Without intervention, proximal end of the injured nerve can lead to neuroma and scar tissue, which hinder the growth of regenerated nerve. The regenerated fiber fails to return to its normal position, thereby leading to functional impairment. Therefore, in order to prevent formation of excessive connective tissue, a segment of nerve or other materials must be used to bridge the gaps.[13–15]

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A number of animal models have demonstrated that nerves will regenerate across a nerve gap through various tubes and conduits. It is also known that peripheral nerve is capable of regenerating across a short nerve gap. Severed peripheral nerves will regenerate across a gap if an appropriate route (space) is provided between the proximal and distal severed stumps.[16,17]

The majority of animal model studies entailed nerve gaps ranging from 10 to 45 mm in length in rodents. Strasberg et al. studied an 80-mm nerve allograft in sheep, and Atchabahian et al. examined an 80-mm nerve allograft in swine, but both studies showed that axonal regeneration across the untreated allograft was very poor.[18–20] Most studies have used short-gaps of <25 mm.[21–27] Few studies about longer gaps reported poor outcomes similar to allografts.[28–34] Most of the studies have been performed on rat or mouse models but these animal models are different from humans (Table 1). The rat sciatic nerve has served as a common model for studies on peripheral nerve regeneration. So far, most reports on these models indicate that histological evaluation was performed mainly on transverse sections of the regenerated nerves. However, the degree of nerve recovery cannot be ascertained with certainty through histologic examination alone; because morphologic evidence is insufficient. It is also necessary to determine functional (electrophysiological) recovery. Therefore larger animals have been used as an experimental animal because in these animals appropriate electrophysiological evaluations can be carried out.[32–34]

Mackinnon and Dellon were the first to study nerve regeneration in monkeys in order to compare the electrophysiologic results of nerve graft versus polyglycolic acid conduit repairs and they used bioabsorbable conduits of various lengths.[28,30] Both of their studies demonstrated that the primate peripheral nerve can regenerate across 3-cm nerve gaps when guided by an appropriate nerve conduit. The authors then applied their findings to humans with nerve gaps of 3 cm or less and demonstrated excel-

Table 1. Development of Conduit Materials Used for Peripheral Nerve Injury

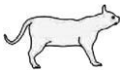
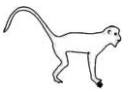
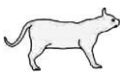
Researcher	Year	Material	Nerve	Gap (mm.)	Animate
Lundborg et al.[24]	1982	Silicone	Sciatic	20	
Politis et al.[35]		Silastic Y		5	
Chiu et al.[36]		Vein		10	
Molander et al.[25]	1983	Polyglactin mesh	Tibial		
Ochi[37]		Silicone X	Peroneal	8	
Uzman et al.[38]		Semipermeable acrylic	Sciatic	3	
Gibby et al.[39]		Collagen	Radial	8	
Williams et al.[40]	1984	Silicone	Sciatic	10	
Longo et al.[41]		Fibronectin			
Scaravilli et al.[42]		Plastic film		5	
Seckel et al.[26]		Polyester tube		20	
Rice et al.[43]		Vein		25	
Politis[33]	1985	Silastic Y	Peroneal	5	
Henry et al.[44]		Polyester	Sciatic	13	
Danielsen et al.[3]	1986	L-tiroxin		50	
Lundborg et al.[1]		Silicone Y		10	
Mackinnon et al.[45]			Femoral	6	
Seckel et al.[46]			Peroneal	8	
Jenq et al.[47]		Silicone	Sciatic		
Anderson et al.[48]		Artery	Peroneal	5	
Fawcett et al.[49]		Muscle	Sciatic	40	
Glasby et al.[32]				10	
Jiming et al.[50]				8	
Smahel et al.[51]		Vein	Femoral	14	
Williams et al.[52]	1987	Fibrin matrix	Sciatic	10	
Williams et al.[53]		Silicone Y			
Brushart et al.[5]			Femoral motor	2, 5	
Bora et al.[21]		Polyothoester	Sciatic	15	
Müller et al.[54]		Silicone	Tibial	16	
Davies et al.[55]		Muscle	Sciatic	10	
Brushart[6]	1988	Silicone	Femoral	0.5	

Table 1. (Continued)

