International Journal of
Recent Innovations in Medicine and Clinical Research
Open Access, Peer Reviewed, Abstracted and Indexed Journal

ISSN: 2582-1075
https://ijrimcr.com/
Volume-5, Issue-3, 2023: 11-21

Review Article

Timing, Duration and Dose of Electrical Stimulation Impact Modulation of Nerve Regeneration in Peripheral Nerve Injury

Thomas Erwin Christian Junus Huwae[1*], Panji Sananta[1], Dwi Indriani Lestari[2], Gutama Arya Pringga[2], Ivan Triangto[2]

[1]Orthopaedic and Traumatology Department, Faculty of Medicine, Universitas Brawijaya–Dr. Saiful Anwar General Hospital Malang, East Java, Indonesia
[2]Physical Medicine and Rehabilitation Department, Faculty of Medicine, Universitas Brawijaya–Dr. Saiful Anwar General Hospital Malang, East Java, Indonesia
*Corresponding Author Email: huwaethomas@ub.ac.id

Received: July 08, 2023 **Accepted:** August 11, 2023 **Published:** August 24, 2023

Abstract: Electrical stimulation (ES) is known as one of the effective and efficient physical modalities in managing peripheral nerve injuries. Peripheral nerve injuries greatly impact an individual's activities of daily living (ADL), which in turn affects the quality of life. Its effect focuses on the enhanced gene expression, which includes (NGF, BDNF, NT 4/5, cAMP, and VEGF), expedites and enhance guidance of axonal regeneration into its proper pathway. Thus, ES allows early onset of regeneration by reducing staggering time, which increases the likelihood for more axons to cross the coaptation site within a proper pathway instead of increasing its regeneration rate. This review aims to understand the physiological nerve regeneration process with the use of ES and the appropriate application to be given in peripheral nerve injuries.
Keywords: Electrical stimulation, nerve regeneration, peripheral nerve injury.

Introduction

Electrical stimulation (ES) is a promising strategy for managing peripheral nerve injury. The following modality allows the acceleration and enhances early regenerative stages, which include neuronal survival and axonal sprout formation [1]. This could be done by the upregulation of neurotrophic factors expression and growth-associated genes [2]. ES also results within the muscular tissue by preventing the denervation of muscle and atrophy [1].

Functional recovery in the injured peripheral nerve plays a vital role in providing improved quality of life, which can be achieved with the help of ES [1]. Despite the promising strategy provided by ES in early regeneration of the peripheral nerves, there seem to have several aspects that resulted in the delay in nerve regeneration and parameters that should be considered while applying ES. Therefore, the scope of this review is to understand the physiological nerve regeneration process using ES and the appropriate application to be given in peripheral nerve injuries.

Literature Review

1. Peripheral Nerve Injury

1.1 Classification

Classification is used to describe the extent of the injury to correlate with its pathophysiology, clinical symptoms, and providing prognosis to patients. Two classifications have been used, Seddon and Sunderland.

Seddon classification divides into three categories, neuropraxia, axonotmesis, and neurotmesis as seen on Table 1. Neuropraxia is the mildest form of injury, which involves focal demyelination without the involvement of axon neither or connective tissue injuries. Axonotmesis is the second category, which involves axonal damage, focal demyelination, and preservation of the nerve's connective tissues. Crush injuries are a common cause of axonotmesis. The most severe state, known as neurotmesis, involves all the peripheral nerve structures, where complete discontinuity is found [3, 4]. Based on the study by Castillo-Galván et al. in Monterrey, Mexico, from 2008 up to 2012, the most frequently found peripheral nerve injury type is neurotmesis (51%), followed by axonotmesis (29%), and neuropraxia (20%) [5].

Table 1. Seddon's Classification [4]

Characteristic	Neuropraxia	Axonotmesis	Neurotmesis
Etiology	Nerve compression injury	Nerve crush injury	Nerve transection injury
Description	Axon is intact Local myelin injury Conduction block	Axonal interruption Connective tissue/ Schwann cell intact Conduction failure	Axonal interruption Connective tissue disruption Conduction failure

Newer classification is done by Sunderland, which divides peripheral nerve injury classification into five categories while still giving account to the previous classification. Its classification is graded between I-V, were grade I represents the mildest form of injury and grade V indicates its most severe form presented in Table 2.

