Send Orders for Reprints to reprints@benthamscience.net

The Open Orthopaedics Journal, 2014, *8*, (Suppl 1: M10) 199-203

Open Access

Peripheral Nerve Injury: Principles for Repair and Regeneration

M.F. Griffin[1], M. Malahias[1], S. Hindocha[*,2] and Wasim S. Khan[3]

[1]*Plastic Surgery Department, Good Hope Hospital, West Midlands, B75 7RR, UK*

[2]*Plastic Surgery Department, Whiston Hospital, Liverpool, L35 5DR, UK*

[3]*University College London Institute of Orthopaedics & Musculoskeletal Sciences, Royal National Orthopaedic Hospital, Stanmore, London, HA7 4LP, UK*

Abstract: Peripheral Nerve Injuries are one of the most common causes of hand dysfunction caused by upper limb trauma but still current management has remained suboptimal. This review aims to explain the traditional view of pathophysiology of nerve repair and also describe why surgical management is still inadequate in using the new biological research that has documented the changes that occur after the nerve injury, which, could cause suboptimal clinical outcomes. Subsequently presentation and diagnosis will be described for peripheral nerve injuries. When traditional surgical repair using end-to-end anastomosis is not adequate nerve conduits are required with the gold standard being the autologous nerve. Due to associated donor site morbidity and poor functional outcome documented with autologous nerve repair several new advancements for alternatives to bridge the gap are being investigated. We will summarise the new and future advancements of non-biological and biological replacements as well as gene therapy, which are being considered as the alternatives for peripheral nerve repair.

Keywords: Anastamosis, biological replacements, clinical outcome, nerve repair, peripheral nerves.

INTRODUCTION

Injuries to peripheral nerves are extremely common in many types of upper limb trauma. Injury to peripheral nerves can cause extreme dysfunction in the hand for the patient disrupting their professional and leisure activities. It is therefore vital that adequate treatment is available to repair peripheral nerves to prevent permanent financial loss for the patient as well as the healthcare economy. Galen was the first to describe the concept of the nerve but it was Paulus Aegineta in the 7th century who documented the first nerve repair and wound closure as a military surgeon. Since this time immense research has taken place to understand nerve pathology and physiology. Currently surgical repair involves either reconstruction with direct end-to-end anastomosis or by the insertion of nerve grafts. Despite the long history and major microsurgical research and improvement peripheral nerve repair remains a challenge to surgeons and still has suboptimal outcomes. This review aims to discuss the pathophysiology of nerve injuries including the limitations of surgical repair at a biological level. We will subsequently describe the current techniques, problems and advances in the surgical management of nerve injuries.

PRESENTATION AND PATHOPHYSIOLOGY OF NERVE INJURIES

The smallest anatomical subunit of a nerve is a nerve fiber. Groups of nerve fibers are surrounded by an inner endoneurium to form fascicles. Each fascicle is bounded by perineurium; which contributes to nerve strength and maintains the intra-fascicular pressure. Groups of fascicles are enclosed by the outer epineurium with loose areolar tissue surrounding it.

Peripheral nerve injuries in the upper extremity are extremely common. The typical patient is usually young, sustaining a laceration from metal sharp objects or machinery [1]. To make the diagnosis of a nerve injury it is important to take a detailed history especially with regards to the timing of the event as this will help with guiding treatment. Sensation can be tested using several methods. Vibration is tested using a turning fork, which can be useful to test, as usually deficits occur before subjective complaints. Two-point discrimination is tested by using a paper clip and good for testing group A axons slow fibers. Pick-up tests have shown to be useful to test sensibility and tactile gnosis where the patient picks up the instructed item from a table full of multiple objects [2, 3]. Sudomotor activity can be interestingly be assessed in children by the absence of wrinkling after water immersion or in adults using the sweat test [3]. Motor function should be tested as like the upper and lower limbs in neurological examination and graded from 0-5. Special tests can be used to support or confirm a nerve injury including electromyography (EMG), nerve conduction studies or electrical muscle stimulation. Most commonly nerve conduction studies are used which measures conduction velocities and responses to amplitudes of a nerve fiber, after a percutaneous depolarizing current is supplied. The test is assessing the number of remaining functional axons and the quality of the myelin sheath. These tests are useful only in compressive lesions and partial lesions 5-7 days post-injury. EMG studies test electrical potentials from muscle fibers after insertion of a needle directly into the muscle belly. Doppler studies are useful to assess the blood flow to the nerve, as

