PART
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Electrical Stimulation of De-Innervated Muscles

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Before Atrophy Presence

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Introduction

In peripheral nerve injuries, sensory and motor losses are seen due to structural damage to the nerve.[1] Damaged axons cannot be completely regenerated after nerve injuries. Appropriate treatment selection is important to increase the growth rate of the nerve and reconnect the nerves in the injured area.[2] Two methods are generally preferred in the treatment of nerve injury. One of them is surgical treatment and the other is non-surgical treatment.[3,4] Motor and sensory shifts that occur as a result of nerve injury significantly affect the daily life and functionality of patients. It does not guarantee recovery of functional losses in patients due to surgical applications. Physiotherapy and rehabilitation is a necessary stage for the functional recovery of patients. Among non-pharmacological treatments, electrical stimulation (ES) therapy plays an important role in the functional recovery of patients by not preventing regeneration and atrophy.[5]

The externally applied electric field affects the internal electric field of the human body. With this effect, ES makes an important contribution to the healing process of the tissue by activating the cells in the injured tissues.[6] Application of ES has been shown to restore the contraction property of denervated muscles whose structure has changed.[7] The therapeutic mechanism of ES promotes muscle re-innervation and reduces muscle atrophy by increasing the expression of structural protective proteins.[5]

It has been stated in studies that applications with long pulse duration in ES play a role in regeneration by preventing the degeneration process in muscle tissue. The protocol for application of ES in denervated muscles begins with a single twitch and follows applications of tetanic stimulation.[8,9]

It has been stated that ES can increase muscle mass by about 1% and improve muscle function by about 10-15%.[10] In addition, there are studies, at the molecular level, stating that ES improves the anabolic/catabolic balance and stimulates the regenerative capacity of satellite cells.[11,12]

In this chapter, the physiological and biochemical contributions of ES in denervated muscle in the pre-atrophy phase was handled.

Physiological and Biochemical Changes in Denervated Muscle

The denervation period is reported as a process that resulted in muscle atrophy but not degeneration. This suggests that the muscles experienced a significant loss of size and strength due to the lack of nerve supply. Daily ES sessions lasting 30 minutes (min) were used to restore muscle mass and histological appearance in a study. The stimulation frequency used in the study was 20-25 Hertz (Hz), which induced fused contractions. Fused contractions refer to sustained muscle contractions where individual muscle twitches merge into a continuous contraction. The study found that the 30 min daily stimulation protocol with a frequency of 20-

25 Hz was effective in restoring muscle mass and histological appearance.[13]

Physiological and Biochemical Effects of Electrical Stimulation Applications

Innervation of skeletal muscles has significant effects on the maintenance of physiological tone and function.[14,15] Traumatic injuries often result in losses in motor and sensory functions.[16] In proximal nerve injuries; 1) neurodegeneration of axotomized motor neurons, 2) the time required for damaged axons to regrow to reach denervated muscle, and 3) problems such as muscle atrophy due to prolonged denervation result in limited motor functional recovery and re-innervation.[17-19]

Motor unit remodeling, fiber repair and recovery are seen through the denervation and regeneration cycle.[20,21] During the protracted process of denervation, the capacity of motor neurons to regenerate axons is compromised.[22] Since injured neurons need to regenerate their axons at a long distance, the innervation process is prolonged in the structures of the damaged area.[23] With the prolongation of this process, a decrease in functional abilities in muscle groups that cannot be innervated and consequently atrophy in the muscles is observed.

Li et al., stated that early innervation of the sensory nerve prevents atrophy of denervated muscle.[24] Polônio et al., reported that the application of ES can partially protect nerve structure and facilitate regeneration in this respect.[25] In the studies carried out, it has been found that ES provides excitability in denervated muscles and increases the mass development of muscle tissue when the stimulation frequency is slightly less than 2 Hz with an inter-pulse interval of 500 milliseconds (ms) or when it consists of 40 ms pulses delivered at 20 Hz.[8,26]

Bueno et al., separated 36 rats with denervated tibialis muscles into 4 groups: the first control group, the last control group, the experimental denervated and therapy group, and the experimental denervated group.[27] They applied Russian ES to 9 rats in the experimental group 3 times a week for 45 days with a frequency of 2500 Hz with a cycle time of 10 min and 0.4 ms periods; 3/1 intervals, 9 s on and 27 s off period mode with 50% modulation percentage and found that ES application prevented muscle atrophy. As a result, they stated that the Russian Current ES does not provide recovery such as a healthy muscle, but it can prevent atrophy due to muscle denervation and reduce morphological and structural changes in denervated muscle. As a result of denervation, severe muscle atrophy and weakness occur with a decrease in resting membrane potential, deterioration in ion balance, and acceleration in protein catabolism.[28-30] Cavalcante et al., emphasized that the application of ES, when applied in an adequate protocol, can delay or prevent muscle atrophy.[31]

In peripheral nerve lesions, especially in cases of nerve injuries at the proximal point or delay in repair, rapid muscle mass loss is observed, and non-contractile tissues in the muscles, increase in permission and endomysial connective tissue, collagen, fat formation, and weakening in functional movements are observed.[32-35] In a study, two pairs of large electrodes, each with an area of 200 cm^2, were attached to the anterior surface of the thighs in proximal and distal positions. Twitch contractions were elicited by biphasic rectangular current pulses of 120 ms duration and 200 milliampere (mA) amplitude, delivering an impulse energy of 1.92 Joules to activate fibers along the Quadriceps Femoris muscles. Training was initiated with a single twitch at 2 Hz and delivered for 15 min a day, 5 days a week. After 4 months, because the excitability of the muscle fibers had sufficiently improved to allow the use of shorter duration pulses, the protocol was reinforced with an additional tetanic pattern of 40 ms pulses delivered at 20 Hz, 2 s on, 2 s off, for 15 min a day, 5 days a week.[26]

ES reduces the loss of myonuclei per muscle mass and protects the satellite cell pool by regulating its apoptosis.[36] Bueno et al., revealed that ES reduces morphological changes resulting from denervation in histological analysis.[27] Application of ES in the denervated muscle also plays a role in the improvement of the mechanical properties of

the muscle.[37] In a study, it was observed that ES applied by direct stimulation of the denervated tibialis anterior muscle for 1 hour per day with a model consisting of rectangular bipolar constant current pulses with a frequency of 20 Hz, a duration of 20 ms per phase, and an amplitude of 4 mA provided growth in myofibrils and contributed to structural recovery by providing a more coherent structure in the fibers.[38]

Katoh reported that the stress fibers in the muscles thickened in the 2-hour ES application and that their thickness increased without an increase in the number of stress fibers in the 20-hour periodic application, which confirms the contraction of the muscle.[39] Staehlke et al., provided new information on the increase of intracellular Ca^{2+} levels in cells stimulated with ES, thus contributing to bone tissue regeneration and cell activation.[40] Tamaki et al., determined that when they applied ES to the denervated Tibialis Anterior muscle in 42 male rats, there was a significant increase in muscle mass and bone strength in the electrically stimulated group.[41]

There are problems with vascularization in denervated muscles and because of serious problems in the nutrition of the tissue, atrophy formations in the muscle structures and ulcerations on the skin can be seen.[42] It has been determined that the application of ES plays an important role in the activation and proliferation of fibroblasts, growth factors, and epithelial cells.[43] It has been shown that the ES used in the field of physiotherapy and rehabilitation increases blood flow and metabolism in the skin and muscles and therefore has positive effects on health.[41-44] ES has an effective role in increasing blood flow in skeletal muscle and also increasing capillary density.[45]

The density of sodium (Na^+) channels present in the sarcolemma differs between slow and fast fiber populations, greatly affecting the firing pattern, which in turn contributes to their phenotypic characteristics. Denervation also affects the Na^+ channel.[46] After denervation, significant changes occur in membrane depolarization, ion current, permeability, and concentrations. One of them is an increase in intracellular Na^+ concentration and a decrease in intracellular potassium ($K^{+)}$ concentration in the first week after denervation.[30] ES facilitates Ca^{2+} transport and plays an important role in K^+ channels.[47]

Although it is different for each muscle after denervation, muscle atrophy usually begins on the 3rd day.[48] This is because oxidative stress and inflammatory response after denervation occur within 5 to 24 hours.[49,50] Inflammation plays a role in muscle atrophy.[51] Activation of proinflammatory cytokines 1 week after denervation causes muscle atrophy.[52] A series of immunological reactions come into play in muscle denervation that occurs after trauma. In these immunological reactions, various cells such as neutrophils, macrophages, mast cells, and lymphocytes, which are immune cells, take part in increasing the wound healing signal by removing pathogens. These immune cells also respond in the presence of an electrical field.[53-56]

Fibers that synthesize and release acetylcholine, which is also a neurotransmitter of the autonomic nervous system, are called cholinergic. Acetylcholine binds to the nicotinic receptor in skeletal muscle fibers, allowing Na^+ to enter the muscle cell and contraction of the depolarized muscle cell by opening voltage-sensitive Na^+ channels. There must be a dynamic interaction between cell membrane proteins and signaling molecules for neurotransmitter release from motor neurons to the synaptic region.[57,58] Thus, for muscle fibers to contract, they must bind to the neurotransmitter acetylcholine located in the plasma membrane. It is stated that neurons in the development process form synapses for biophysically and biochemically dynamic interactions. In the literature, it has been reported that the electrical activity in the form of ion transition contributes to neuron development before and after synapse formation.[59-61]