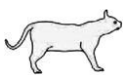
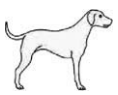
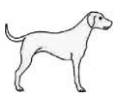
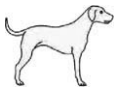
Researcher	Year	Material	Nerve	Gap (mm.)	Animate
Chiu et al.[56]	Vein	Sciatic	5		
Suematsu et al.[57]			10		
Rich et al.[58]	1989			NGF	
Risitano et al.[59]		Vein		Peroneal	
Gibson et al.[60]		Silicone	Sciatic	5	
Rosen et al.[61]	1990	Collagen-PGA conduit	Peroneal	0.5	
Brushart[10]		Silicone	Femoral motor		
Brushart[11]		Mesothelium	Sciatic	8	
Hoppen et al.[62]		Caprolactone		7	
Evans et al.[12]	1991	Silicone	Peroneal	5	
Rath et al.[63]		Muscle Y	Femoral motor	6	
Archibald et al.[64]		Collagen	Sciatic	4	
Ochi et al.[65]	1992	Aortic Y	Tibial	10	
Zhao et al.[66]		Silicone Y	Sciatic	4	
Abernathy et al.[13]			Peroneal	6	
Hems et al.[67]		Muscle		50	
Brunelli[68]	1993	Vein-muscle	Sciatic	20	
Brushart[14]		Silicone	Femoral	0.5	
Wang et al.[69]		Vein	Sciatic	10	
DenDunnen et al.[22]		PLC			
Ozcan et al.[70]		Amnion	Femoral		
Maeda et al.[71]		Silicone	Sciatic	24	
Benito-Ruiz et al.[72]	1994	Vein		10	
Yutaka[15]		Silastic Y	Saphenous	4	
Stevenson et al.[73]		Polyethylene	Peroneal		
Chen et al.[74]		Muscle	Sciatic	10	
DeFranzo et al.[75]				5	
Kiyotani et al.[76]	1995	PGA+ Collagen		25	
Langone et al.[77]		Polyphosphazine		10	
Ellis et al.[78]	1996	Glycosaminoglycan		15	
Francel et al.[79]	1997	Silicone			
Ide et al.[80]	1998	bFGF	Peroneal	30	
Arai et al.[81]	2000	Synthetic longitudinal matrix	Sciatic	15	
Hobson et al.[82]		VEGF		10	
Matsumoto et al.[83]		PGA	Peroneal	80	
Lee et al.[84]	2003	NGF	Sciatic	13	
Wang et al.[85]	2005	PGA+Chitosan		30	
Chang et al.[86]		PLGA		10	
Lee et al.[87]	2006	PLGA+Collagen	Peroneal	15	
Dong et al.[88]		PDLLA/NGF	Sciatic	10	
Li Q et al.[89]		NGF/CNTF			
Tos P et al.[90]	2007	Muscle+Vein	Median		
Chang et al.[91]		PLGA	Sciatic		
Kim et al.[92]		Schwann cell			

Table 1. (Continued)

Researcher	Year	Material	Nerve	Gap (mm.)	Animate
Zhang et al.[93]	2007	TGF-ß	Sciatic	15	
Sinis et al.[94]		Schwann cell	Median	20	
Yang et al.[95]		Silk fibroin	Sciatic	10	
Waitayawinyu et al.[96]		PGA+Collagen			
Cui et al.[97]	2008	Stem cell			
Zavan et al.[98]		Hyaluronic acid			
Liu[99]		Proantocyanidine			
Lin et al.[100]		Chitosan			
Hu et al.[101]		PGA			
Zhang et al.[102]		Chitosan			
Kalbermatten et al.[103]		Schwann cell		10	
Chang[104]	2009	NGF		15	
Alluin et al.[105]		Collagen	Peroneal	10	
Chang[104]		Polycaprolactone		12	
Kempton et al.[106]		VEGF		10	
Lu et al.[107]		PLA			
Wang et al.[108]		PCL			
Hsu et al.[109]		Stem cell			
Guo et al.[110]			Facial		
Okamoto et al.[111]		Collagen	Peronel	30	
Whitlock et al.[112]			Sciatic	14	
Meek et al.[113]		Polyganics		10	
Santiago et al.[114]		Adipose-derived precursor cell		6	

lent recovery in 33% of their patients, achieving static two-point discrimination of 6 mm or less.[115]

Rodent animal models of allotransplantation have also been developed, and successful regeneration with systemic immunosuppression across allografts ranging from 1 to 4.5 cm has been demonstrated.[18] However nerve allograft segments that are 2 cm or shorter allow some degree of regeneration in the absence of immunosuppression. Large animals permit the creation of longer gaps and provide model that is more closely applicable to the challenge of human grafting. A reliable model of long nerve without immunosuppression has also been was recently developed in swine.[19]

When stumps of the injured nerve cannot be directly approximated, nerve grafts are used to bridge the gaps. There are two types of conventional bridging materials, both of which were described in many experimental and clinical practice reports in the 1980s. The first type is autogenous nerve, including autogenous nerve with or without vessels, skeletal muscle, blood vessel, membrane tube and other natural biological active materials. Although autogenous materials have good compatibility with human body, they nevertheless lead to problems such as tubular collapse, poor regeneration, scar tissue proliferation and adhesion after ischemia except autogenous nerve. Autogenous nerve grafting can be performed with nonvascularized autogenous nerve, vascularized nerve, interpositional conduits and nerve allografts. However, because of the problems mentioned above, biological materials have been abandoned gradually in the past few years. The second type is nonbiological material like decalcified silicone tube, bone tube, nylon fiber tube, polyurethanes, etc. These can provide tubular support for nerve regeneration, but unfortunately they cannot be degraded or absorbed in vivo. Consequently they become foreign bodies after nerve repair and they thereby initiate foreign body reaction to the nerve. As a conclusion, the problem of poor outcomes in of nerve gap repair still remains a challenge.