Table 2. Sunderland's Classification [3]

Classification	Description
Grade I	Also known as neuropraxia, conduction block occurs
Grade II	Also known as axonotmesis, axonal injuries without damage to connective tissues
Grade III	Grade II + involvement of endoneurium
Grade IV	Grade III + perineurium injury
Grade V	Also known as neurotmesis, sums up all the peripheral nerve structure injuries

1.2 Injury Mechanism

Peripheral nerve injuries may be caused by two main mechanisms, compression and crush and transection injury. Compression injuries are commonly mild in their form, in which neuropraxia or Grade I injuries are frequently found. Compression may be acute or chronic, depending on its underlying mechanism. In a chronic state, myelin sheaths are degraded and thinner with decreased internodal length. The following findings result in Schwann cell proliferation, dedifferentiate and increase in Schmidt-Lanterman incisures (SLIs), which are part of Schwann cell in the maintenance of myelin sheath metabolism. Its increase indicates the likelihood of increasing Schwann cell metabolism to undergo remyelination in the presence of demyelination [3]. In contrast to compression injuries, crush injuries come in different degrees of severity towards the neurons, depending on the extent of the injury. Crush injuries are acute state injuries resulting from blunt traumas. Transection injuries are acute injuries with complete discontinuation of the nerve, also known as neurotmesis or grade V injuries. Sharp or ballistic injuries may cause the following [3].

1.3 Peripheral Nerve Healing

Injuries to peripheral nerves bring out the degeneration process as part of regeneration. Nerve degeneration can occur in two different types: Wallerian and axonal. The difference between the two is the starting point of its degeneration process, in which Wallerian degeneration occurs in a

proximal to distal fashion, whereas axonal degeneration is the opposite. Wallerian degeneration occurs more frequently than axonal degeneration within three weeks after injury [4].

The degeneration process begins with an injury of an intact nerve. Following the injury, within 48 hours, the injured myelin and axons are transformed into 'ellipsoids' and droplets. There's continued axonal transport within the distal stump in a proximal-distal fashion for up to two days, thus allowing continued capacity in conducting action potential. The injury also resulted in slow rise calcium influx at injured site and progressed as a wave throughout cytoplasm and mitochondria of the distal stump. Calcium then triggers endogenous proteolysis and degeneration of the axonal cytoskeleton, followed by fragmentation, disintegration, and phagocytosis by the inflammatory agents [6]. As inflammatory reactions occur, the monocytes play a role in entering the damaged endoneurial sheaths to engulf the debris and then turn to macrophages. These macrophages have their phagocytic action. Apart from that, it also has a mitogenic to Schwann cells and together with Schwann cells, it provides trophic (feeding) and tropic (guidance) factors for regenerating the injured axons [7]. Degeneration does not only take place from the injury site to its distal aspect, but it also affects proximally, limited to the first node of Ranvier as a result of calcium released from intracellular stores. Within the degeneration of the distal nerve stump, downregulation of myelin-associated genes (choline acetyltransferase, acetylcholinetransferase and neurofilament) and upregulation of growth-associated genes (GAP-43, tubulin, actin, and glial derived neurotrophic factor (GDNF)) (Figure 1) [6].

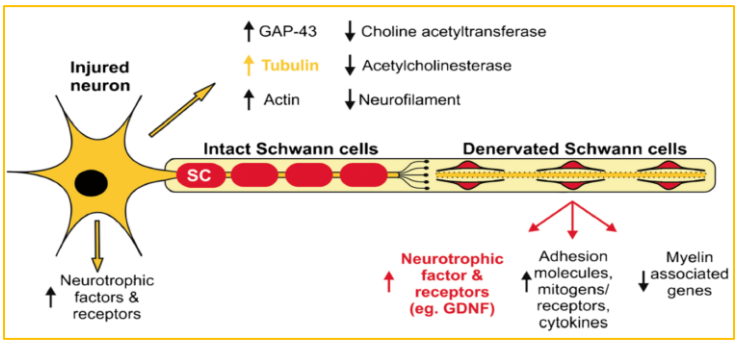


Figure 1. Upregulation of growth-associated genes and downregulation of myelin-associated genes within an injured nerve [6].

As degeneration occurs, with the increasing amount of time, there's a decline in the previously upregulated growth-associated genes, such as tubulin and GDNF (Figure 2a-b). The number of macrophages also showed a reduction in amount with time (Figure 2c), thus indicating that degeneration slows down and will then come to a point where the process stops and is continued with the regeneration process [6].