An Overview of Electrical Stimulation Methods

A nerve impulse can be initiated by an electrical stimulus. For this, the ES must be in sufficient intensity and variable current. The plasma membrane in

the nerve fibers creates resistance in series in the tissues, causing a potential difference during current flow. The surface of the membrane close to the cathode becomes negative relative to the surface close to the anode. Increases the resting potential difference across the nerve's plasma membrane near the anode. The additional charges on the side closer to the cathode are of opposite polarity from those on the resting membrane and therefore reduce the potential difference. If the potential difference falls below the level at which the membrane becomes permeable to sodium ions, these ions begin to enter the axon and initiate a nerve impulse event.[62]

ES is commonly used for 10-30 min of Galvanic or Faradic Current, depending on the lesion type.[63,64] Unidirectional and rectangular beats 5 to 10; 30 to 300 ms pulse duration per day and 4 or more seconds between beats used in denervated muscles.[63,65]

Güzelant et al., conducted a study on the effect of ES on individuals with Facial Paralysis. They defined one group as a home exercise program and the other group as an ES group in addition to rehabilitation. They applied the Galvanic Current to the motor points of 8 muscles innervated by the Facial nerve. Facial nerve innervates the following muscles which usually are denervated in Facial Paralysis: M. Frontalis, M. Corrugator Supercilii, M. Orbicularis Oculi, M. Levator Labii Alaeque Nasii, M. Nasalis M. Levator Labii Superioris, M. Orbicularis Oris, M. Depressor Labii Inferioris. In the ES group at a current density that would produce minimal contraction (100 ms intermittent Galvanic current for motor point treatment, 3 sets of 30 repetitions per point) was given for ES therapy. Considering the findings, it was seen that the rehabilitation program and ES patient group showed a more significant improvement in the 6th week when compared before and after the treatment, while the home exercise program group did not show a significant difference. The authors concluded that recovery was faster in patients treated with the ES. ES in addition to exercise in the treatment of Facial Paralysis appears to be able to minimize muscle atrophy, to maintain muscle strength, and to prevent trophic disorders during the time required for peripheral nerve regeneration in denervated muscles. Therefore, ES therapy is an acceptable and effective method in the treatment of facial paralysis.[66]

In the case report of a child with shoulder dystocia at birth, Jeyanthi applied ES to prevent muscle atrophy and increase limb awareness (muscles such as the Deltoid, Supraspinatus, Biceps Brachii, supinator, wrist, and finger extensors). The application procedure was applied as intermittent rectangular Galvanic Current with a pulse duration of 100 ms and 30 maximal muscle contractions in groups of 10 with 1 min rest. As a result, the author reported that the patient's motor and functional activities' score improved. Therefore, in addition to conventional treatment, nerve branch ES can improve the motor and functional activity of the Obstetric Brachial Plexus Injury patient.[67]

Phansopkar et al., included a 26-year-old male who was diagnosed with Radial Nerve Palsy as a result of a traffic accident in a case study. During the rehabilitation process, the authors applied scar tissue mobilization in addition to the ES with Faradic Current and stretching exercises under pressure, with a 1 second (s) surged duration and a 3 s surge interval, at an intensity sufficient to produce visible contractions with passive movement of the wrist joint for 10 repetitions. They reported that strengthening exercises, muscle retraining, and ES provided significant improvements in muscle strength and functional independence.[68]

The excitability of a denervated muscle is influenced by two key parameters: stimulation amplitude and pulse duration. The relationship between these parameters is known as the strength-duration curve. This curve describes how the minimum stimulation amplitude required to elicit a response from the tissue varies with different pulse durations. The two important points on the strength-duration curve are rheobase and chronaxie. The rheobase refers to the minimum stimulation amplitude necessary to evoke a response from the tissue when the pulse duration is infinitely long. In other words, it represents the threshold at which the tissue starts responding to stimulation when the pulse duration is very large. Rheobase is typically measured in units of current (mA). The

chronaxie is the pulse duration at which the stimulation amplitude required to elicit a response is twice the rheobase. It is a measure of the tissue's time constant, indicating the time it takes for the tissue to respond to a stimulus. Chronaxie is typically measured in units of time (ms).[69]

Kern et al., in 1999 suggested that the response time for denervated muscle is significantly longer than that for innervated muscle. Specifically, they found that it may take about 100-1000 times longer for the denervated muscle to respond to stimulation compared with the innervated muscle. This indicates a substantial decrease in the excitability of denervated muscle tissue.[70] Additionally, the study by Ashley et al., in 2005 supports this notion by indicating that denervated muscles require longer pulse durations compared to those sufficient to elicit a response in innervated muscles. This finding further emphasizes the altered response characteristics of denervated muscle tissue.[69]

Kern et al., conducted a study on denervated muscle stimulation, and they recommended and used the following stimulation parameters in their studies and found that these parameters are effective in denervated muscles. Stimulation modulations were 120-150 ms pulse duration, 300-500 ms pulse interval, 1-2 Hz frequency, 2:4 s on and 1–2 s- off (implying alternating periods of stimulation and rest), 2 times per day for 15 min in each session, a 3-min pause is given after 5 min of stimulation to prevent muscle overstrain. Stimulation time can be increased up to 2 times per day for 30 min each session. They used large anatomically shaped electrodes, with a size of 200 cm^2, made of silicone-graphite material. They concluded that ES below 25-30 ms would not be effective because no sufficient contraction could be produced. In addition, the researchers reported that the use of anatomically shaped large electrodes helps ensure better contact with the skin and increases the distribution of ES over a larger area, which will be beneficial when targeting denervated muscle tissue, as the lack of specific nerve pathways can be compensated for and the chances of activating a greater number of muscle fibers in the targeted area will be increased.[70]

Galvanic Stimulation

The Galvanic Current is preferred in cases where there is a conduction disorder in the muscles due to nerve damage. Since the Galvanic Current has a long pulse duration, the denervated muscle responds to the Galvanic Current stimulus.[71] The interrupted Galvanic Current, which refers to a direct current with intermittent interruptions, can stimulate both innervated and denervated muscle fibers. However, the response of innervated muscle fibers to interrupted Galvanic Current is typically stronger than that of denervated fibers. The use of long and rectangular Direct Current impulses can help elicit a response in both innervated and denervated muscle fibers.[72] The response of the muscle and nerve to the Galvanic Current stimulation in the state of partial and complete degeneration is normal. However, while there is no response to Galvanic Current in the nerve in the definitive degeneration reaction, there is a protracted response in the muscle.[73]

The Galvanic Current stimulation increases blood flow to the treated area. It helps to minimize the formation of atrophy by enabling the muscle to contract similarly to the voluntary contraction and by providing the necessary oxygen and nutritional needs of the muscle with the effect of vasodilation.[70,74]

Protocol for Galvanic Stimulation

In a clinical context, initial muscle atrophy resulting from denervation can progress to degeneration within the second year. This suggests that as time passes after denervation, the muscle undergoes further deterioration and loss of structure and function.[13] Studies have shown that denervated muscle fibers are trainable to some extent. While denervated muscle fibers may experience atrophy and reduced function initially, they can still exhibit some level of responsiveness and adaptability.[75]

Recommended Stimulation Parameters:[70]

Stimulation duration: 200 ms

Pulse duration: 100-500 ms (implying that the stimulation is turned on for a variable duration within this range)

Pulse interval: 2000 ms (implying that there is a pause of 2 s between stimulation cycles)

Treatment frequency: Applied 3 times per week for 15 min each session.

Electrode size: When muscles are denervated, the loss of nerve supply means that the normal pathways for the conduction of stimuli are disrupted. As a result, the ES used to activate the denervated muscle must be applied more broadly to ensure that a sufficient number of muscle fibers are reached and recruited. Using larger electrode sizes helps achieve selective stimulation of the denervated muscle tissue. Larger electrodes have a greater contact area with the skin, allowing for a broader distribution of the electrical current and increasing the likelihood of activating a larger number of muscle fibers within the targeted area. Surface electrodes with sizes ranging from 20 to 50 cm^2 are used to achieve selective stimulation of paralyzed muscle tissue.[70,75]

Waveform: Triangular pulses are commonly used for ES of denervated muscle. The long rise time and pulse duration of triangular pulses are suitable for stimulating denervated muscle fibers because they have higher chronaxie values. Rectangular pulses with a duration of 30 ms or more, or triangular pulses with long durations of 100-500 ms, are typically used for ES of denervated muscle in clinical practice. Specifically, triangular pulses with pulse durations of 200 ms or 500 ms are commonly utilized.