*Address correspondence to this author at the Department of Plastic Surgery, Whiston Hospital, Warrington Road, L355DR, UK;
Tel: + 44(0)1244366265; Fax: +44(0)1244366266;
E-mail: hindocha2001@yahoo.com

1874-3250/14

ischaemia can cause direct changes to the motor and sensory nerves.

The sequel of the nerve regeneration involves a series of regulated steps; understanding this sequel of events is important for determining timing and techniques of nerve repair [4].

During the first few hours chromatolysis and swelling takes place in the cell body and nucleus [4]. Oedema and swelling then continues in the axonal stump for the first few days. Within two to three days Wallerian degeneration commences which involves axonal and myelin disintegration both in an antergrade and retrograde direction [4]. Antegrade Wallerian degeneration then continues with Schwann cells and macrophage infiltration to remove cell debris, leaving only the basement membrane for about 3-6 weeks [5]. Schwann cells then start to proliferate and organize guiding the axonal sprouts between the basement membranes of the two nerve ends [4]. Nerve regeneration then begins on the columns of Schwann cells called Bunger bands. The proximal intact axon then sprouts a growth cone. The lamellipodia and filopodia cytoplasmic extensions allow the axon to explore the new environment and help in guiding the repair. Actin found in the axon allows elongation, within the tube. Growth continues at the restricted rate of 1-3 mm/day but simultaneously scar tissue interferes with growth [4].

CLASSIFICATION OF NERVE INJURIES

Nerve injuries were classified into neuropraxia, axonotmesis and neurotmesis by Seddon *et al.* after his World War 2 experience of nerve injuries, in injured soldiers [6]. Sunderland expanded on this classification according to histological diagnosis [7].

Neuropraxia (Sunderland Type 1)

This is an injury to the myelin sheath only [6]. The axonal sheath is preserved and consequently is classified as the least severe nerve injury [6]. This injury is usually a consequence of compression or stretching. No Wallerian degeneration occurs and recovery is to be expected within days or weeks [6].

Axonotmesis (Sunderland Type 2-4)

In this type of injury the axon is affected and Wallerian degeneration occurs distal to the injury site [6]. Type 2 injuries involve the axon only; Types 3 and 4 disrupt the endoneurium and perineurium respectively [6]. Type 2 injuries usually show full recovery but Types 3 and 4 are expected to fail. Type 4 injuries usually require surgical intervention, with most surgeons advocating a 8-10 week wait to ensure that they do not improve spontaneously [6].

Neurotmesis (Sunderland Type 5) 'Neuroma-in-Continuity'

This is the most severe type of injury, which results in complete disruption of the nerve; with the epineurium being transected surgical intervention is required [6].

TIMING OF NERVE REPAIR

Primary repair is the optimal approach for peripheral nerve injuries taking place within the first couple of days [8]. Secondary repair takes place one week or more after the injury [8]. Partial injuries (15% of injuries) as a consequence of stretch or contusions are commonly managed with secondary repair [9-11]. For complete injuries the method of repair depends on what is found during exploration. If the epineurium is found to be neatly divided then primary repair without tension is usually undertaken but if the ends are ragged then a graft may be required [12].

TECHNIQUE OF NERVE REPAIR

There are four main steps to a primary end-to-end repair – the most commonly used nerve repair technique.

1. Preparation – The nerve ends are prepared to get visible ends with necrotic tissue being removed with blades leaving two normal looking ends. Flexing the joint above the nerve injury and bone shortening can be given more length if this is required [13].
2. Approximation – The nerve ends are mobilized and brought together leaving a minimal gap by applying appropriate tension. Tensionless repairs have shown to have better outcomes. During the approximation the nerve ends can be mobilised but extensive intrafasicular dissection should be avoided [13].
3. Alignment – Bloods vessels must be aligned and proper rotational alignment undertaken [13].
4. Maintenance – The nerve repair is maintained by stitches into the epineurium, commonly 9-0 or 10-0 non-absorbable sutures. Hence, it is the epineural repair that keeps the repair together. The sutures need to be placed to avoid malrotation of the nerve ends. Sometimes individual fasiscular groups are identified for attachment (group fascicular nerve repair). These types of repair are usually preferred for larger nerves where sensory and motor fibers can be repaired separately [14].