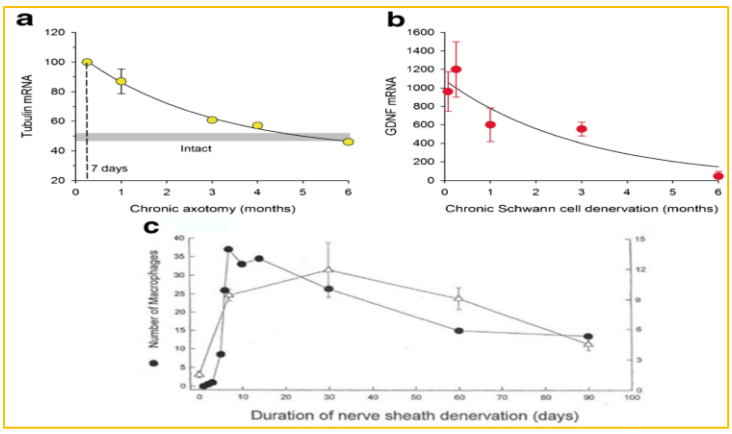
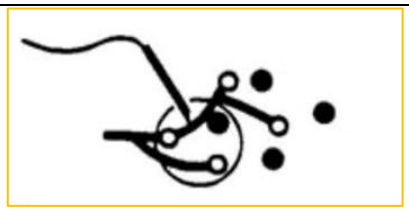
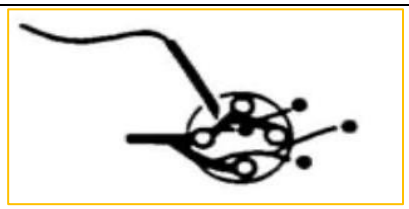
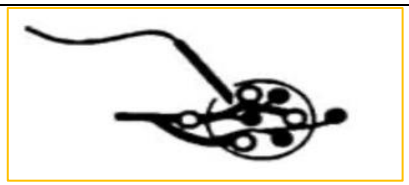
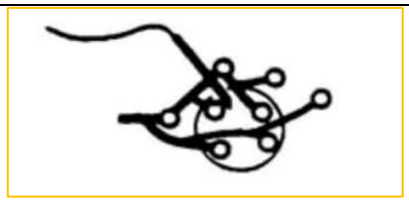


Figure 2. (a) Decrease of tubulin, (b) GDNF and (c) macrophages with increasing amount of time [6].

Regeneration occurs in two different forms, depending on the post-injury condition. The muscle may undergo collateral sprouting of neurons from an entire motor unit and innervating the denervated muscle fibers of an injured motor unit. The newly formed connections have smaller terminal branches, thinner myelin, and weaker neuromuscular junctions (NMJs) despite the reinnervation. As the original nerve innervating the specific muscle fiber type is lost, the newly formed neural connections will take over the denervated muscle and the characteristic muscle fiber type based on the intact nerve shown in Table 3. Thus, this resulted in poor firing synchronicity [4].

Table 3. Regeneration Process [4]

Time and condition	Illustration	Description
Normal		A normal motor unit, light circles indicating type I muscle fibers and darks circles are type II fibers
2-3 weeks post denervation		After 2-3 weeks of denervation, loss of connection is found within the distal stump with its innervation to the type II fibers
1-2 months post denervation		Around 1-2 months after denervation, collateral sprouting are seen, in which the intact motor unit with its original innervation to type I muscle fibers, sprouts of to the denervated type II muscle fibers with smaller branches, thinner myelin and weaker NMJs
2-6 months post reinnervation		Within 2-6 months, the newly formed connections will then mature
6 months–2 years post reinnervation		After 6 months, the denervated type II muscle fibers are then taken over to the intact motor unit which took over, converting it into type I muscle fibers

Another mechanism of regeneration that is frequently studied is axonal regeneration. Axon will then regrow through its original pathway toward its muscle fiber within this process. Although promising, its growth is limited to 1 mm/day or 1 inch/month (35 mm/month) if its supporting connective tissue remains intact. Similar to the previous mechanism, despite the newly formed connection, it has its limitation of the nerve characteristics, such as thinner axonal diameter, thinner myelin, and shorter intermodal distance (Figure 3). Thus, resulting in slower transmission of action potential within the nerve [4]. With the proximal degeneration limited to the closest first node of Ranvier by calcium release results in the sealing. Calcium signaling stimulates retrograde signaling through mitogen-activated protein kinase (MAPK) and calmodulin-dependent protein kinase (CaMK), thus activating expression of injury responsive genes which then allows axonal outgrowth. The following injury is followed with synthesis of rapamycin (mTOR) and PTEN, an mTOR antagonist, in which mTOR

functions by binding dynein through adaptor proteins such as ß1, transporting it in a retrograde fashion towards neuronal nucleus and undergo regulation of transcriptional process [6].

The following cell response to injury, allows axonal sprouting to take place from its proximal stump [6] and the sprouts are mitogenic toward each Schwann cell it encounters (Figure 4E) [7]. Axonal regeneration appears to be time-consuming, as the axonal sprouts "wonder" within the space between proximal and distal stump and is also known slow or "staggered" growth [6, 8]. Within five days of denervation, sensory and motoric specific neurotrophic factors begin to be expressed. mRNA levels have not reached its peak levels approximately ten days after nerve repair [6] and Schwann cells move into the surgical site and are align in parallel as the Bands of Büngner help to guide the growth cones with its filopodia across the suture site (Figure 4F) [6,8]. Two-three weeks after, the newly formed connections regenerate with their axons branch randomly into the appropriate and inappropriate connections (Figure 5). Within 15 days, the mRNA levels have reached its peak values, allowing appropriate branching progressively over eight to ten-week period (Figure 4G-H and Figure 5) [6].