The cathode (negative electrode) is generally more effective in stimulating excitable tissue, including denervated muscle. Therefore, the cathode is typically placed in proximity to the target area to achieve the desired stimulation. To prevent overstimulation of the muscle, it is essential to plan the ratio of pause duration to stimulus duration. By providing adequate pauses between stimulation pulses, the muscle can recover and avoid excessive fatigue or damage. [72,76,77]

Faradic Stimulation

Faradic current has a pulse duration of 0.1-1 ms and a frequency of 50-100 Hz, which is a fast but not instantaneous type of stimulation.[78] The Faradic current stimulation, is commonly used for muscle stimulation. However, it primarily stimulates muscles that are normally innervated, meaning muscles that still receive nerve signals from the central nervous system. Denervated muscle fibers, which lack nerve supply, do not effectively respond to the Faradic current stimulation. Innervated muscles are generally more excitable than denervated muscles. Innervated muscle fibers have intact nerve supply and functional neuromuscular junction, which enable the efficient transmission of electrical signals.[72]

Since the duration of the Faradic current is 0.1-1.0 ms, the muscle in the definitive denervation and complete denervation reaction does not respond to the Faradic current. For stimulation of the muscle in the partial denervation state, higher current intensity is required compared to the healthy muscle and nerve.[73]

The Faradic current stimulates motor nerves and provides contraction in the muscle innervated by those nerves.[72] After innervation in the denervated muscle, contraction is observed in the muscle with the use of the Faradic current; as a result of stimulation, it increases tolerance to muscle fatigue and prevents atrophy.[79] It also plays a role in minimizing atrophy by retraining muscle movement.[80,81]

In addition, the form of current, in which the peak current intensity applied to the patient is rhythmically increased and decreased and the rate of increase and decrease in peak amplitude is slow, is called Surged Faradic current. The main application area of Surged Faradic current is functional paralysis treatment. This type of current is often required for the treatment of spasm and pain.[82]

Surged Faradic Stimulation

The surged type of Faradic current 1 to 2 and 2 to 3 is used in muscle stimulation for muscle activation and retraining of muscle movement. In Surged Faradic current, the peak current density increases and decreases rhythmically. The rate of increase and decrease in peak amplitude is slow. Ripples can be produced at different times, frequencies and waveforms. Surge current is generally used in paralysis situations.[82]

The surges can be adjusted as 2 to 5 s surge continuously or by selecting frequencies of 6 to 30 surge/min. The rest period given for the muscle to return to its normal state should be at least 2 to 3 times longer than the pulse duration. In gradual exercise, the ratio of the interval to the rising time can be changed.[78]

Progressive Exponential Currents

Progressive Exponential currents are very similar to unidirectional sinusoidal currents. It is used for diagnostic purposes in stimulating the denervated muscle. When stimulating denervated muscle with exponentially progressive currents some issues need to be considered. The impulse duration should be as short as possible while still long enough to effectively stimulate the muscle. This implies that the duration of the electrical impulse should be tailored to the specific needs of the individual and the desired outcomes of the stimulation. The gradient refers to the rate at which the intensity of the electrical current increases. It is recommended to have a steep gradient that ensures a progressive increase in current intensity. However, the gradient should also be adjusted to be gradual enough to avoid discomfort or adverse reactions. The length of the pause between stimuli should be at least four to five times longer than the stimulus duration. This recommendation aims to prevent muscular fatigue, allowing the muscle to recover between stimulation cycles. The current intensity should be set at a level that can produce a moderately strong contraction in the muscle being stimulated. It is important to achieve an appropriate level of contraction without causing unnecessary discomfort to the patient.[72,83]

Conclusion

As a result of this chapter, it was concluded that the denervated muscle can be prevented from atrophy with ES, that even the atrophied muscle can be redeveloped and healed, and that ES that starts in the early period after denervation has a positive effect on the prognosis.

References

1. Robinson LR. Traumatic injury to peripheral nerves. Muscle Nerve. 2022;66(6):661-70. doi:10.1002/mus.27706.
2. Jensen PH, Li JY, Dahlström A, Dotti CG. Axonal transport of synucleins is mediated by all rate components. Eur J Neurosci. 1999;11(10):3369-76. doi:10.1046/j.1460-9568.1999.00754.x.
3. Rabia J, Qiang A. Nanoparticles in peripheral nerve regeneration: A mini-review. J Neurorestoratology. 2022;10:1-12. doi:10.26599/JNR.2022.9040001.
4. Sharma HS, Chopp M, Chen L, Sarnowska A, Xue M, Ao Q, et al. The 2021 yearbook of Neurorestoratology. J Neurorestoratology. 2022;10:100008. doi:10.1016/j.jnrt.2022.100008.
5. Ni L, Yao Z, Zhao Y, et al. Electrical stimulation therapy for peripheral nerve injury. Front Neurol. 2023;14:1081458. doi:10.3389/fneur.2023.1081458.
6. Song B, Gu Y, Pu J, Reid B, Zhao Z, Zhao M. Application of direct current electric fields to cells and tissues in vitro and modulation of wound electric field in vivo. Nat Protoc. 2007;2(6):1479-89. doi:10.1038/nprot.2007.205.
7. Helgason T, Gargiulo P, Jóhannesdóttir F, Ingvarsson P, Knútsdóttir S, Gudmundsdóttir V, et al. Monitoring muscle growth and tissue changes induced by electrical stimulation of denervated degenerated muscles with CT and stereolithographic 3D modeling. Artif Organs. 2005;29(6):440-3. doi:10.1111/j.1525-1594.2005.29073.x.
8. Kern H, Boncompagni S, Rossini K, Mayr W, Fanò G, Zanin ME, et al. Long-term denervation in humans causes degeneration of both contractile and excitation-contraction coupling apparatus, which is reversible by functional electrical stimulation (FES): A role for myofiber regeneration? J Neuropathol Exp Neurol. 2004;63(9):919-31. doi:10.1093/jnen/63.9.919.
9. Kern H, Carraro U. Home-based functional electrical stimulation of human permanent denervated muscles: A narrative review on diagnostics, managements, results and byproducts revisited 2020. Diagnostics (Basel). 2020;10(8):529-43. doi:10.3390/diagnostics10080529.
10. Adams V. Electromyostimulation to fight atrophy and to build muscle: Facts and numbers. J Cachexia Sarcopenia Muscle. 2018;9(4):631-4. doi:10.1002/jcsm.12332.
11. Paillard T. Muscle plasticity of aged subjects in response to electrical stimulation training and inversion and/or limitation of the sarcopenic process. Ageing Res Rev. 2018;46:1-13. doi:10.1016/j.arr.2018.05.002.
12. Zhang BT, Yeung SS, Liu Y, Wang HH, Wan YM, Ling SK, et al. The effects of low frequency electrical stimulation on satellite cell activity in rat skeletal muscle during hindlimb suspension. BMC Cell Biol. 2010;11:87-96. doi:10.1186/1471-2121-11-87.
13. Mayr W, Hofer C, Kern H, Bijak M, Lanmüller H, Rafolt D, et al. The European R&D Project RISE - Use of electrical stimulation to restore standing in paraplegics with long-term denervated degenerated muscles (DDM). IFMBE Proceedings. 2009;25(9):540-2. doi:10.1007/978-3-642-03889-1_145.
14. Zorzato F, Volpe P, Damiani E, Quaglino D Jr, Margreth A. Terminal cisternae of denervated rabbit skeletal muscle: Alterations of functional properties of Ca^{2+} release channels. Am J Physiol. 1989;257(3 Pt 1):C504-11. doi:10.1152/ajpcell.1989.257.3.C504.
15. Dulhunty AF. Excitation-contraction coupling from the 1950s into the new millennium. Clin Exp Pharmacol Physiol. 2006;33(9):763-72. doi:10.1111/j.1440-1681.2006.04441.x.
16. Rochkind S, Filmar G, Kluger Y, Alon M. Microsurgical management of penetrating peripheral nerve injuries: pre, intra- and postoperative analysis and results. Acta Neurochir Suppl. 2007;100:21-4. doi:10.1007/978-3-211-72958-8_4.