Traditional nerve repair techniques of suturing severed nerve ends together to repair small deficits (4 mm or less) or harvesting nerve grafts to bridge larger deficits (5 mm or greater) are fraught with difficulty. It is clear that multiple factors effect the regeneration of nerve fibers and a gap between nerve ends allows expression of various growth factors. Nerve gap regeneration in rodents is limited to 1 cm. Mackinnon and Dellon examined regeneration in primates with bioabsorbable conduits of varying materials and lengths. They were the first to identify that nerve regeneration could occur in conduits and up to limits as of 3 cm in primates.[28,30]

AUTOGRAFTING

Nerve autografting is the most common surgical procedure currently used to repair nerve defects.[19,33,34,116–119] The typical graft of choice is a nerve autograft harvested from another site of the body. Nerve autografting is the first choice for repairing peripheral nerve gaps. The success of autologous nerve grafts arises from the presence of Schwann cells and basal lamina endoneural tubes, which provide neurotrophic factors, and endoneural tube surface adhesion molecules to regenerating axons.

Autografting depends upon tissue availability, the absence of secondary deformities and compatibility in tissue structure and size. It also has several disadvantages such as loss of function at the donor site, donor site morbidity (e.g., scarring and, occasionally, neuroma pain) and the need for multiple surgeries. An autogenous nerve graft obtained from cutaneous nerves contains smaller diameter fibers, leading to problems in the repair of large-diameter nerves.[5,6,32,47,51] In addition, endoneural tubes cannot be exactly approximated, leading to mismatching of regenerating axons and consequent nonspecific incomplete reinnervation and poor recovery of nerve function. To overcome these disadvantages of nerve autografts, surgeons have tried to improve the outcomes of grafting and to replace nerve by alternative materials.[45,70,71,81,120]

ALLOGRAFTING

Allografts have been tried to repair nerve defects but they require immunosuppression and their success rate is very poor.[18,21] Autologous and allogenous organs or tissues such as blood vessels and skeletal muscle have also been used as blood vessels and skeletal muscles have also been used for nerve grafting with varying degrees of success, but they are still accompanied by some of the same problems as autografts and allografts.[118,121,122]

Nerve allografts, fresh or pretreated by various methods (e.g., freezing, freeze-thawing, freeze-drying, predegeneration, and chemical tretments with or without immunosuppressants) have also been reported.[123] Nerve autografts have been widely used for peripheral nerve regeneration however only 50% of patients can regain useful function through autografts to date.[20]

Allografts (e.g., cadaver nerve grafts) and xenografts (e.g., animal nerve grafts) have also been used for peripheral nerve regeneration.[61,124] The main drawback of allografts and xenografts lies in the possibility of an undesirable immune response, depending on the patient and the source of the material. Preprocessing of natural materials or immunosuppression is necessary to remove potential immunogenity and to prevent rejection.[81,119]

NEURAL CONDUITS

Various neural conduits can be used for nerve gap repair.[2,22,23,25–28,31,121,124,36,125–134] These conduits can be biological material such as muscle or vessels, nondegradeable materials such as silicone tube or biodegradeable synthetic materials.[15,35,37,39,41,42,46,54,62,65,67,73,77,84,95,99,113,135–137]

Biological Materials

Muscle. Skeletal muscle tissue has been widely used as a conduit material. The skeletal muscle tissue contains longitudinally oriented basal lamina and extracellular matrix components direct and enhance regenerating nerve fibers. The three-dimensional environment provided by skeletal muscle basal lamina provides a microenvironment that promotes cell adhesion to extracellular matrix. 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. There are studies indicating that skeletal muscle grafts can be effective for repairing short nerve gaps (<3 cm) in laboratory animals. Most studies point to 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 reducing.[49,50,55,63,68,74,75,90,138–142]

Arteries and veins. Arteries and veins have been experimentally used as grafting.[36,57,138–140,142–145] Vein autografts, which are more abundantly available and induce less donor-site morbidity compared with nerve autografts, were found to be as effective as nerve conduits for bridging short nerve gaps in the sciatic nerve rat model as well as in humans.[143] In order to overcome these disadvantages of nerve autografts, surgeons have tried to improve the outcomes of grafting and to replace nerve by alternative materials. Vein graft offers an alternative to nerve graft in cases where the nerve defect does not allow direct approximation. Some clinical studies suggest that vein conduits are practical and reliable procedure for nerve defects between 2.0 cm and 4.5 cm.[53,43,48,56,59,68,69,72,90,146]

Tendon. In experiments using other possible graft materials such as tendon from the tail of the rat was used to bridge a 10 mm defect in its sciatic nerve.[147] Brandt et al. suggest 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 in the rat sciatic nerve based on functional and morphometric evaluation.[147–149] The human plantaris tendon possesses similar features as the rat tail tendon, as it is possible to spread it into a collagenous membrane, (implying a possible future clinical application in the future). Abundant graft material with limited loss of function is the advantage of tendon graft for nerve bridging.[148–150]

Nondegradable Materials

Commonly preferred nondegradable materials for nerve guides are briefly described below.