Postoperatively nerve repairs should be protected by immobilization for 10-14 days and sometimes surgeons advocate up to six-weeks depending on the nerve injury severity and cause [13]. After this period full passive and active range of motion is initiated for rehabilitation [13]. Postoperatively axons may take time to learn how to process new information especially following sensory nerves [15, 16]. Age is the most vital factor to determine the outcome of nerve repair and can account for 50% of the variance in success [17].

Another technique that can be used to repair nerves is the end-to-side nerve repair, which involves the attachment of one or two distal injured nerve end to the side of the uninjured nerve ends. This is a useful technique when the ends are not available as sources of axons [18].

WHY IS REGENERATION FOLLOWING SURGICAL REPAIR INCOMPLETE?

Recent research has helped understand the limitations of surgical practice for peripheral nerve repair. As highlighted above the decision to operate is usually several months following the injury, when healing has not occurred. Over this time axotomy induces atrophy of motoneurons which is only partially reversible [19]. Furthermore the velocity of growth is only 1-3 mm/day and so there is time for

neurotrophic factor production in the distal segments of the nerve to fall preventing fast regeneration [20, 21]. A major factor affecting repair is that the axotomised nerve needs to cross the coaptation site, which occurs in a random manner otherwise the axon may fail to reach the distal stump altogether [22]. Another challenge affected gaining adequate repair is the misalignment of the motor and sensory axons. If motor axons mistakenly enter sensory end organs there are 'pruned' in a process call preferential motor reinnervation [23]. Alternatively muscle axons towards muscle can result in random innervation of inappropriate muscles [24]. Furthermore, after a long period of inactivity the target muscles that the nerves are trying to reinnervate have undergone denervation-induced atrophy, causing adverse clinical outcomes [20].

OTHER TECHNIQUES REQUIRED FOR NERVE REPAIR

Nerve Grafting

In severe nerve injuries the defect between the two nerve ends may be too large or cause inappropriate tension for end-to-end repair; then a bridge is indicated, by using a nerve graft [25, 26]. Typically donor grafts are autologous sensory nerves including the medial or lateral antebrachial cutaneous nerves, dorsal cutaneous nerve branch of the ulnar nerve, lateral femoral cutaneous nerve and superficial sensory branch of the radial [25, 26]. The surgeon must take into account the length of the nerve gap to be repaired, donor site morbidity and dissection difficulty when considering the most appropriate nerve to use [25, 26]. Nerves should be grafted within six-months to achieve full recovery. Most surgeons agree to harvest 10-20% longer than the measured defect to allow for contraction [25, 26]. Postoperative splinting usually occurs for 1-14 weeks, to achieve adequate clinical outcome. In recent years alternatives are being sought for autologous nerve grafts as the 'gold standard' [27] for bridging the gap. Limitations of nerve harvesting include morbidity at the donor site, and that only 40-50% of patients achieve notable functional improvement [28]. Grafts are not always successful because the size and number of fascicles in the proximal and distal nerve stumps or the expressions of the neurotrophic factors is commonly not ideal for regeneration.

Improving Autologous Nerve Grafts

One idea which is being investigated, is the application of growth factors to peripheral nerve lesion sites to sustain the regenerative pathway of axons, which results in a down regulation of nerve growth factor expression [29]. However, despite articles showing some encouraging evidence the timing of growth factors and delivery is still being refined [29]. Application of electrical stimulation to peripheral nerves has shown to improve peripheral nerve lesions gaps but has shown to shorten the delay of fibers crossing the nerve injury site and not the speed of fiber growth. The effects of ES have shown to be only short lasting, with no difference in effect after three months [30, 31]. Phototherapy is a new exciting frontier, that uses low-power laser therapy [32]. Despite improvements in axon regeneration and myelination, reports are limited to support the advantages of laser therapy [32].