17. Carlstedt T. New Treatments for spinal nerve root avulsion injury. Front Neurol. 2016;7:135-9. doi:10.3389/fneur.2016.00135.
18. Casas C, Isus L, Herrando-Grabulosa M, Mancuso FM, Borrás E, Sabidó E, et al. Network-based proteomic approaches reveal the neurodegenerative, neuroprotective and pain-related mechanisms involved after retrograde axonal damage. Sci Rep. 2015;5:9185. doi:10.1038/srep09185.
19. Eggers R, Tannemaat MR, De Winter F, Malessy MJ, Verhaagen J. Clinical and neurobiological advances in promoting regeneration of the ventral root avulsion lesion. Eur J Neurosci. 2016;43(3):318-35. doi:10.1111/ejn.13089.
20. Holloszy JO, Carlson BM. Factors influencing the repair and adaptation of muscles in aged individuals: Satellite cells and innervation. J Gerontol A Biol Sci Med Sci. 1995;50 Spec No:96-100. doi:10.1093/gerona/50a.special_issue.96.
21. Kadhiresan VA, Hassett CA, Faulkner JA. Properties of single motor units in medial gastrocnemius muscles of adult and old rats. J Physiol. 1996;493(Pt 2):543-52. doi:10.1113/jphysiol.1996.sp021402.
22. Sulaiman OA, Gordon T. Effects of short- and long-term Schwann cell denervation on peripheral nerve regeneration, myelination, and size. Glia. 2000;32(3):234-46. doi:10.1002/1098-1136(200012)32:3<234::aid-glia40>3.0.co;2-3.
23. Kawabuchi M, Zhou CJ, Wang S, Nakamura K, Liu WT, Hirata K. The spatiotemporal relationship among Schwann cells, axons and postsynaptic acetylcholine receptor regions during muscle reinnervation in aged rats. Anat Rec. 2001;264(2):183-202. doi:10.1002/ar.1159.
24. Li QT, Zhang PX, Yin XF, Han N, Kou YH, Deng JX, et al. Functional recovery of denervated skeletal muscle with sensory or mixed nerve protection: A pilot study. PLoS One. 2013;8(11):e79746. doi:10.1371/journal.pone.0079746.
25. Polônio JDT, Mazzer N, Barbieri CH, Mattiello-Sverzut AC. Eletroestimulação seletiva mantem estrutura e função do tibial anterior desnervado de ratos. Acta Ortopédica Brasileira. 2010;18:85-9. doi:10.1590/S1413-78522010000200005.
26. Kern H, Salmons S, Mayr W, Rossini K, Carraro U. Recovery of long-term denervated human muscles induced by electrical stimulation. Muscle Nerve. 2005;31(1):98-101. doi:10.1002/mus.20149.
27. Bueno CRS, Pereira M, Favaretto IA Junior, Bortoluci CHF, Santos TCPD, et al. Electrical stimulation attenuates morphological alterations and prevents atrophy of the denervated cranial tibial muscle. Einstein (Sao Paulo). 2017;15(1):71-6. doi:10.1590/S1679-45082017AO3808.
28. Pellegrino C, Franzini C. An electron microscope study of denervation atrophy in red and white skeletal muscle fibers. J Cell Biol. 1963;17(2):327-49. doi:10.1083/jcb.17.2.327.
29. Purves D, Sakmann B. Membrane properties underlying spontaneous activity of denervated muscle fibres. J Physiol. 1974;239(1):125-53. doi:10.1113/jphysiol.1974.sp010559.
30. Kotsias BA, Venosa RA. Sodium influx during action potential in innervated and denervated rat skeletal muscles. Muscle Nerve. 2001;24(8):1026-33. doi:10.1002/mus.1106.
31. Cavalcante EVV, Silva LGMd, Montenegro EJN, Pontes Filho NTd. Efeito da eletroestimulação no músculo desnervado de animais: Revisão sistemática. Fisioterapia em Movimento. 2012;25(3):669-78. doi:10.1590/S0103-51502012000300022.
32. Midha R. Epidemiology of brachial plexus injuries in a multitrauma population. Neurosurgery. 1997;40(6):1182-8; discussion 1188-9. doi:10.1097/00006123-199706000-00014.
33. Carlson BM. The biology of long-term denervated skeletal muscle. Eur J Transl Myol. 2014;24(1):3293. doi:10.4081/ejtm.2014.3293.
34. Carraro U, Rossini K, Mayr W, Kern H. Muscle fiber regeneration in human permanent lower motoneuron denervation: Relevance to safety and effectiveness of FES-training, which induces muscle recovery in SCI subjects. Artif Organs. 2005;29(3):187-91. doi:10.1111/j.1525-1594.2005.29032.x.
35. Caierão QM, Betini J, Teodori RM, Minamoto VB. O efeito do intervalo da estimulação elétrica no músculo desnervado de rato. Braz J Phys Ther. 2008;12. doi:10.1590/S1413-35552008000200011.
36. Guo BS, Cheung KK, Yeung SS, Zhang BT, Yeung EW. Electrical stimulation influences satellite cell proliferation and apoptosis in unloading-induced muscle atrophy in mice. PLoS One. 2012;7(1):e30348. doi:10.1371/journal.pone.0030348.
37. Matheus JPC, Gomide LB, Oliveira JGPd, Volpon JB, Shimano AC. Efeitos da estimulação elétrica neuromuscular durante a imobilização nas propriedades mecânicas do músculo esquelético. Rev Bras Med. 2007;13. doi:10.1590/S1517-86922007000100013.
38. Ashley Z, Salmons S, Boncompagni S, Protasi F, Russold M, Lanmuller H, et al. Effects of chronic electrical stimulation on long-term denervated muscles of the rabbit hind limb. J Muscle Res Cell Motil. 2007;28(4-5):203-17. doi:10.1007/s10974-007-9119-4.
39. Katoh K. Effects of electrical stimulation on the signal transduction-related proteins, c-src and focal adhesion kinase, in fibroblasts. Life (Basel). 2022;12(4):531. doi:10.3390/life12040531.
40. Staehlke S, Bielfeldt M, Zimmermann J, Gruening M, Barke I, Freitag T, et al. Pulsed electrical stimulation affects osteoblast adhesion and calcium ion signaling. Cells. 2022;11(17):2650. doi:10.3390/cells11172650.
41. Tamaki H, Yotani K, Ogita F, Hayao K, Kirimto H, Onishi H, et al. Low-frequency electrical stimulation of denervated skeletal muscle retards muscle and trabecular bone loss in aged rats. Int J Med Sci. 2019;16(6):822-30. doi:10.7150/ijms.32590.
42. Liu LQ, Nicholson GP, Knight SL, Chelvarajah R, Gall A, Middleton FR, Ferguson-Pell MW, Craggs MD. Pressure changes under the ischial tuberosities of seated individuals during sacral nerve root stimulation. J Rehabil Res Dev. 2006;43(2):209-18. doi:10.1682/jrrd.2005.04.0078.
43. Houghton PE, Campbell KE, Fraser CH, Harris C, Keast DH, Potter PJ, et al. Electrical stimulation therapy increases rate of healing of pressure ulcers in community-dwelling people with spinal cord injury. Arch Phys Med Rehabil. 2010;91(5):669-78. doi:10.1016/j.apmr.2009.12.026.
44. Griffin M, Bayat A. Electrical stimulation in bone healing: critical analysis by evaluating levels of evidence. Eplasty. 2011;11:e34. PMID:21847434.
45. Ziada AM, Hudlicka O, Tyler KR, Wright AJ. The effect of long-term vasodilatation on capillary growth and performance in rabbit heart and skeletal muscle. Cardiovasc Res. 1984;18(12):724-32. doi:10.1093/cvr/18.12.724.
46. Desaphy JF, Pierno S, Léoty C, George AL Jr, De Luca A, Camerino DC. Skeletal muscle disuse induces fibre type-dependent enhancement of Na(+) channel expression. Brain. 2001;124(Pt 6):1100-13. doi:10.1093/brain/124.6.1100.
47. Franklin BM, Maroudas E, Osborn JL. Sine-wave electrical stimulation initiates a voltage-gated potassium channel-dependent soft tissue response characterized by induction of hemocyte recruitment and collagen deposition. Physiol Rep. 2016;4(12):e12832. doi:10.14814/phy2.12832.
48. Castets P, Rion N, Théodore M, Falcetta D, Lin S, Reischl M, et al. mTORC1 and PKB/Akt control the muscle response to denervation by regulating autophagy and HDAC4. Nat Commun. 2019;10(1):3187. doi:10.1038/s41467-019-11227-4.