Silicone tube. Silicone tubes have frequently been used for nerve regeneration.[24,151] Silicone is not biodegradable, nor is it permeable to large molecules. Typical controls are autografts, empty silicone tubes or silicone tubes filled with saline. Chen et al. 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.[152] Other reports have been focused on the control of neuronal outgrowth by filling silicone tubes with longitudinal oriented fibers made of nonabsorbable polyamide, or with oriented collagen or laminin gels.[125,152–154] It has also been reported that in three young adult male patients ulnar and median nerves have been successfully reconstructed by the use of silicone guides with gap lengths ranging between 3 and 5 mm.[154] However, an inflammatory response has been reported around the guide resulting with a fibrotic capsule. Nondegradable artificial nerve guides have also been fabricated using an acrylic polymer[40,52,54,58,60,66,79,155]

Other nondegradable materials. Elastomer hydrogel or porous stainless steel has been used for nerve regeneration.[125,156] However, these artificial materials have the disadvantages of engendering chronic foreign body reaction due to scar tissue formation, inflexibility, and lack of stability.

Biodegradable Synthetic Materials

The nerve tube has been investigated as a method of repairing peripheral nerve through the use of various artificial materials. To avoid problems associated with nondegradable polymeric conduits, recent research has been focused on the production of biodegradable artificial nerve guides, which degrade within a reasonable period of time and manifest only mild foreign body reactions. Biodegradable materials offer several advantages, such as the possibility of attaching Schwann cells or bioactive molecules on the polymer surface through physicochemical modifications and delivering them during biodegradation. The chemical agents or cells have to be released over a long time period, and exert their effect during the critical stages of nerve growth. Biodegradable synthetic polymers are advantageous because of their flexibility. Their biocompatibility, degradation behavior, porosity and mechanical strength can be altered by changing their chemical or engineering properties.

Collagen. Collagen is the major component of the extracellular matrix and is known to promote cellular proliferation and tissue healing[7,8,61,83,96,105,111,112,157–159] Several investigators indicate that as a material for nerve conduits; collagen possesses superior biologic properties for peripheral nerve regeneration.[30,61,122,153,157–159] Conduits derived from biologic molecules like collagen have demonstrated improved regeneration.[64,78,76,160–162] Archibald and associates 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.[159] However despite these successful results in primate trials, no clinical trials in human have been reported in the literature to date. This product is commercially available marketed under the name NeuroGen® (LLC, Bel Air, MD). These conduits are available in diameters of 2, 3, 4, 5, and 6 mm and are 2.2 cm in length.[126]

Polyglycolic acid. Polyglycolic acid (PGA) is a bioabsorbable substance that is currently used as a commonly chosen suture material for wound closure.[29,32,128,156] It is also used in mesh form to wrap internal organs that have sustained injury as a result of trauma. It is absorbed in the body by hydrolysis within 90 days of implantation.[48,129,155,163–166] The PGA tube is a flexible corrugated woven tube. Compared with nerve autografts, PGA fiber has already produced superior results across gaps of 8–30 mm in humans. However, the gap lengths involved were mostly less than 30 mm.[163]

PGA tube is commercially available as the PGA-hollow tube (Neurotube, Neuroregen, L.L.C., USA) and its use is restricted to sensory nerve defects with gaps less than 30 mm. The polyglycolic acid conduit unfortunately has two drawbacks. First, tube costs more than the suture used in a standard repair. But this factor may be offset by a potentially shorter operative time. Operative time was not recorded for this protocol, but the length of time needed to place the tube seems to be shorter than a nerve graft. Second, the extrusion risk of the tubes. It is reported that extrusion of the tube can be encountered due to the poor quality of the skin overlying the tube. However, this complication can be prevented by providing a healthy soft tissue at the site of repair site.[8,76,83,86,87,91,101,115,160,167]

Polyesters and copolyesters. Aliphatic polyesters and copolyesters have been reported as suitable for nerve regeneration. Examples include poly (L-lactic acid) (PLLA), poly (lactic acid-ϵ-caprolactone), poly (L-lactide-*co*-glycolide), poly (1, 3-trimethylenecarbonate-ϵ-caprolactone) and poly (caprolactone) (PCL).[22,130,131,155,163–166,168] Copolymerization has been used to obtain these materials with characteristics in terms of tailored to degradation behavior, mechanical performance, thermal properties and wettability. The repair of clinically relevant nerve defects generally requires a period of up to one year for nerve regeneration and maturation. Materials for the fabrication of nerve guides are required to be slowly degrading and to have a low degree of swelling, as well as suitable mechanical properties for the bearing of stresses during the surgical procedure (handling and suturing) and the implantation time (movements of the patient). Nerve guides should be flexible, tough and capable of bending without kinking.

Sufficient permeability of nerve devices is needed for the exchange of fluids between the regeneration environment and the surrounding tissue, avoiding the build up of pressure due to fluid retention.[166] Polymer crystallinity affects permeability and biodegradation of nerve guides. Crystalline phase is inaccessible to water and other permeable molecules. Biodegradation and permetion decrease with an increase in crystallinity. Crystalline debris formed during degradation may cause an inflammatory response which may jeopardize regeneration process and the recovery of nerve function. On the other hand, some degree of crystallinity is required, as the existence of physical crosslinks between the polymer chains stabilizes the structure of nerve guides. Pego et al. investigated the physicochemical properties of synthetized copolymers of trimethylenecarbonate (TMC) and ϵ-caprolactone with the aim of assessing their potential in the development of flexible and slowly degrading artificial nerve guides.[168] Porous structures were obtained by an immersion-precipitation technique and the combination of this method with salt-leaching. Immersion precipitation failed to impair porosity to poly TMC membranes, as the rubbery property behavior of the material caused the polymer chains to eventually relax, resulting in consequent collapse of the pores. The addition a small amount of poly (ethylene oxide) (PEO) was found to stabilize the porous structure of poly (TMC).[44,107,108,169]