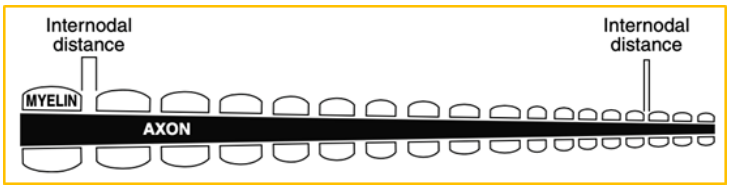


Figure 3. Axonal regrowth, with reduced axonal diameter, thinner myelin and shorter intermodal distance [2, 4].

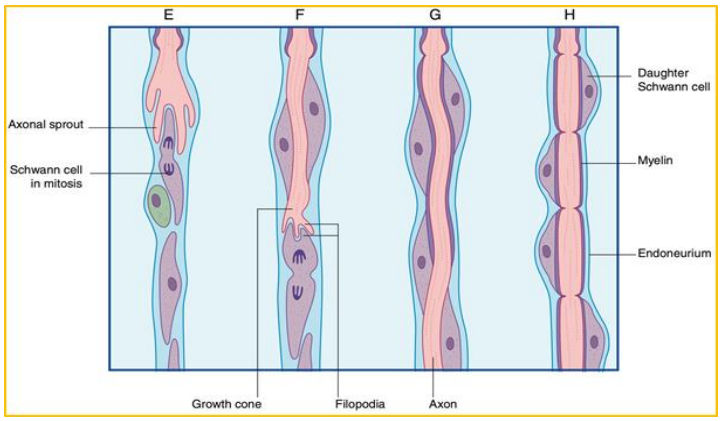


Figure 4. (E) Axonal sprouting within axonal regeneration, (F-H) occurs due to the attachment of growth cones via filopidia to the Schwann cells towards the guided pathway by Bands of Büngner [7].

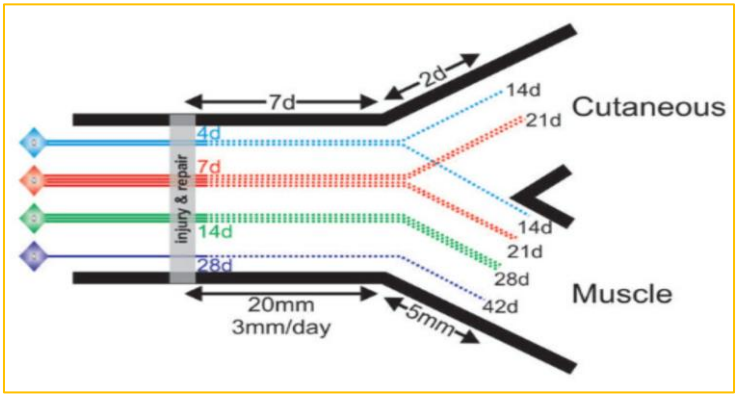


Figure 5. Non selective motor neuron regeneration within 2-3 weeks to appropriate and inappropriate connections and is then followed by appropriate motor connections [6]

Nerve regeneration continues towards the muscles, as mentioned previously that muscle fibers innervated by one motor neuron within a motor unit, occupy a territory within the muscle. The motor unit territory will increase with the increase in number of muscle fibers within the territory. Partial nerve injuries also result in downregulation of muscle function through its innervation distribution, in which it does not appear to be dispersedly distributed or mosaic distribution, instead it is distributed in "clumped" pattern (Figure 6) [6].

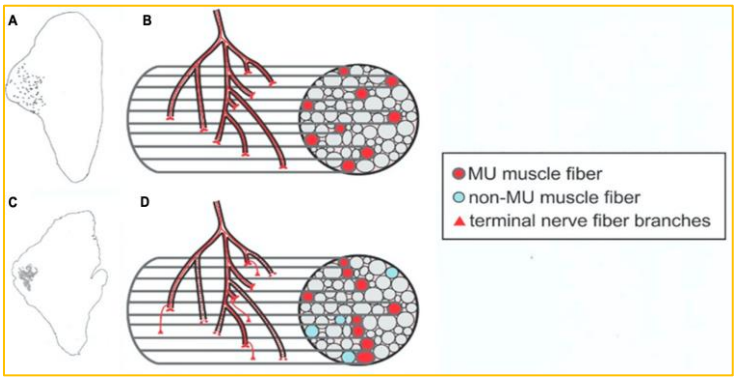


Figure 6. (A & B) Mosaic pattern of muscle fiber, (C & D) Clumped distribution of muscle fibers [6].

2. Electrical Stimulation Enhances Peripheral Nerve Regeneration

Electrical stimulation (ES) has been found to accelerate nerve regeneration. The following finding was studied in the 1980's by Al-Majed et al. that both continuous 4Hz of ES of proximal stump caused by crush injury affecting the lateral gastrocnemius and soleus muscle of a rabbit and 20Hz of ES of plantar extensor affects nerve regeneration. The effect was also evident within a mice study with ES and sham (non-ES) study, in which motor reinnervation of appropriate pathway took place within three weeks period as compared to approximately 6 weeks and all motoneurons regenerated their axons into motor nerve branch within three weeks instead of eight to ten weeks (Figure 7). Therefore, ES increases outgrowth of axons in earlier muscle reinnervation and functional recovery for both motor and sensory nerve within animal and human model (Figure 8 A-D) [8].