49. Pharaoh G, Brown JL, Sataranatarajan K, Kneis P, Bian J, Ranjit R, et al. Targeting cPLA2 derived lipid hydroperoxides as a potential intervention for sarcopenia. Sci Rep. 2020;10(1):13968. doi:10.1038/s41598-020-70792-7.
50. Shen Y, Zhang R, Xu L, Wan Q, Zhu J, Gu J, et al. Microarray analysis of gene expression provides new insights into denervation-induced skeletal muscle atrophy. Front Physiol. 2019;10:1298. doi:10.3389/fphys.2019.01298.
51. Londhe P, Guttridge DC. Inflammation induced loss of skeletal muscle. Bone. 2015;80:131-42. doi:10.1016/j.bone.2015.03.015.
52. Cisterna BA, Cardozo C, Sáez JC. Neuronal involvement in muscular atrophy. Front Cell Neurosci. 2014;8:405. doi:10.3389/fncel.2014.00405.
53. Reich JD, Cazzaniga AL, Mertz PM, Kerdel FA, Eaglstein WH. The effect of electrical stimulation on the number of mast cells in healing wounds. J Am Acad Dermatol. 1991;25(1 Pt 1):40-6. doi:10.1016/0190-9622(91)70171-w.
54. Wang K, Parekh U, Ting JK, Yamamoto NAD, Zhu J, Costantini T, Arias AC, Eliceiri BP, Ng TN. A platform to study the effects of electrical stimulation on immune cell activation during wound healing. Adv Biosyst. 2019;3(10):e1900106. doi:10.1002/adbi.201900106.
55. Gürgen SG, Sayın O, Cetin F, Tuç Yücel A. Transcutaneous electrical nerve stimulation (TENS) accelerates cutaneous wound healing and inhibits pro-inflammatory cytokines. Inflammation. 2014;37(3):775-84. doi:10.1007/s10753-013-9796-7.
56. Thannickal VJ, Fanburg BL. Reactive oxygen species in cell signaling. Am J Physiol Lung Cell Mol Physiol. 2000;279(6):L1005-28. doi:10.1152/ajplung.2000.279.6.L1005.
57. Dalva MB, McClelland AC, Kayser MS. Cell adhesion molecules: Signalling functions at the synapse. Nat Rev Neurosci. 2007;8(3):206-20. doi:10.1038/nrn2075.
58. Lin W, Burgess RW, Dominguez B, Pfaff SL, Sanes JR, Lee KF. Distinct roles of nerve and muscle in postsynaptic differentiation of the neuromuscular synapse. Nature. 2001;410(6832):1057-64. doi:10.1038/35074025.
59. Blankenship AG, Feller MB. Mechanisms underlying spontaneous patterned activity in developing neural circuits. Nat Rev Neurosci. 2010;11(1):18-29. doi:10.1038/nrn2759.
60. Spitzer NC. Electrical activity in early neuronal development. Nature. 2006;444(7120):707-12. doi:10.1038/nature05300.
61. Johnson AM, Connor NP. Effects of electrical stimulation on neuromuscular junction morphology in the aging rat tongue. Muscle Nerve. 2011;43(2):203-11. doi:10.1002/mus.21819.
62. Seju Y, Rajput V. Efficacy of Theragun and Surge Faradic Stimulation in Subjects with Trapezitis: A randomized controlled trial. IJSR. 2021;10(4):46-9. doi:10.21275/SR21330105408
63. Fernández AM. Electrodiagnóstico y electroestimulación de músculos denervados. Fisioterapia. 2001;23:23-35. doi:10.1016/S0211-5638(01)72970-7.
64. Eberstein A, Eberstein S. Electrical stimulation of denervated muscle: Is it worthwhile? Med Sci Sports Exerc. 1996;28(12):1463-9. doi:10.1097/00005768-199612000-00004.
65. Solomen S, Babu B, Muralidharan P, Sreejith K, Gafoor A. Conservative management of brachial plexus injury through a structured rehabilitation protocol: A case report. RGUHS J Physiother. 2021;1(3):31-8. doi:10.26463/rjpt.1_3_1.
66. Güzelant AY, Sarıfakıoğlu AB, Saraçoğlu Varol G, Can I, Ünal A. Impact of electrical stimulation on rehabilitation process in peripheral facial paralysis. Acta Medica Mediterranea. 2014;30:1375.
67. Jeyanthi S. The effect of nerve branch stimulation in adjunct to conventional treatment on C6-C7 obsteric brachial plexus injury: A case report. Indian J. Physiother Occup. Ther. 2015;9;150-5. doi:10.5958/0973-5674.2015.00071.4
68. Phansopkar P, Athawale V, Birelliwar A, Naqvi W, Kamble S. Post-operative rehabilitation in a traumatic rare radial nerve palsy managed with tendon transfers: A case report. Pan Afr Med J. 2020;36(30):141. doi:10.11604/pamj.2020.36.141.23994.
69. Ashley Z, Sutherland H, Russold MF, Lanmüller H, Mayr W, Jarvis JC, et al. Therapeutic stimulation of denervated muscles: The influence of pattern. Muscle Nerve. 2008;38(1):875-86. doi:10.1002/mus.21020.
70. Kern H, Hofer C, Strohhofer M, Mayr W, Richter W, Stöhr H. Standing up with denervated muscles in humans using functional electrical stimulation. Artif Organs. 1999;23(5):447-52. doi:10.1046/j.1525-1594.1999.06376.x.
71. Woodcock AH, Taylor PN, Ewins DJ. Long pulse biphasic electrical stimulation of denervated muscle. Artif Organs. 1999;23(5):457-9. doi:10.1046/j.1525-1594.1999.06366.x.
72. Cummings JP. Conservative management of peripheral nerve injuries utilizing selective electrical stimulation of denervated muscle with exponentially progressive-current forms. J Orthop Sports Phys Ther. 1985;7(1):11-5. doi:10.2519/jospt.1985.7.1.11.
73. Simsek N, Kırdı N. (2015), Elektroterapide temel prensipler ve klinik uygulamalar. Ankara: Hipokrat Yayınevi. ISBN:978-605-9160-03-2.
74. Özdinçler Razak A. (2014), Fiziksel modaliteler ve elektroterapi. İstanbul: İstanbul Tıp Kitabevi. ISBN:9786057607379.
75. Kern H. Funktionelle Elektrostimulation paraplegischer Patienten. Eur J Transl Myol. 2014;24(2):2940. doi:10.4081/ejtm.2014.2940.
76. Pieber K, Herceg M, Paternostro-Sluga T, Schuhfried O. Optimizing stimulation parameters in functional electrical stimulation of denervated muscles: A cross-sectional study. J Neuroeng Rehabil. 2015;12:51. doi:10.1186/s12984-015-0046-0.
77. Low J, Reed A. (2000), Electrical stimulation of nerve and muscle. Low J, Reed A, (Ed). Electrotherapy explained: principles and practice. Oxford, UK: Butterworth-Heinemann; 2000. p. 53-140. ISBN:0750600497.
78. Satardekar MB, Bhoir DV. Analysis and enhancement in the performance of electrical muscle stimulator. Int J Eng Sci Res Technol. 2017;235-41. doi:10.5281/zenodo.246592.
79. Sanjiv Kumar M, Tiwari SP. Effect of neuromuscular reeducation in bilateral facial palsy on patient with GBS. Int J Physiother Res. 2014;2(2):449-52. ISSN:2321-1822.
80. Heggannavar AB, Kulkarni PK, Naik KK, Oza AN. Compare the effect of 50% ramp-up and 100% ramp-up faradic stimulation in patients with non-specific trapezius spasm-A randomised clinical trial. IOSR-JSPE. 2018;5(2):1-5. doi:10.9790/6737-05020105.
81. Low J, Reed A. (2000), Electrical stimulation of nerve and muscle. Low J, Reed A, (Ed). Electrotherapy explained: Principles and practice. Oxford, UK: Butterworth-Heinemann. p. 195-207. ISBN:0750600497.
82. Nanivadekar P, Kar S. Microcontroller based rehabilitation stimulator. Int J Comput Appl. 2013;17-21. ISBN:973-93-80877-85-8.
83. Thorn H. Possibilities and limits of electrotherapy of paralysis. Arch Phys Ther (Leipz). 1955;7(3):272-6. PMID:13249572.

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After Atrophy Presence

DILEK HANDE ESEN • ESRA DOGRU HUZMELI

Introduction

Electrical stimulation (ES) is a safe and effective method for the treatment of denervated muscles and can be useful in preventing the atrophy and preserving the functional properties, appearance, and morphological features of the denervated muscles.[1,2] Since the early 2000s, it has been shown that ES can accelerate peripheral nerve regeneration, prevent muscle atrophy and fibrosis, increase strength, and promote functional recovery in denervated muscle after peripheral nerve injury, in studies first on animals and then on humans.[3-8]

Morphological Changes in the De-Innervated Muscle

Innervation is important for maintaining the functional and structural integrity of muscles. Muscles due to denervation cannot be stimulated by their own motor nerves. As a result, first, rapid and severe loss of muscle mass and voluntary function and secondarily, increased atrophy and loss of sarcomeric organization occurs. Finally, the loss of denervated muscle mass is followed by fibrosis (muscle fiber degeneration, and fat and fibrous connective tissue replacement of muscle). Muscle loses its excitability, its ability to contract, stretch, and become irritable.[9-12] Abnormalities of muscle fiber composition also occur. Slow-oxidative muscle fibers begin to transform into fast-twitch muscle fiber types. The muscle's capacity to produce power, its resistance to fatigue, and isometric contraction speed are reduced. In addition, the denervated muscle becomes more susceptible to injury.[13-15] It has also been shown in some animal experiments that denervation facilitates apoptosis in the myofibrils of skeletal muscle and leads to morphological disruptions of the transverse tubules, resulting in reduced connectivity between adjacent transverse tubules, with destruction in the membrane architecture.[16-18]

Denervated Muscle Stimulation

After a nervous system injury, ES of denervated muscle is a typical treatment approach used in physiotherapy and rehabilitation program to enhance neuromuscular recovery. Therefore, the primary purpose of ES of denervated muscle is to maintain the function of the corresponding nerve of the focused de-innervated muscle fiber until re-innervation is complete. Other purposes of stimulation are to prevent or delay muscle atrophy, to prevent loss of cortical representation of original movement patterns, to facilitate functional recovery, and to support the development of neuromuscular control during the denervation phase. Therefore, not the motor nerves, the muscle fiber is activated directly by ES via superficial electrodes.[6,19,20] Arakawa et al., stimulated the Soleus muscle of 19 rats, whose sciatic nerve was resected, using a rectangular impulse with a duration of 0.5 millisecond (ms) and a frequency of 2 Hertz (Hz) via 2 surface electrodes.[7] As a result of this study, it was reported that ES applied for 1 hour a day for 4

weeks increased the expression of some genes that suppress denervated muscle apoptosis and denervated muscle fiber atrophy could be prevented.