Replacing Autologous Nerve Grafts

Autologous biological tissues (non-nerve grafts) have been considered as an alternative as they would be immunologically compatible and non-toxic. However, harvesting samples with appropriate size and dimensions is difficult. Tissues, which have proved useful in promoting a degree of axon regeneration, include blood vessels and freeze-thaw killed skeletal muscles [33, 34]. A different approach is to use non-autologous sources, to bridge the gap between nerve lesions. These tissues offer unlimited supply but have an associated immunogenic risk, including transmission of disease and graft *versus* host disease reactions. The treatment of allogenic nerves with freeze/thawing has shown to provide graftable nerve samples in clinical trials [35]. Several animal trials have shown encouraging results, including the 'Advance Processed Cadaveric Nerve Graft' (AxoGen, Inc, Alachua, Florida) and 'Neurogen Bovine Collagen Conduit' (Interga) [36].

CONSIDERATIONS FOR REPLACEMENTS OF AUTOLOGOUS NERVE GRAFTS

When constructing a nerve conduit for nerve repair, four elements need to be taken into consideration: Firstly the scaffold for axonal proliferation, then the support cells for Schwann cells and lastly the growth factors and extracellular matrix.

SCAFFOLDS

The scaffold serves to act as the structure for supporting axonal regeneration [37]. Natural materials have been tested including laminin, fibronectin and collagen due to their advantages of decreased toxic effect, improved biocompatibility and enhancement of the migration of support cells [37] but there is documented evidence that they loose their ability to regenerate when stored for long periods of time and there can be batch to batch variability [38]. Synthetic materials have been used and tested and although useful as can be manipulated to the exact configuration, long-term consequences of the conduit on the nerve are unknown. Clinically approved materials for bridging peripheral nerve injuries are few from the US Food and Drug Administration (FDA) and from the European Union with a Conformite European (or CE) certification. Currently one biodegradable nerve conduit (SaluBridge from SaluMedica) and four biodegradable nerve conduits (Neurotube from Synovis Micro Companies Alliance; NeuroMatrixTM or NeuroFlexTM from Collagen Matrix Inc.; Neurolac from Polyganics BV; NeuraGenTM from Integra Neuroscience) have received such approval.

Supports Cells (SC), Growth Factors and the Extracellular Matrix (ECM)

Support cells (SCs) have shown to enhance axon migration and produce structural and adhesive ECM molecules which promote nerve regeneration. Investigators

have tried to take advantage of the function of the SC to produce CNS and PNS regeneration [39-41]. Numerous growth factors are involved with peripheral nerve repair including nerve growth factor (BGF), brain derive neurotrophic factor (BDNF), insulin like growth factor (IGF-1, IGF-2), platelet derived growth factors (PDGF), fibroblast growth factor (FGF), and ciliary neurotrophic factor (CNTF). These growth factors as explained above, can be directly incorporated into the nerve conduit [42-44].

The extracellular matrix molecules are important for axonal extension and act as guiding the nerve regeneration. It has been found that ECM molecules including fibronectin, collagen and laminin incorporated into the conduit, act as a guidance channel and have had variable results [45, 46].

NERVE TRANSFERS

More recently nerve transfers are becoming more frequent. This procedure means less needed nerve fascicles from a donor nerve are transected, dissected and then attached to a more important distal nerve segment. This transforms a proximal nerve injury to a distal one with short regeneration [47]. This technique is useful for transferring nerve trunks in brachial plexus injuries. Examples include the thoracodorsal nerve to the deltoid muscle for axillary nerve lesions; pronator quadratus branch of the anterior interosseous never (AIN) to the motor branch of the ulnar nerve at the Guyon's canal [47].