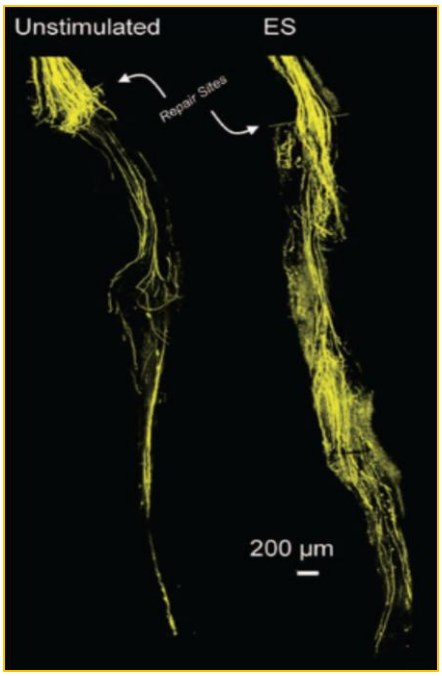


Figure 7. Mice study using yellow fluorescent protein (YFP) showing an accelerated outgrowth of axons across the suture site toward the distal stump with the common peroneal nerve treated with 20Hz of one-hour stimulation within ES group as compared to sham group [8].

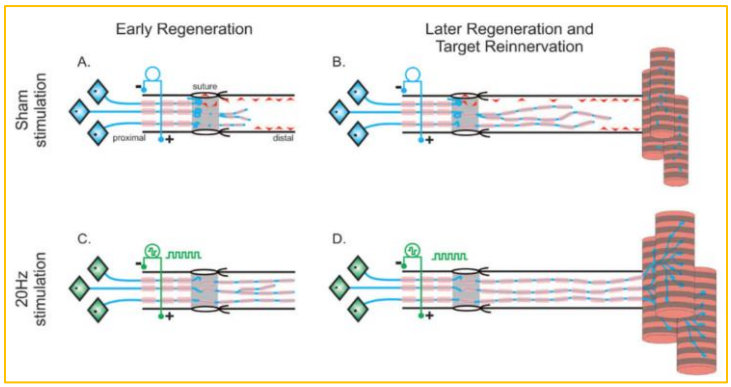


Figure 8. (A-D) Electrical stimulation enhances target reinnervation [8].

2.1 Molecular basis of ES accelerated effect on axon outgrowth

A study by Javeed et al. illustrate several molecular effects displayed by ES. Following nerve injury and providing immediate ES revealed calcium influx, generating retrograde signal (Figure 9). Alongside with enhanced gene expression, an additional molecular structure which plays a vital role in peripheral nerve regeneration, development and maintenance modulated by ES include nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), and Neurotrophin 4/5 (NT 4/5) [1]. NGF functions to promote neuronal survival by its anti-apoptotic effect. The following growth factor is limited to certain set of neuronal population within the central and peripheral nervous system, such as peripheral sympathetic and sensory neurons [9]. Increased BDNF expression is observed after a rise in intracellular calcium. BDNF act on its receptor tyrosine kinase B (trkB), which function to enhance axonal growth [1, 9]. Apart from its action towards its receptor, it also acts to prevent degradation of cAMP through phosphodiesterase inhibition, allowing the sustained rise of cAMP level [1]. Similar to NGF, BDNF are limited to certain subpopulation of neurons, such as sensory dorsal root ganglion neurons, motoric neurons and minimal effect on sympathetic neurons [9].