Modified Direct Current (Interrupted Galvanic Current)

The denervated muscle responds to modified direct current (interrupted galvanic current). The direct current is a current that has a unidirectional flow of electrons toward the positive pole (Figure 26.1). It can also be called Galvanic current or uninterrupted direct current.[21] To stimulate the denervated muscle fiber, the direct current must be interrupted. Interruption is the most common modification of direct current. In interrupted direct/Galvanic current, current starts and stops flowing at regular intervals.[22]

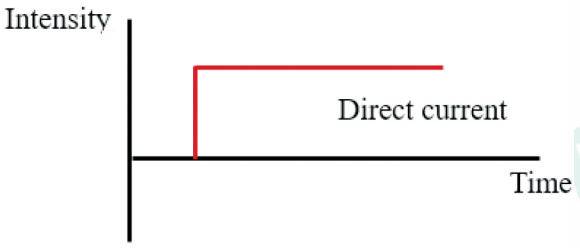

Figure 26.1 Direct current.

The interrupted galvanic current is produced in all modern clinical type electrotherapy devices. The modulation of the frequency, pulse duration and waveform of this current can be done in different ranges on electrotherapy devices.

Therapeutic Effects

The therapeutic effects of interrupted Galvanic current used in denervated muscle stimulation can be listed as follows:[9,23]

- Creating contraction in the denervated muscle.
- Delaying disuse atrophy and/or reducing atrophy.
- Maintaining muscle force.
- Preserving the morphological and biochemical properties of muscles.
- Facilitating the early repair of damaged nerves.
- Supporting vascular drainage and metabolic activity through muscle contractions.

Stimulation Parameters

The effectiveness of ES on a muscle that has been chronically denervated depends on the stimulus parameters, which have a significant impact on the development of atrophy.[24] In other words, the contraction response of the denervated muscle fibers to the stimulation depends on the intensity of the current, frequency of the current, duration of the pulse, type of the impulse (it means the waveform of the pulse), and pole of the selected active electrode. At the same time, the selective stimulation of muscle fibers is required to promote functional recovery. Therefore, it is important to know the electrostimulation parameters suitable for denervated muscle fibers in the treatment area. The key limiting factor for the choice of stimulation parameters is the non-selective stimulation of pain fibers and nearby muscles/tissue between the stimulation site and the targeted muscles, which must be taken into account when designing an appropriate muscle stimulation. Moreover, the amplitude required to activate denervated muscle fibers functionally is 10-100 times more than the amplitude required to activate healthy nerve fibers. At the same time, to obtain desired excitability and contraction, the pulse duration must be 100-1000 times longer than that in an innervated muscle. Consequently, it is far more challenging to excite a denervated muscle safely.[25-29]

The interrupted Galvanic currents are known as monophasic currents with long pulse duration.[21] Stimulation parameters of interrupted Galvanic currents:[9]

- The pulse duration is between 1 ms up to 300 or 600 ms.
- The pulses per second is between 1 and 100 Hz.
- The amplitude (intensity) may suddenly (such as rectangular impulses) increase or decrease, or the rise and fall of amplitude may be gradually (such as triangular, saw-tooth or trapezoidal impulses) (Figure 26.2).

After the type of the impulse is decided, the current intensity is increased slowly until a visible contraction is obtained.

Rectangular and triangular impulses are most commonly preferred in denervated muscle stim-

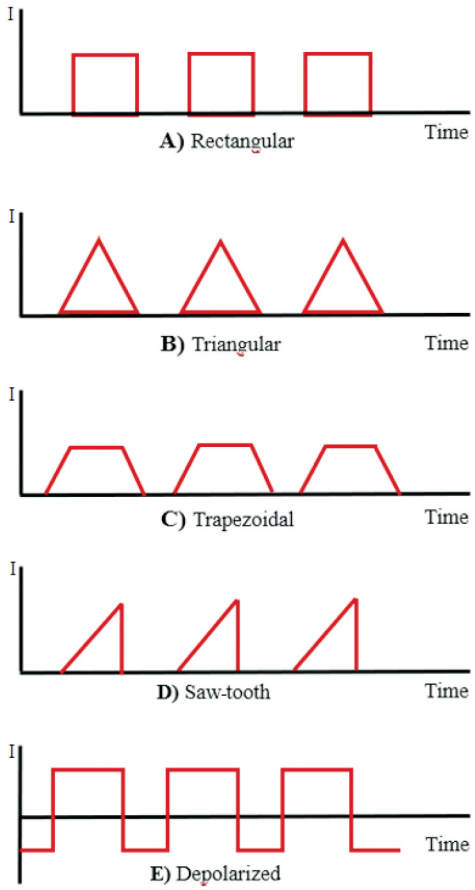

Figure 26.2 Modified direct current impulses[9].

ulation. The advantage of rectangular pulses over others is the use of a lower intensity than that required for motor nerve stimulation during contraction. Thus, the innervated muscles in the region cannot be stimulated and unwanted contractions are eliminated.[20,22] On the other hand, the advantage of triangular pulses is that patients experience less discomfort compared to the rectangular waveform.[25]

In cases where denervation takes a long time, the contractile response produced by a rectangular impulse may be insufficient. In such a case, the muscle contraction can be achieved with a slowly rising current. Stimulation with each is recommended to determine which impulse type produces a satisfactory contraction. It often happens when a slower increase in current density is required in case of longer denervation.[23]

Preparation of the Equipment Apparatus

The therapist must be familiar with the electrical stimulator device. Before starting the treatment, the therapist should ensure that the stimulator is working, check the other apparatus (electrode, main cable, and cable terminal), and feel the current on himself or herself.[23]

Application Techniques

Different types of electrodes are used in the stimulation. The most commonly used electrode types in clinical cases are as follows (**Figure 26.3**):

- The self-adhesive plate/surface electrodes.

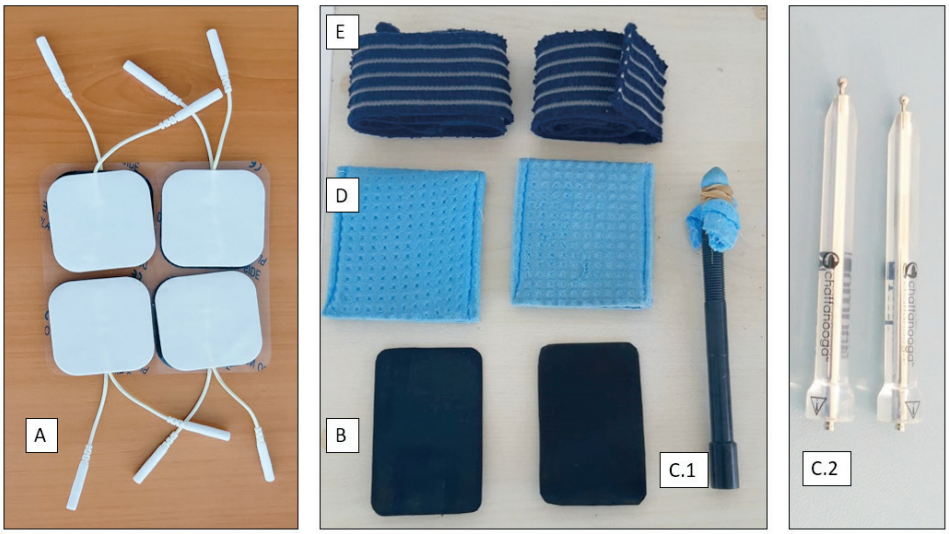

Figure 26.3 **A.** The self-adhesive plate/surface electrodes, **B.** The carbon-rubber electrodes, **C1.** The steel disc electrodes covered with sponge pad, **C2.** The stainless-steel disc electrodes, **D.** The sponge pads for carbon electrodes, **E.** Velcro for fixed the carbon electrodes.

- The carbon-rubber electrodes.
- The stainless-steel disc electrodes mounted on a pen holder.

Disc, square, or rectangular plate electrodes are used depending on the size of the treatment area, the size of which can vary from 1 square cm to 10 square cm. In order to avoid direct skin contact with the steel disc electrode mounted on the pen holder or carbon-rubber electrode, the electrodes should be covered with at least 1/2 cm thick sponge pad or cotton. The disc electrodes covered with sponge should always be soaked in water before use. If the carbon-rubber electrodes are used, after the sponge pads are wetted, electrodes should be placed inside.[23]

In general, contraction occurs more easily when the active electrode is the cathode (the electrode is connected to the negative pole). But this is not always the case. The electrode that will be the active electrode is decided by testing each patient, and the pole that produces the best contraction response in the muscle is selected as the active electrode.[22]

Approximately 300 contractions are required for each muscle in one treatment session. However, in this case, the muscle will get tired. Therefore, for an effective treatment, at least 90 contractions should be taken during the stimulation for each muscle. Ninety contractions can be obtained by dividing into 2 or 3 sets. Short breaks are given between sets according to the fatigue level of the muscle. The intensity of the current is gradually increased until a *good-visible contraction* is achieved. After that, it is continued with the same current intensity. If fatigue sets in quickly, the frequency of contractions may be decreased, and the duration of treatment may be increased.[9] The therapy should be performed in an environment with the highest level of privacy and good tangential lighting so that you can easily view the contraction of the muscles.