GENE THERAPY

Gene therapy offers another exciting alternative to autologous nerve grafts for enhancing peripheral nerve repair. The main advantages are that the transduced cells will express the gene for an extended period of time which is useful as the neurotrophic factors inserted usually have a short half life [48]. Furthermore, the expression in the selected cells is restricted to the cell at the site of the injection of the viral vector meaning the therapy is selective, localised and specific. Various vectors are being trialed and tested with different types of neurotrophic factors but the main three cellular targets for gene therapy are the Schwann cells, injured neurons and the muscles fibers. So far gene therapy has been successfully applied in rodent models to counteract the atrophy of spinal motor neurons following ventral root avulsion [49]. Furthermore, selective viral over expression of NGF in the sensory saphenous branch resulted in increased correct sensory reinnervation after injury, which could help the challenge of misrouting the regenerating sensory axons [50]. Lastly, studies have shown the long term expression of neurotrophic factors by Schwann cell in the injured nerve is possible with gene therapy [51, 52]. Unfortunately, there are several obstacles preventing the translation of successful animal results to humans, including choosing the correct factor and target cell, biosafety regarding vectors and long term risk including mutagenesis.

CONCLUSION

Over the last decade there has been extensive research into alternatives for surgical repair, as the clinical outcome often remains inadequate [53-56]. Although the concept of using a nerve conduit for peripheral nerve repair is quicker for the surgeons and avoids harvesting morbidity, it has not resulted in better outcomes in the literature so far. Many growth factors have been indentified which influence nerve regeneration, which gives hope to the development of the ideal combination of growth factor and nerve conduit. It is clear that many conduits are currently being researched but they are still in their experimental stage with few being approved for clinical application. Similarly to other solutions for reconstructive surgery, the surgical advancements of the future to the surgical approach to peripheral nerve injuries will be focusing on cell and tissue modification and transplantation.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] McAllister RM, Gilbert SA, Calder JS, Smith PJ. The epidemiology and management of upper limb peripheral nerve injuries in modern practice. J Hand Surg 1996; 21B: 4-13.

[2] Omer GE. Methods of assessment of injury and recovery of peripheral nerves. Surg Clin North Am 1981; 61: 303.

[3] O'Riain S. New and simple test of nerve function in hand. Br Med J 1973; 3: 615-6.

[4] Deumens R, Bozkurt A, Meek MF, *et al*. Repairing injured peripheral nerves: Bridging the gap. Prog Neurobiol 2010; 92(3): 245-76.

[5] Fu SY, Gordon T. The cellular and molecular basis of peripheral nerve regeneration. Mol Neurobiol 1997; 14: 67-116.

[6] Seedon HJ. Peripheral nerve injuries. Medical Research Council. Special Report Series 282. London: Her Majesty's Stationery Office 1954.

[7] Sunderland S. Rate of regeneration of I: sensory nerve fibers and II: motor fibers. Arch Neurol Psychiatry 1947; 58: 1-14.

[8] Jabaley M. Primary nerve repair. In: Peripheral nerve surgery: Practical applications in the upper extremity. Slutsky DJ, Hentz VR, Eds. Philadelphia: Churchill Livingstone Elsevier 2006; pp. 23-38.

[9] Kline DG. Physiological and clinical factors contributing to the timing of nerve repair. Clin Neurosurg 1977; 24: 425-55.

[10] Kline DG, Hackett ER. Reappraisal of timing for exploration of civilian peripheral nerve injuries. Surgery 1975; 78(1): 54-65.

[11] Brown PW. Factors influencing the success of the surgical repair of peripheral nerves. Surg Clin North Am 1972; 52: 1137-55.

[12] Seddon HJ. Surgical Disorders of the Peripheral Nerves. 2nd ed. Edinburgh: Churchill Livingstone 1972.

[13] Mackinnon SE, Dellon AL. Surgery of the peripheral Nerve. New York: Theime Medical Publishers 1988.

[14] Young L, Wray RC, Weeks PM. A randomized prospective comparison of fascicular and epineural digital nerve repairs. Plast Reconstr Surg 1981; 68: 89-93.

[15] Lundborg G, bjorkman A. Cortical effects of nerve injury. In: Upper extremity nerve repair – tips and techniques: A master skills publication. Slutsky D, Ed. ASSH 2008; pp. 29-37.

[16] Rosen B, Lundborg G. Sensory re-education following nerve repair. In: Upper extremity nerve repair – tips and techniques: A master skills publication. Slutsky D, Ed. ASSH 2008; pp. 159-78.