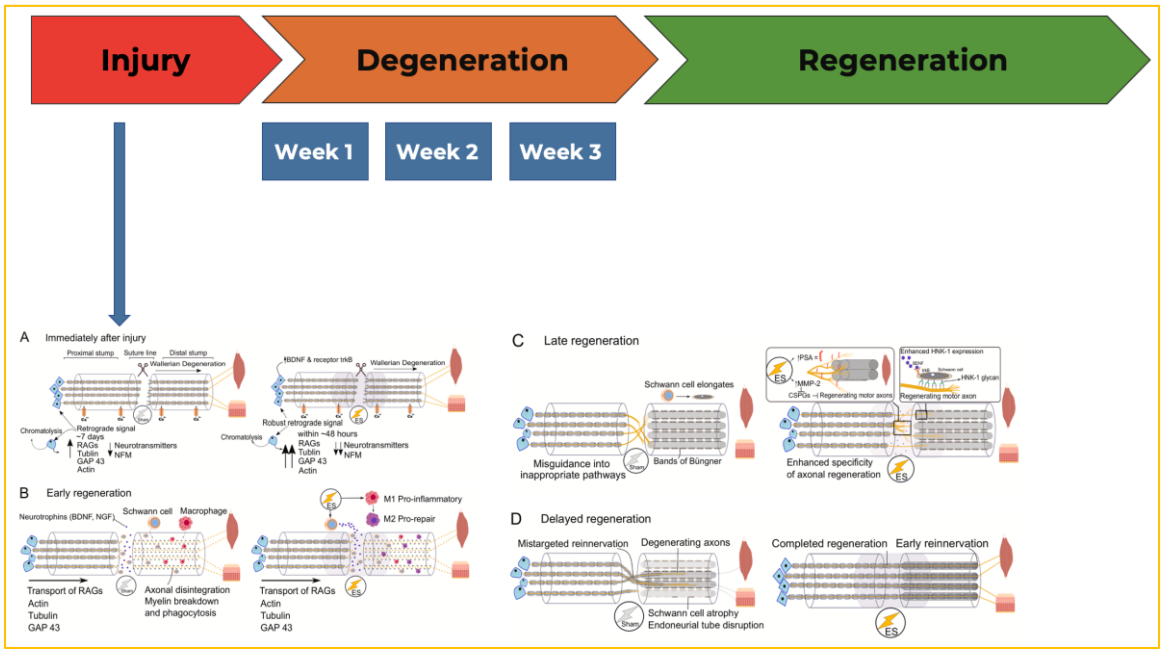


Figure 9. (A) Peripheral nerve healing timeline in relation to appropriate application of ES. Immediate application of ES, (B) enhances early nerve regeneration through the release of neurotrophins by axons and Schwann cells, (C) ES reduces staggering time by approximately 3 weeks instead of 8 to 10 weeks. PMR is achieved by enhanced PSA and HNK-1 expression with M2 macrophage to clear myelin, (D) Reduction of misguided reinnervation and an organ protection from atrophy by ES retrograde signaling allows cell activation leading to nerve regeneration. The following was achieved within 48 hours of injury as compared to sham study through the enhance expression of genes, which include actin, tubulin, and growth associated protein-GAP-43 [1].

The role of ES also acts on cAMP in enhancing neural growth and axonal guidance. The following is achieved through cAMP induced by ES, activating phosphokinase A (PKA) mediated phosphorylation of CREB (cAMP response element binding protein). Therefore, BDNF expression is increased and neurite growth take place. Besides acting on neural axon, cAMP also overcome inhibition from myelin and inhibitory chondroitin sulfate proteoglycans (CSPGs), which are encountered within regenerating axons [1]. Vascular endothelial growth factors (VEGF), also plays a vital role in neuronal regeneration. The following allows neuronal regeneration through angiogenesis. Increase angiogenesis helps to promote increase vascularization, which then allows regeneration of nerve fibers, axonal outgrowth, and neuronal survival [9]. This could be achieved by ES through the increase of VEGF mRNA and VEGF protein, thus promoting angiogenesis and endothelial cell proliferation. With the utilization of ES, metabolic imbalance take place that allows the increase of VEGF in promoting angiogenesis through continuous muscle contraction, causing the increase usage of nutrients and oxygen. Increase of angiogenesis allows increase of oxygen delivery, utilized by type-1 muscle fibers through electron transport chain for ATP synthesis and muscle contraction. Besides the following, ES increases the proliferation and differentiation of myoblast into myocytes that is caused by the increase in expression of genes associated with myogenic differentiation [9].

Within a sham study, the following molecular structures are not recognizable due to its low amount during the early phases of denervation process and peak after 15 days following injury (Figure 10) [2, 6]. Following an injury, nerve regeneration occurs with random and non-specific fashion, causing staggering before reuniting with the distal Schwann tubes. The staggering mechanism becomes the main delaying factor within nerve regeneration process of an injured nerve, it the regenerating axons demand crossing the coaptation site. With longer periods of the delay will result in denervation of muscle and atrophy, followed with poor functional recovery.

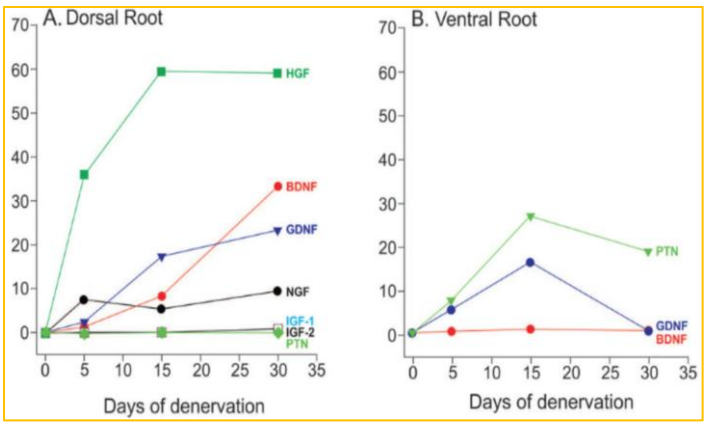


Figure 10. Delayed neurotrophic factors upregulation within the dorsal (A) and ventral (B) nerve roots [6].