Monopolar technique: The passive electrode is placed on the origin of the muscle and fixed with velcro or bandage. The active electrode is moved over the motor point of the muscle during application to stimulate the maximum muscle fiber.[30] In general, the plate/pad electrode is chosen as passive electrode. The smaller disc electrode is preferred as the active electrode. A minimum of 90 contractions are obtained from each muscle (Figure 26.4).[22]

Bipolar technique: It is used to stimulate more than one muscle simultaneously. Stimulation is made by placing 2 equal-sized plate or pad electrodes on the origin and insertion of the relevant muscle group. The anode (passive electrode) is

Figure 26.4 **A.** Application of monopolar technique in hypothenar muscle stimulation, **B.** Application of bipolar technique in hypothenar muscle stimulation plantar flexor muscle group.

placed more distally, if sufficient contraction cannot be achieved, the electrode locations are changed. Each stimulation session can be designed as 3 set 10-minute (min) stimulation cycles separated by 5-min rest intervals.[6]

The duration of treatment varies according to the technique used and the amount of contraction to be obtained for each muscle.

Hazards, Precautions, and Recommendations

Hazards: Skin rashes or etching may occur due to over-stimulation or prolonged treatment sessions.

Precautions: Shaving should be performed before treatment to minimize the skin resistance in the treatment area.

Recommendations: The patient is advised to use moisturizing lotion/cream after treatment.

3.1.6. Contraindications

In the presence of the open wound, severe skin rashes or acne, superficial metal implant, and if the patient does not want stimulation are contraindicated.

Applications of Interrupted Galvanic Current in Some Common Clinical Conditions

Facial paralysis / Bell's palsy

The target muscles: Facial muscles (Frontalis, Corrugator Supercilii, Palpebral Part of Orbicularis Oculi, Levator Labii Superioris Alaeque Nasi, Levator Labii Superioris, Levator Anguli Oris, Risorius, Orbicularis Oris, Depressor Anguli Oris, Depressor Labii Inferioris, And Levator Menti) (Figure 26.5).

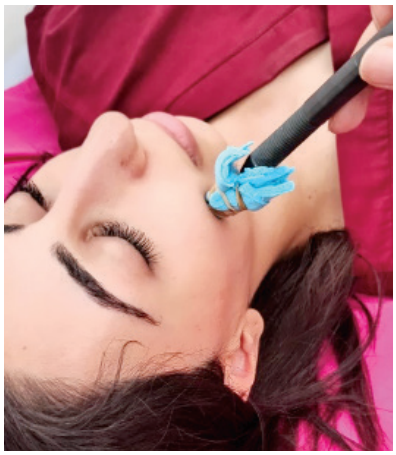

Figure 26.5 Placement of the disc electrode for transcutaneous facial muscle stimulation.

Parameters of current: A monophasic rectangular waveform having 100 ms of pulse duration, 300 ms of interpulse interval, and a pulse rate of 2.5 Hz can be used.[31]

The application technique: Monopolar technique, with passive electrode of 5x5 cm square, carbon-rubber, and with active electrode of 1x1 cm stainless steel disc on pen holder.

Patient position: Supine lying in a bed.

Electrode placement: Anode (positive-passive electrode) placed same sided arm, a cathode (negative-active electrode) placed at motor points of individual muscles. Due to the small size of the associated muscle, a disc active electrode (pen electrode) is being used to stimulate the motor point of muscles (Figure 26.5).

Note: If the bipolar technique is desired, a 7 cm^2 cathode electrode may be placed over the proximal portion of the ipsilateral arm and a 3 cm^2 anode electrode may be placed over each muscle.[31]

Duration of treatment: Each therapy session includes 3 sets of minimum 30 contractions and can be applied 5 days a week. The duration of treatment can vary from 2 to 6 months. Treatment should be carried out by the same physiotherapist.[31,32]

Denervation of Zygomaticus Muscle

The target muscle: Zygomaticus muscle

Parameters of current: Biphasic triangular and rectangular waveform trains of 20 pulses each, at 50 ms pulse duration, at 7 pulses per second, and a pause of 50 ms.

Patient position: Upright sitting.

Electrode placement: In order to avoid non-specific activation of other facial muscles, two 60x40 mm oval surface self-adhesive plate electrodes are positioned in correlation with the target muscle as close as possible to the mouth corner. The cathode is on top and the anode is at the bottom (Figure 26.6).[25]

The application technique: Bipolar technique. Without using a reference electrode to target the electrical field to the zygomaticus region, the muscle is stimulated bipolarly. The amplitude is raised incrementally by 0.5 milliampere (mA) until a movement of the mouth corner that can be seen is

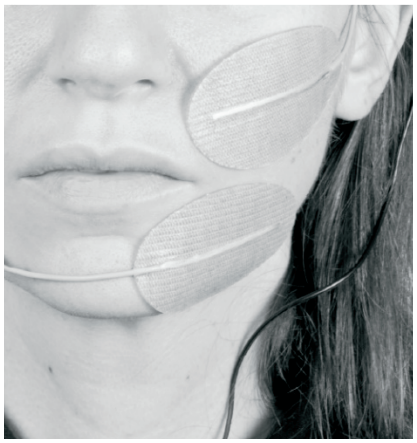

Figure 26.6 Example of surface electrode placement for Zygomaticus muscle stimulation.

noticed. This amplitude value, from which a visible contraction is obtained, is maintained throughout the treatment. At the end of each session, a temporary slight redness can be seen under the electrode sites.

The duration of treatment: For each muscle, 30-60 contractions.[23]

Suggestion: In order to benefit from the treatment at the maximum level, the parameters selected in the first session and the electrode placement can be changed in any of the other sessions.[25]

Brachial Plexus Injury

- Sample-1

The target muscles: Long flexor muscles of the wrist and fingers

Parameters of current: Rectangular impulses with pulse durations between 100 and 300 ms or specific trapezoidal impulses for prolonged stimulation, at 1 Hz (one pulse per second).

Patient position: Sit upright in a chair with a backrest, forearm in front of the trunk, treatment area can be supported on a table with a pillow.

Electrode placement: A plate electrode is used as the passive electrode (positive pole) and is placed on the common origin of the forearm flexors in the proximal part of the forearm at the Medial Epicondyle level. A metal disc electrode covered with a sponge and fixed on the pen holder is used as the active electrode (negative pole) and is placed in motor point of muscle (Figure 26.7) and

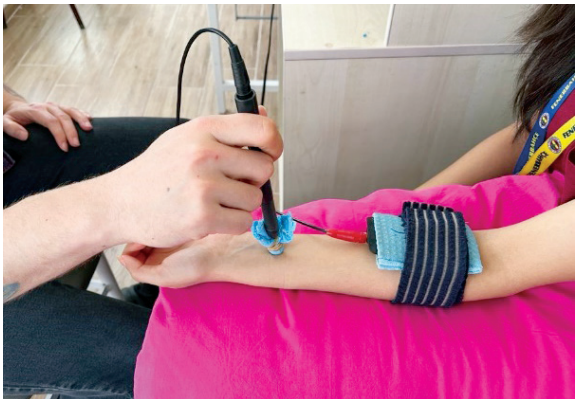

Figure 26.7 Electrode placement for forearm flexor muscle group stimulation.

moved up-down for the best visible contraction is achieved for each stimulated muscle.

The application technique: Monopolar technique.

The duration of treatment: At least 90 contractions in one sitting for each muscle.

- Sample-2

The target muscles: Intrinsic muscles of the hand

The parameters of current: It is as in the stimulation of the long flexor muscles of the wrist and fingers.

Patient position: It is as in the stimulation of the forearm flexor muscle group.

Electrode placement: The passive (anode) electrode is placed on the distal 1/3 of the forearm, where the Median and Ulnar nerves are superficial. The active (cathode) electrode is placed on the belly of the intrinsic muscle, one after the other, to give each muscle the required number of contractions (Figure 26.8).

Figure 26.8 The placement of electrodes for intrinsic muscles of the hand stimulation.

Duration of treatment: At least 90 contractions are obtained from each rehabilitated muscle in one session.

The application technique: Monopolar technique.

Drop Foot

The target muscles: Dorsiflexor and evertor muscle groups (Tibialis Anterior, Extensor Hallucis Longus, Extensor Digitorum Longus and Brevis, Fibularis Longus and Brevis) (Figure 26.9).

Figure 26.9 Placement of the carbon-rubber electrodes for muscles of the anterior-lateral compartment of the leg.

The parameters of the current: Rectangular impulses, pulse of duration 100 ms, frequency of pulse 1 Hz.

Patient position: Supine on a bed.

Electrode placement: The passive electrode (+ pole) covers the head of the Fibula at the origin of the dorsiflexor and evertor muscles, the area where the Common Peroneal nerve is superficial. The active electrode (- pole) is placed on the junction of the proximal 2/3 and distal 1/3 of the leg's anterolateral compartment muscles, in order to give all the muscles, the necessary number of contractions.