Chitosan. The nerve conduit material used under the name of "chitosan" [(1→4)-2-amino-2-deoxy-ß-D-glucan] is obtained after the crab tendon is separated from the calcium phosphates and proteins.[85,133] This material is rich in deacetylate chitin polysaccharide and includes cellulose.[85,102] It is a polysaccharide obtained from the *N*-deacetylation of chitosan chitin, and consists of D-glucosamine and *N*-acetyl-D-glucosamine copolymers.[85]

Chitosan shows molecular similarity to the glycosaminoglycans in the basal membrane and extracellular matrix. Therefore, there are interactions between the extracellular adhesive molecules such as chitosan and laminin, fibronectin and collagen.

Chitosan is a biodegradable scaffold which has a very good tissue adaptation.[85,133] Chitosan has quite positive effects on the nerve regeneration.[100,85] It has been demonstrated that when chitosan is used as a conduit material, it facilitates nerve healing and improves the nerve differentiation and growth. When chitosan tube was used in rat sciatic nerve defect of 15 mm; the inflammatory cells were observed at the surface of chitosan tube up to six weeks from the implantation and then the tissue reaction reduced rapidly.[85] Similarly, the chitosan provided successful results when used in the rabbit facial nerve defects of 10 mm.

In the experimental studies, it has been demonstrated that the chitosan is depolymerized by lyzozyme included in the glucosamine units in the body. Chitosan is used in some applications that are useful for the body thanks to its biological content. Since the chitosan has an antitumor and antibacterial efficiency, the studies on the chitosan are one of the interesting fields of tissue engineering.[85]

Chitosan and protein (or peptide) combination is an effective method to improve the nerve healing. By this combination, the affinity between the nerve cells and the chitosan and poly-L-lysine tube may be increased.[133]

Wang et al. used the chitosan as a dual-component nerve graft. In this application, the external part of graft consisted of the chitosan, and the internal part consists of the PGA.[85] The chitosan conduit acted as a supporter by ingrowth of blood vessels, and also enabled the diffusion of nutritive molecules in this new design. The function of PGA filaments in this component was to facilitate the function of Schwann cells.[85]

The in vivo degradation outcomes of chitosan and polyglycolic acid are similar to the basic glucosamine and acidic glycolic acid. The catabolites of chitosan and PGA are removed by the normal metabolic pathways of body. The chitosan/PGA artificial nerve grafts were analyzed six months after the implementation and it has been observed that the chitosan/PGA has completely collapsed and absorbed, and instead, the nerve-like tissue replaced the defect. In the light microscopy images, the regenerated nerve tissue shown as well-organized epineurium, multifascicular nerve fibrils, and perineurium.[85]

It has been determined that when chitosan is used in a dog sciatic nerve defect of 30 mm, the nerve continuity is restored after six months, the electrical conduction is functionally regained, and a reinnervation is observed in the target muscle cells. The chitosan conduit may be used as an alternative to the conventional nerve autografts.[85,102]

SUPPORT WITH NEUROTROPHIC COMPONENTS/ GROWTH FACTORS

Studies about the use of various growth factors for improving the peripheral nerve regeneration was gradually increased recently.[8,132,170] In parallel with these improvements, many growth factors that increase the nerve growth and proliferation around the nerve have been defined.[132] The neurotrophic components are released from the nerve ending especially following a nerve cut and have an effect on nerve growth, differentiation and survey.[9,132,170] This knowledge has led up the studies related to the application of factors that increase the nerve regeneration to the conduit lumen. The researchers concentrate on the subjects such as the neurotrophic effects and electroconductivity in order to control the conduits and promote the regeneration rate.[170] There are limited number of compilations related to the role of

growth factor in the in vitro axonal continuity and repair.[134]

The neurotrophic factors are the molecules that are naturally released in the process of nerve regeneration.[2,171,172] The examples neurotrophic factors are nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF) and insulin-like growth factor-1 (IGF-1) which are secreted from Schwann cells.[163,171] Macrophages secrete platelet derived growth factor (PDGF) and interleukin-1 (IL-1). These neurotrophic factors occur at different times of nerve regeneration and accelerate the axonal growth. While the regeneration process continues, the exogenous factors are included in the process in addition to these molecules. After clarification of these mechanisms, the pharmacological agents that affect the synthesis and release of these proteins have been worked on and the manipulation of regeneration has been begun with the agent technologies that show controlled release.[2,171]

The soluble neurotrophic factors can be used by directly insertion into the conduit lumen.[9,83,171] This group includes the extracellular signals and growth factors and they start the nerve regeneration.[8,134,171] The most detailed studies on this subject have been carried out on the NGF, BDNF, CNTF, IGF-1 and 2, PDGF-BB and AB, IL-1, acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF).[9,132,133,171,172]