[17] Rosén B, Lundborg G, Dahlin LB, Holmberg J, Karlsson B. Nerve repair: Correlation of restitution of functional sensibility with specific cognitive capacities. J Hand Surg 1994; 19b: 452-8.

[18] Bontioti E, Kanje M, Lundborg G, Dahlin LB. End-to-side nerve repair in the upper extremity of rat. J Peripher Nerv Syst 2005; 10: 58-68.

[19] Fu SY, Gordon T. Contributing factors to poor functional recovery after delayed nerve repair: Prolonged denervation. J Neurosci 1995; 15: 3886-95.

[20] Eggers R, Tannemaat MR, Ehlert EM, Verhaagen J. A spatio-temporal analysis of motoneuron survival, axonal regeneration and neurotrophic factor expression after lumbar ventral root avulsion and implantation. Exp Neurol 2010; 223: 207-20.

[21] Hoke A, Redett R, Hameed H, *et al*. Schwann cells express motor and sensory phenotypes that regulate axon regeneration. J Neurosci 2006, 26: 9646-55.

[22] McDonald D, Cheng C, Chen Y, Zochodne D. Early events of peripheral nerve regeneration. Neuron Glia Biol 2006; 2: 139-47.

[23] Madison RD, Archibald SJ, Lacin R, Krarup C. Factors contributing to preferential motor reinnervation in the primate peripheral nervous system. J Neurosci 1999; 19: 11007-16.

[24] Ijkema-Paassen J, Meek MF, Gramsbergen A. Reinnervation of muscles after transection of the sciatic nerve in adult rats. Muscle Nerve 2002; 25: 891-7.

[25] Millesi H. In: Nerve grafting. Terzis JK, Ed. Clinic in Plastic Surgery Philadelphia: WB Saunders 1984; pp. 105-13.

[26] Millesi H. In: Indications and techniques of nerve grafting. Gerlberman RH, Ed. Operative Nerve Repair and Reconstruction. Vol 1. Philadelphia: JB Lipincott 1991; pp. 525-43.

[27] Dellon AL, Mackinnon SE. Basic scientific and clinical applications of peripheral nerve regeneration. Surg Ann 1988; 20: 59-100.

[28] Lee SK, Wolfe SW. Peripheral nerve injury and repair. J Am Acad Orthop Surg 2000; 8: 243-52.

[29] Boyd JG, Gordon T. Glial cell line-derived neurotrophic factor and brainderived neurotrophic factor sustain the axonal regeneration of chronically axotomized motoneurons *in vivo*. Exp Neurol 2003; 183: 610-9.

[30] Ahlborn P, Schachner M, Irintchev A. One hour electrical stimulation accelerates functional recovery after femoral nerve repair. Exp Neurol 2007; 208: 137-44.

[31] Irintchev A, Angelov DN, Guntinas-Lichius O. Regeneration des N. facialis im Vergleich zu anderen peripheren Nerven (German). Hals-Nasen-Ohren Heilkunde (HNO) 2010; 58: 426-32.

[32] Van Breugel HH, Bar PR. He-Ne laser irradiation affects proliferation of cultured rat Schwann cells in a dose-dependent manner. J Neurocytol 1993; 22: 185-90.

[33] Chiu DTW. Autogenous vein graft as a conduit for nerve regeneration. Surgery 1982; 91: 226-32.

[34] Meek MF, Varejao AS, Geuna S. Use of skeletal muscle tissue in peripheral nerve repair: review of the literature. Tissue Eng 2000; 10: 1027-36.

[35] Marmor L. Regeneration of peripheral nerves by irradiated homografts. J Bone Joint Surg 1964; 46-A: 383-94.

[36] Whitlock EL, Tuffaha SH, Luciano JP, *et al*. Processed allografts and type I collagen conduits for repair of peripheral nerve gaps. Muscle Nerve 2009; 39: 787-99.

[37] Wang KK, Costas PD, Bryan DJ, Jones DS, Seckel BR. Insideout vein graft promotes improved nerve regeneration in rats. J Reconstruc Microsurg 1993; 14: 608-18.

[38] Gulati AK. Peripheral nerve regeneration through short- and long-term degenerated nerve transplants. Brain Res 1996; 742: 265-70.