ES has proven to be a modality of choice to enhance the staggering time and expedite regeneration of motor neurons within three weeks, compared to eight to ten weeks in sham study and doubles the number within sensory axon regeneration. Preferential motor reinnervation (PMR), a term to describe motor axon regeneration to project its axons into the appropriate motor pathway. In order to guide regenerating axons into its proper pathway, the following could be achieved through the aid of polysialic acid (PSA), and HNK-1 glycan. PSA has been linked to neural cell adhesion molecule (NCAM) and HNK-1 glycan are expressed specifically by motor axons. ES has shown to increase the following factors [1].

The muscular system, the end organ of a motoric nerve, provide trophic signals that allows attraction of motor neuron regeneration, thus efficient motoric axon regeneration to occur efficiently. Despite the loss of connection within the motoric nerve with its end organ, together with its trophic signal

loss, ES allows the increase of trophic signals within the distal nerve segment without the presence of end organ connection [1].

ES in comparison to exercise, exercise still proves to be more superior in enhancing nerve regeneration. The following could be achieved through enhance motor neurons regeneration without decreasing topographic specificity, accelerate crossing injury site by sustaining pro-growth signaling throughout regeneration process [10]. The sum of all the following effect, enhanced gene expression (NGF, BDNF, NT 4/5, cAMP, and VEGF), expedites and enhance guidance of axonal regeneration into its proper pathway, are accomplished by ES. Thus, ES allows early onset of regeneration through reduction of staggering time, which increases the likelihood for more axons to cross the coaptation site within a proper pathway, instead of increasing its regeneration rate [1].

2.2 ES Parameters on Peripheral Nerve Injuries

Study by Javeed et al. has shown that early nerve regeneration modulated by ES proved to be beneficial in its effects, thus immediate application of ES is highly recommended [1]. Al-Majed et al. studied the speed and accuracy of motor axonal regeneration within sciatic nerve of rats, utilizing continuous 20Hz stimulation. The low frequency is chosen due to which it is physiologically relevant frequency of hindlimb motoneuron discharge [11]. Neuromuscular electrical stimulation (NMES) that are commonly used for patients, uses stimulation intensity that is capable of causing muscle contraction that moves the joint in full range of motion (ROM) [12].

Javeed et al. also described that by using brief ES for as long as one hour is capable of enhancing motor and sensory neuron regeneration [1]. The study was proven by Geremia et al. who compared continuous electrical stimulation duration applied to proximal site to injury site between one hour, three hours, one day, seven days and two weeks using implantable stimulator in transected adult rat femoral nerve. Following three weeks of study, brief electrical stimulation of one hour proved to increase the number of regenerating sensory fibers (Figure 11) [13]. Al-Majed et al. also showed brief electrical stimulation of one hour using 20 Hz promotes early regeneration across the repair site and enhanced regeneration of the injured sensory neurons and enhances motor neuron regeneration across surgical site and shortens the time for motor neuron to select the appropriate nerve branch by three-fold [11]. Longer stimulation of three hours showed reduced levels of GAP-43 associated gene expression, which then resulted in reduced axonal regeneration [11]. With increased duration of stimulation, displayed to be a less effective method in nerve regeneration [13].

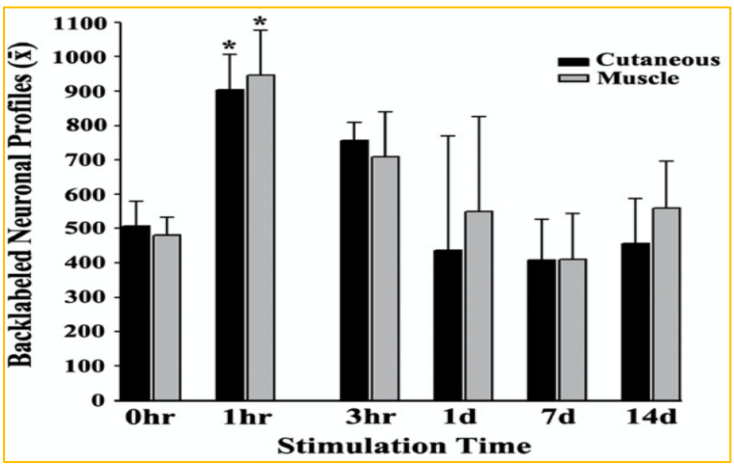


Figure 11. Mean number of backlabeled neuronal profiles in relation to different duration times of ES. Brief ES of 1 hour showed the highest mean number of backlabeled neuronal profiles [13].