Fibroblast growth factor

FGF is a cytokine family member of which number is over 23, and a material that has a role in the cell growth and regeneration and is released from the damaged nerve ending.[80] The first data on the use of FGF for the nerve repair is related to the correction of erectile dysfunction by using it in a defect of rat cavernous nerve in 1992. In 1993, Walter et al. applied recombinant acidic FGF into the synthetic conduit of 15 mm in the rat peripheral nerve defect.[173] It has been observed that the functional motor return, nerve amplitude and muscle action potential increased in the FGF group in comparison with the control group.[171] Likewise, the basic FGF is a material that provides advantageous effects in the animal models.[163] Ide et al. determined an increase in the number of myelin axons by using bFGF in a sciatic nerve defect of a dog in 1998.[80] Li and Cao observed that the axonal regeneration significantly improved in comparison with the control group by using 0.2 ml bFGF solution (4,000 U/ml) in the vein graft conduit in 2000.[174] In the subsequent studies, the combination of FGF with the other structural components has been worked on. Midha et al. used the synthetic tube bridge material with 10 μg/ml of FGF-1 and collagen matrix in a nerve defect of 10 mm and determined an increase only in the regeneration in comparison with the collagen matrix group.[175]

Corderio et al. used acidic FGF in a rat's sciatic nerve defect of 5 mm with the collagen-contained polyethylene conduit, and showed evaluated the axonal regeneration.[176] They ultimately observed an increase in the number of myelin axons. However, the mechanism of aFGF that improves the regeneration is not clear.[132] However, there are some theories such as it increases the number of Schwann cells in the field of nerve cut, increases the vascular support by creating angiogenic effect, recovers the dying nerve cells, and it has a tropic effect for ensuring the continuity of newly occurred axons are included in these theories.[132,134]

Neuron growth factor. NGF is a member of neurotrophin family and has an important role in the natural process of nerve healing and regeneration. There are literatures data regarding the most successful results are provided with NGF.[9,145,163] However, the NGF's action mechanism that improves the regeneration could not be demonstrated in vitro.[132] The possible theories for this action is; (i) its effect on the retrograde transport in the central body of nerve (ii) its effect on the environment around the growth of nerve substrate (iii) direct effect in the non-neuronal cells (for example, the stimulation of myelin production of schwann cells).[132,133] Following an axotomy, the concentration of NGF receptors had shows increase in the Schwann cells in the distal nerve segment.[133,163] NGF is an exogenous agent that ensures the maintenance of survival of the sensory nerve cell bodies following an axotomy.[163]

In 1989, Rich et al. investigated the effects of silicone conduit and NGF on the rat sciatic nerve defect.[58] They determined that the number of myelin axons almost doubles following the injection of NGF into a silicone tube within 1 mg/ml saline, and the thickness of myelin sheath increases by 58%, and the nerve appearance is more mature in comparison with the normal saline solution.[132] These findings have led subsequent studies.[170] There are sophisticated applications that have concentrated on the NGF-releasing materials in the advanced studies.[88,104,170] In 1998, Hadlock et al. used a growth-promoting substance (inosine, neurotrophic purine analogues) within the conduit, and obtained successful results of nerve regeneration.[172] The other systems released in a controlled way include the microspheres and adenoviruses that express NGF.[170]

In 1989, Rich et al. obtained results that are close to those obtained with isograft in a defect in the rat sciatic nerve using NGF.[58] Inserting of Schwann cell into the conduit is a relatively simple method and also an alternative method that increases the NGF production. The exact and final results on the nerve regeneration are not yet obtained, and continue to develop in time.[170]

Glial growth factor. Glial growth factor (GGF) is released from neuron and induces the Schwann cell pro-

liferation. It has role in the interaction between neuronal and glial cells in respect of the peripheral nerve healing.[134] When the GGF is applied into the conduit in the defects of 2–4 cm in rabbit peroneal nerve, it increased the number of newly formed Schwann cells and improved significantly the axonal regeneration; and a considerable decrease in the muscle mass lost in comparison with the control group.[134]

Ciliary neurotrophic factor. CNTF is an important tropic factor in the nerve regeneration.[89] It is contained in the cytoplasm of myelin Schwann cells.[132,133] It increases the neuron survival following axotomy.[132] It is directly released from the circumference of neuron and has been used within the silicone conduit in the rat sciatic nerve defect of 10 mm, and increased the diameter and number of axons. It increases myelinization and motor nerve conduction rate, and creates an increase in the amplitude of muscle action in the examination of anterior tibial muscle in comparison with control group.[170]

Vascular endothelial growth factor. Primarily, vascular endothelial growth factor (VEGF) has an active role in the vascular tissue; however, it is determined that VEGF also has positive effects on the nerve regeneration.[106] In 2000, Hobson et al. applied laminin-based gel (Matrigel) and VEGF (500–700 ng/ml) into the silicone conduit in a model in which a defect of 1 cm was formed in the rat sciatic nerve.[82] With the application of VEGF, they observed that the blood vessel penetration to around of nerve cell and Schwann cell migration have increased and the axonal regeneration has improved.[170]

INTRALUMINAL CONDUIT COMPONENTS/SCAFFOLDS

Within one week after the peripheral nerve damage, the nerve healing is started substantially by the acellular fibrin matrix in the damaged nerve ending. Then, the cellular aggregates such as the Schwann cells, fibroblast and macrophage which act as a scaffold (frame) are accumulated in the nerve ending. Starting from this mechanism, the agents considered as the nerve regeneration enhancers have been inserted into the conduit, and it has attempted to increase the healing rate and successfully repair the larger nerve defects.[113] Many studies have proven that the nerve regeneration is stimulated by inserting neurotrophic and neurotropic factors to the conduit lumens of conduits and this caused to become a center of attention for many new research.[170,171,177]