[39] Woerly S, Plant GW, Harvey AR. Neural tissue engineering: From polymer to biohybrid organs. Biomaterials 1996; 17: 301-10.

[40] Zhang Y, Campbell G, Anderson PN, Martini R, Schachner M, Lieberman AR. Molecular basis of interactions between regenerating adult rat thalamic axons and schwann cells in peripheral nerve grafts II: Tenascin-c. J Comp Neurol 1995; 361: 210-24.

[41] Zhang Y, Campbell G, Anderson PN, Martini R, Schachner M, Lieberman AR. Molecular basis of interactions between regenerating adult rat thalamic axons and schwann cells in peripheral nerve grafts I: Neural cell adhesion molecules. J Comp Neurol 1995; 361: 193-209.

[42] Griffin CC, Letourneau PC. Rapid retraction of neurites by sensory neurons in response to increased concentrations of nerve growth factor. J Cell Biol 1980; 86: 156-61.

[43] Yip HK, Rich KM, Lampe PA, Johnson EM Jr. The effects of nerve growth factor and its antiserum on the postnatal development and survival after injury of sensory neurons in the rat dorsal root ganglia. J Neurosci 1984; 4: 2986-92.

[44] Sterne GD, Brown RA, Green CJ, Terenghi G. Neurotrophin-3 delivered locally *via* fibronectin mats enhances peripheral nerve regeneration. Eur J Neurosci 1997; 9: 1388-96.

[45] Valentini RF, Aebischer P, Winn SR, Galletti PM. Collagen and laminin containing gels impede peripheral nerve regeneration through semipermeable nerve guidance channels. Exp Neurol 1987; 98: 350-35.

[46] Williams LR, Danielsen N, Muller H, Varon S. Exogenous matrix precursors promote functional nerve regeneration across a 15-mm gap within a silicone chamber in the rat. J Comp Neurol 1987; 264: 284-90.

[47] Nath RK, Mackinnon SE. Nerve transfers in the upper extremity. Hand Clin 2000; 16: 131-9.

[48] Hoyng SA, Tannemaat MR, De Winter F, Verhaagen J, Malessy MJA. Nerve surgery and gene therapy: a neurobiological and clinical perspective. J Hand Surg Eur Vol 2011; 36: 735.

[49] Eggers R, Tannemaat MR, Ehlert EM, Verhaagen J. A spatio-temporal analysis of motoneuron survival, axonal regeneration and neurotrophic factor expression after lumbar ventral root avulsion and implantation. Exp Neurol 2010; 223: 207-20.

[50] Hu X, Cai J, Yang J, Smith GM. Sensory axon targeting is increased by NGF gene therapy within the lesioned adult femoral nerve. Exp Neurol 2010; 223: 153-65.

[51] Haastert K, Grothe C. Gene therapy in peripheral nerve reconstruction approaches. Curr Gene Ther 2007; 7: 221-8.

[52] Tannemaat MR, Verhaagen J, Malessy M. The application of viral vectors to enhance regeneration after peripheral nerve repair. Neurol Res 2008; 30: 1039-46.

[53] Chimutengwende-Gordon M, Khan WS. Recent advances and developments in neural repair and regeneration for hand surgery. Open Orthop J 2012; 6(1): 103-7.

[54] Rayanmarakkar F, Khan WS, Hardingham TE. In: Hand Surgery: Preoperative Expectations, Techniques and Results. Beckingsworth RH, Ed., Principles of Tissue Engineering Approaches for Tendons, Skin, Nerves and Blood Vessels in the Hand. New York: Nova Science Publishers 2009; pp. 85-96.

[55] Picardo NE, Khan WS. Tissue engineering applications and stem cell approaches to the skin, nerves and blood vessels. Curr Stem Cell Res Ther 2012; 7(2): 115-21.

[56] Khan WS, Pastides P, Hardingham TE. Tissue Engineering Approaches for Neurovascular Structure. Khan WS and Pastides P, Eds. In: Tissue Engineering and the Musculoskeletal System: A Limitless Cure? New York: Nova Science Publishers 2012; pp. 107-18.

Received: November 2, 2013 Revised: February 1, 2014 Accepted: April 2, 2014