2.3 ES Application on Post-Repair of Chronic Nerve Injuries

ES have the potential to regenerate in cases of post repair of chronic nerve injuries. These cases are commonly found due to early nerve repair that is not possible to be repaired as a result of extensive

soft tissue trauma, accompanied with wound contamination. Study by Huang et al. showed improved functional recovery after delays up to 24 weeks with the use of ES for 20 minutes duration and 20 Hz frequency [14]. Distal stump of chronically denervated Schwann cells have the ability to retain regenerative capacity. ES allows regeneration for both cases of chronic axotomy and denervation of Schwan cells, although its regenerative ability declines progressively from 14 days to 24 weeks after repair of chronic nerve injuries [1].

Conclusion

ES proved to be effective and increase efficiency in the management of peripheral nerve regeneration. Suitable parameters to be used in the use of ES include immediate application, brief continuous stimulation with one hour of duration and frequency of 20Hz. Although early use of ES is highly recommended, application on chronic nerve injuries after repair can still be found effects of nerve regeneration, followed with progressive decline of its regeneration ability. Keeping in mind that the earlier studies that have taken place are within animal study.

Declarations

Acknowledgements: This manuscript is made possible by the support of parents, family, and friends.

Conflict of Interest: We declare that no competing financial interests or personal relationships could have appeared to influence the work reported in this manuscript.

Ethical Approval: Health Research Ethics Commission of Dr. Saiful Anwar General Hospital provided ethical approval for this study.

Funding: This study received no specific grant from funding agencies, commercial or not-for-profit sectors.

Informed Consent: Not applicable.

Author Contributions: Thomas Erwin Christian Junus Huwae: conceptualization, writing original draft preparation, data interpretation, supervision, validation.
Panji Sananta: data interpretation, supervision, validation.
Dwi Indriani Lestari: data interpretation, supervision, validation.
Gutama Arya Pringga: writing the paper and editing, supervision, validation.
Ivan Triangto: writing the paper and editing, data interpretation, data collection.

References

1. Javeed S, Faraji AH, Dy C, Ray WZ, MacEwan MR. Application of electrical stimulation for peripheral nerve regeneration: Stimulation parameters and future horizons. Interdiscipl Neurosurg. 2021;24:101117.
2. Gordon T. Electrical stimulation to enhance axon regeneration after peripheral nerve injuries in animal models and humans. Neurother. 2016;13(2):295-310.
3. Menorca RM, Fussell TS, Elfar JC. Peripheral nerve trauma: mechanisms of injury and recovery. Hand Clin. 2013;29(3):317.
4. Cuccurullo SJ. Physical Medicine and Rehabilitation Board Review. 3rd Edition. Barry B, editor. New York: Demos Medical; 2020.670 p.
5. Castillo-Galván ML, Martínez-Ruiz FM, de la Garza-Castro O, Elizondo-Omaña RE, Guzmán-López S. Study of peripheral nerve injury in trauma patients. Gaceta Med Mex. 2014;150(6):527–32.
6. Gordon T. Peripheral nerve regeneration and muscle reinnervation. Int J Mol Sci. 2020;21(22):1–24.
7. Mtui E, Gruener G, Dockery P. Fitzgerald's Clinical Neuroanatomy and Neuroscience. 7th Edition. Philadelphia: Elsevier, Inc.; 2016;102–109 p.

8. Gordon T, English AW. Strategies to promote peripheral nerve regeneration: electrical stimulation and/or exercise. Euro J Neurosci. 2016;43(3):1–29.
9. Moskow J, Ferrigno B, Mistry N, Jaiswal D, Bulsara K, Rudraiah S, et al. Review: Bioengineering approach for the repair and regeneration of peripheral nerve. Bio Mat. 2019;4(1):107–13.
10. McGregor CE, English AW. The role of BDNF in peripheral nerve regeneration: Activity-dependent treatments and Val66Met. Front Cell Neurosci. 2019;12:522.
11. Al-Majed AA, Neumann CM, Brushart TM, Gordon T. Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration. J Neurosci. 2000;20(7):2602–8.
12. Cameron MH. Physical Agents in Rehabilitation-An Evidence-Based Approach to Practice. 5th Edition. Missouri: Elsevier;2018.
13. Geremia NM, Gordon T, Brushart TM, Al-Majed AA, Verge VMK. Electrical stimulation promotes sensory neuron regeneration and growth-associated gene expression. Exp Neurol. 2007;205(2):347–59.
14. Huang J, Zhang Y, Lu L, Hu X, Luo Z. Electrical stimulation accelerates nerve regeneration and functional recovery in delayed peripheral nerve injury in rats. Euro J Neurosci. 2013;38(12):3691-701.

Citation: Huwae TECJ, Sananta P, Lestari DI, Pringga GA, Triangto I. Timing, Duration and Dose of Electrical Stimulation Impact Modulation of Nerve Regeneration in Peripheral Nerve Injury. Int J Rec Innov Med Clin Res. 2023;5(3):11-21.