The environment of a conduit lumen could not be completely understood until recently.[126,134] The substrates and extracellular matrix components in the conduit lumen are the molecules that are very effective on the nerve healing.[126,134] Many luminal components have been applied in the nerve defects, and a great number of different results have been obtained in the nerve regeneration.[172] It is reported that the additionally inserting of an interposition nerve segment into the conduit lumen is also effective on the achievement of good nerve regeneration, especially in the cases with a long nerve defect.[8,134]

The scaffolds are the components that increase the axonal growth. Scaffolds should have a low antigenity, support the vascularization, be porous in order to provide the oxygen diffusion, and should not cause a long-term nerve compression.[178]

A scaffold may be derived from either natural or synthetic materials.[95,99,178–180] The natural materials include the veins, skeletal muscle fibrils and collagen.[105,111,112,178] The synthetic materials include the silicone, polyglycolic acid (PGA), polilactic acid (PLA), poly-L-lactide-*co*-glicolide (PLGA), poli-ϵ-caprolactone (PCL), poly-lactide-*co*-caprolactone (PLC) and poly-3-hydroxybutyrate (PHB).[96,87,91,101,107,108,167,169,178]

The success rate of autologous vein grafts is minimal especially in the long nerve defects.[178] The reason for this unsuccessful results is it the wall of vein conduit which is thin and has a risk of collapse, and also subjected to the constriction by the surrounding scar tissue.[134,178] Therefore, the scaffolds with a less risk of collapse may be prepared by inserting the intraluminal Schwann cell, collagen or muscle fibrils into the vein conduit.[36,178,103] It has been demonstrated that especially the scaffolds filled with the Schwann cells induce the axonal elongation in the nerve defects of 40 mm in rabbits.[178] The vein conduits filled with collagen provide successful results in the nerve defects of 15 mm in rabbits.[160,178] In rabbit model using muscle-vein scaffolds, successful nerve regeneration was obtained in a defect length of 55 mm.[172,178] Since the results of silicone-used scaffolds are not optimum, the biodegradable materials are mostly preferred.[135,178] For example; the synthetic poly-lactic-*co*-glycolic acid (PLGA) is a conduit material that is suitable for use in the nerve defects shorter than 3 cm.[171] In the longer defects, the components that are biologically active and show interactions with the nerve tissue are preferred in general.[28,85,92,94,171] It is possible to increase the axonal elongation and accelerate the nerve generation by the Schwann cell production.[133,181,92,182,183]

Many components are used and comparative studies are carried on in the scaffold technology.[178] The comparative studies are also carried out between the "isotropic" scaffolds with a homogenous content and between the "anisotropic" scaffolds which are not homogenous and with an irregular settlement of intraluminal content. The scaffold applications that have a wide range of alternative combinations will achieve successes similar to the results of autogenous nerve grafting in the course of time, in parallel with the developments of tissue engineering technology.[35,41,178,184,185]

BIOARTIFICIAL NERVE GRAFTS AND NEURAL TISSUE ENGINEERING

A variety of resorbable artificial nerve grafts were used for nerve regeneration. The majority of artificial polymers studied belong to the polyester family. When considering substrate materials, it is imperative to choose one which exhibits good biocompatibility. The materials must be strong enough so that they will not collapse during the patient's normal activities. Beside strength 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.[2] Grafts may also be constructed of two layers derived from different materials. This type of construction allows support and retention.[22,161,182,183] Nonporous thin skin on the inner surface of the tube is the primary permeability barrier and serves to retain neurotrophic factor. An external layer of thicker porosity external layer provides structural of anisotropic ultrafiltration membranes used for separating proteins from cells and/or smaller molecules. With controlled release, compounds with short in vivo half lives can be supplied slowly to the regenerating axons over the life of the graft. Extended release of basic fibroblast growth factors has been shown to enhance the growth of myelinated and unmyelinated axons across a 15-mm gap in rat sciatic nerve compared with conventional tubes.[186] Controlled release is one means of supplying factors to enhance nerve regeneration in a synthetic conduit. Many of the neurotrophic factors that have been or will be considered for controlled release are made by Schwann cells which play important roles in nerve regeneration. Schwann cells from embryonic rat dorsal ganglia or sciatic nerves have been cultured by a variety of methods for more than 20 years. When carefully constructed the combination of experiments and mathematical models can provide an important tool for understanding and optimizing biological processes.

Tissue engineers put their signatures under biomaterial studies that make very rapid progress, concerning the nerve regeneration.[85,97,171,178] Researchers modify synthetic materials and carry on their search of obtaining a component that will provide optimum nerve recovery.[90,172,171] With the studies of tissue engineering, it is attempted to constitute components alternative to the conventional nerve autografts. By the conduit materials obtained through the tissue engineering, successful results can now be obtained, which are equal to the autografts in the nerve defects shorter than 10 mm. However, the optimal nerve regeneration could still not be provided through the conduit components obtained using this method in the long nerve defects.[178]

Nerve tissue engineering (NTE) is one of the most promising methods in biomedical engineering for restoring central nerve systems in humans and for repairing or replacing the function of defective or damaged tissues or organs.[187] Nerve tissue repair is a prized treatment concept in human health care, because it has a direct impact on the quality of life. It is well known that the adult central nerve system (CNS) cannot be regenerated on its own after trauma or disease.[188] Therefore, restoring its function poses a challenge for neurobiologists and neurologists. Traditionally, tissue transplantation or peripheral nerve grafting has been used to repair damaged or diseased regions in the CNS. Recently, tissue engineering has provided a new medical therapy as an alternative to conventional transplantation methods because it uses by using polymeric biomaterials with or without living precursor cells. 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 extracellular matrix (ECM).[179,184] Cells live in a complex mixture of pores, ridges and fibers of ECM at nanometeric scales.[162,180,189] Hence, a nano-structured porous scaffold having interconnective pores and a large surface area is needed as an alternative to natural ECM for improved cell in-growth in a three-dimensional (3D) fashion. The literature reports as per literature several methods that have been employed to fabricate polymeric nano-fibers or submicronfibers. Three-dimensional distribution and growth of cells within the porous scaffold are of have clinical significance.

The studies of tissue engineering are categorized in four subgroups: scaffold formation, growth factors, extracellular matrix components, and cellular studies.[178,186–188,97,114] The tissue engineering studies aim at obtaining alternative conduit materials and scaffolds by implanting the growth factor or various cells into the nerve conduits.[85,93,109,110] In the tissue engineering studies carried out for increasing the conduit success especially in the large nerve defects, the scaffold formation takes the first place.[178] Use of longitudinal biomaterials in the nerve defects is also one of the studies that fall within the field of tissue engineering.[85]

One of the most important points considered during the studies of tissue engineering is the composition of material used. The reason for this is that the variety of inflammatory response developed by the body against the material used significantly differs in comparison with the component. And this difference is a factor that directly affects the regeneration.[171] The biological adaptation is a key feature required when using the synthetic materials. The elements constituting these features include the permeability, mechanical resistance ratio and melting ratio. These features are the specific variables in the studies of obtaining optimal nerve conduit.[171]

The physical structure of conduit channels also dramatically affects the quality of nerve regeneration. Therefore, the studies of tissue engineering and modifications on the channel structure of conduit constitute the focus of these studies. These physical characters include the dimension of conduit, wall permeability, surface properties of luminal compartment and electrical contents.[171]

Using the methods of tissue engineering, the polymers are obtained from the natural biological tissues and these polymers have an excellent tissue adaptation and also a minimal risk of toxic effect. The extracellular matrix components such as the laminin, fibronectin and collagen are the most common components used as the natural polymers.[133] In the current studies of tissue engineering, the development of three-dimensional scaffold and regeneration-enhancing components are worked on in the nerve defects longer than 20 mm.[178]

The multicomponent nerve conduits are one of the complex molecules developed by the tissue engineering in the field of peripheral nerve regeneration, and this molecules are also named as "nerve grafts of tissue engineering."[85]

The tissue engineering is an application that reduces the cost of health problems and improves the life quality.[136,185,188] As long as the principals of tissue development, regeneration and repair; and information on the complex biological processes are completely clarified, the applications of tissue engineering will further make progress.[185,189] In order to develop molecules with tissue adaptation and absorbed in tissue, the research for tissue engineering are still continued.[28,181,188]

CONCLUSIONS

Clinical data indicate that simple monotissue biological conduits such as veins or skeletal muscles hold a good chance of succeeding if they are used for short gaps. This is also true for silicone tubes. If longer defects have to bridge combined biologic tubes vein plus muscle and vein plus nerve can be employed. These techniques have already been successfully used in patients with success for gaps longer than 30 mm. In addition in large multicentered clinical trial PGA conduits also yielded. Beside this it has been suggested that nerve regeneration across longer gaps can be enhanced by filling the nerve tube with certain substances, rather than using a hollow fiber.[136,137,170] Many luminal fillers in nerve conduits have shown beneficial effect on nerve regeneration. Most impressive are neurotrophic factors such as NGF or FGF-1 impregnated into collagen/laminin fibrils which are already manufactured. Several other luminal filler alternatives are less practical but could be used in short distances. These nerve conduits should be further researched.

Although researches on nerve regeneration have been extensive, the underlying mechanism for axonal proliferation remains poorly understood. Also axonal proliferation is limited to 10–15 mm long in nerve conduits. Most of the research has been carried out on rat or mouse models which are totally different in humans.

Most authors agree that despite the donor site morbidity that is associated with its harvesting autografting must still be considered the first choice strategy for repair of peripheral nerve defects, especially in the case of long gaps. Recent advances in tubulization might change this view. Experiments have demonstrated that tissue engineered tubes are effective in nerve repair for gaps longer than 4 cm results that were previously thought to be possible only by nerve graft. Thus in selected clinic situations, tubulization represents a viable in alternatives to autogenous nerve grafts.

All of these discoveries are making their way into clinic where they are showing great potential for improving both the extent and rate of functional recovery compared with alternative nerve guides. The availability of conduits with material properties appropriate for nerve regeneration will continue.

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