The application technique: Bipolar technique.

Duration of treatment: A combination of 10 min of stimulation and 3-5 min of rest is considered 1 set, each session includes 2-3 consecutive sets, depending on the fatigue state of the muscles. The treatment duration ranges from approximately 30-45 min.

Suggestion: The absence of hair in the treatment area will help reduce skin resistance by increasing the surface area of the electrodes in contact with the skin. If possible, the patient is asked to shave the area before coming for treatment.[18]

Alternating Current (Biphasic Current)

The direct current, also known as a monophasic current, generates waveforms in which each pulse has just one phase. Alternating current, also known as biphasic current, on the other hand, generates waveforms with 2 separate phases during each individual pulse. Biphasic alternating current has bidirectional current flow, involving a single change in polarity or direction with each pulse (Figure 26.10). A single current can either flow in one direction (direct current) or in the opposite direction (alternating current). The direct and/or alternating current form can be modified as the pulsed current form. With pulsed currents, there is usually an interruption in the current flow. This means that there are intervals between pulses where there is no short-term current flow.[9]

Therapeutic Effects

Alternating current is an effective current option for reducing atrophy after denervation and preventing the development of atrophy in the denervation phase. It has also been shown to be useful in maintaining denervated muscle strength.[24]

Stimulation Parameters

Biphasic alternating currents can be symmetrical or asymmetrical. In symmetrical biphasic currents, the phases within each pulse have the same pulse duration, amplitude, and waveform. The waveform produced by the electrotherapy source in alternating current can be rectangular, sinusoidal, or triangular. Alternating currents can be used in continuous or interrupted modulations during stimulation. The interrupted modulation of alternating current is generally preferred for denervated muscle stimulation. After denervation, chronaxie increases because the excitability of the muscle decreases. For this reason, impulses with a longer pulse duration are needed to adequately stimulate the denervat-

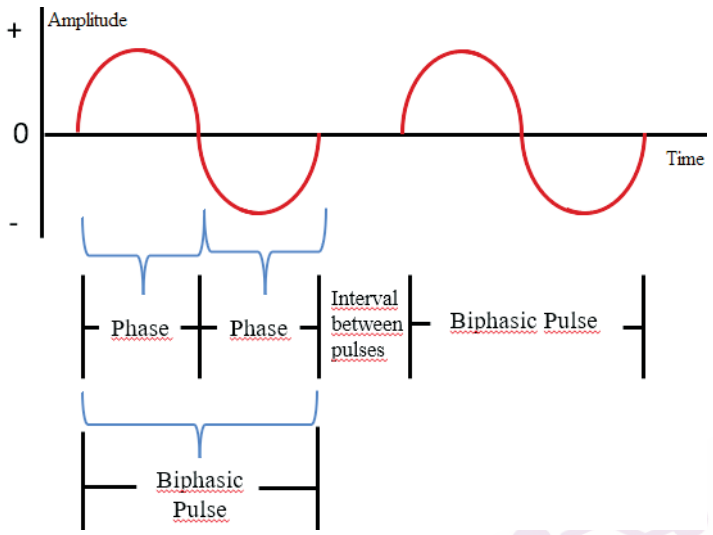

Figure 26.10 Biphasic alternating current in sine waveform.

ed muscle compared with the innervated muscle. Therefore, the pulse duration is longer than 1 ms.[33] The current frequency used is usually below 50 Hz to avoid tetanic contraction (tetanic contraction quickly causes fatigue). Twenty-five pulses per second (25 Hz) may be sufficient to simultaneously stimulate slow and fast muscle fibers. With low current intensity in mA, the desired visible contraction can be achieved. Each pulse's amplitude corresponds to the current's intensity. Voltage and current intensity are concepts that are interchangeable with amplitude. The voltage or intensity increases as the amplitude increases. The peak of the highest point in a phase should not be confused with the overall current. Consequently, the average current or the amount of current flowing per unit of time is not very high. Increases in pulse frequency, pulse duration, or a combination of the two can all increase the average current.[9,24] The initial state of the target denervated muscle is very important. The longer the denervation process in the muscles, the longer the treatment duration of the ES applied to obtain the desired contractile response.[34] Therefore, the sooner denervated muscle electrostimulation is started, the faster the treatment progresses.

The Application of Alternating Current in Some Denervation Conditions

In previous years, some researchers have studied the effect of ES using alternating current on denervation in people whose quadriceps femoris muscle is fully denervated for at least 6 months to 10 years. In these studies, some researchers called the stimulation of denervated muscles "Functional Electrical Stimulation (FES)". Treatment was performed with biphasic rectangular impulses with current intensity up to 250 mA, pulse duration of 30-150 ms, pulse frequency varying between 2 and 22 Hz, 5 days a week. Pulse duration was reduced as healing occurred. At the same time, the pulse frequency was increased as the pulse duration decreased. For example, the initial pulse duration above 100 ms can be shortened to 30-50 ms after 3 months, while the pulse frequency is gradually increased to 15-25 Hz to allow the stimulated muscles to gradually produce tetanic contractions. A pulse could be a single or a series of pulses called a pulse train. The mentioned treatment sessions continued for more than 1-2 years.[14,29,34-36] To conclude, a summary of the related studies are as follows; when an alternating current containing the above parameters is applied to the long-denervated muscles of people with lower motor neuron lesion due to spinal cord injury, muscle atrophy can be mitigated and hypertrophy can be achieved in denervation.

Mokrusch et al. developed a new concept of ES involving short treatment time with minimum current intensity that can preserve muscle strength in rabbits.[24] In this study, stimulation was started on

the 28th day after denervation, and treatment was continued once a day, every day for an average of 16 weeks. The focus was on the denervated right hind leg flexor muscle group. The knee was semi flexed and the ankle was in a neutral position. Metal disc electrodes with a contact area of 8 x 12 mm were covered with cotton and wetted before being placed on the treatment area. Alternating current was used in the bipolar technique for stimulation. The current parameters were as follows: biphasic (pulse changes direction after 10 ms) rectangular impulse with pulse duration of 20 ms, current intensity 20 mA, 20 ms rest time was given after 20 ms flow. Two sessions were applied 12 hours apart each day. Each treatment session lasted 6 min. Every 1 min continuous stimulation was followed by a 5 min break. Fatigue was low during treatment. The results of this study reported that the muscle fiber diameter of the chronically denervated muscles was preserved by 72-86% due to ES, whereas the muscle fiber diameter of the unexcited animals was reduced by 40% compared to normal.

Conclusion

It has been known for many years that ES can induce contraction by stimulating the muscle externally. In the last 30 years, studies have begun to investigate the use of electrotherapy modalities to strengthen the target muscle in denervation conditions caused by spinal cord injuries or severe peripheral neuropathies in humans. In this context, ES can be considered an integral part of the denervated muscle rehabilitation. Scientific research has shown that ES has a positive effect on the contractile activity of denervated muscles, but there is no consensus on this issue due to the low level of available evidence. However, evaluating the efficacy of stimulation can be somewhat complex because there are many factors that can affect functional recovery following nerve injury. Although ES was found to promote axonal regeneration and functional rehabilitation after de-innervation, the specific mechanisms of successful stimulation and the stimulation parameters of effective treatment are unclear.[37] Moreover, ES can have side effects even though it is effective for treating the denervation. According to Hussain et al., prolonged stimulation can cause anomalies in the neuromuscular junction and decrease the excitability of the skeletal muscles.[38] In addition, stimulating innervated skeletal muscles may impair the survival of asynchronous nerves. Functional reinnervation may be hampered by electrostimulation if the stimulated nerves and muscles link asynchronously. In order to address the negative effects of ES and determine the best stimulation protocol, more studies are required.

Most previous research has focused on denervation caused by peripheral nerve injuries. However, in humans, the effects of interrupted Galvanic stimulation for lower motor neuron denervation after spinal cord injury have been recently investigated, and similar results to peripheral nerve injuries have been reported. According to these results, ES is an effective strategy for increasing muscle cross-sectional area, size of muscle fibers, and building muscle in lower motor neuron denervation after spinal cord injury. In summary, a modified Galvanic current is a novel stimulation technique for denervated muscles in humans with spinal cord injury.[29]

Because of denervation, the sarcolemma of each target muscle fiber must be depolarized with appropriate stimulation parameters in order to achieve contraction. As a result, in the literature studies, the recommended parameters for denervated muscle stimulation are listed below:

- Rectangular impulses are generally the first choice as the current type.
- The pulse duration should be greater than or equal to the chronaxie of denervated muscles. After denervation, the chronaxie period of the targeted muscle is prolonged. Impulses with a longer pulse duration are needed to adequately stimulate the denervated muscle compared with the innervated muscle. Therefore, an impulse of at least 100 ms may be required to ensure the stimulation of all denervated muscle fibers during the first sessions of treatment.[29] Also, in the literature studies it has been reported that the pulse duration of the current used usually up to 10-40 ms or even 200 ms.[32]

- The pulse frequency ranges from 1 to 25 Hz. It is not recommended to use currents below 30 Hz to avoid muscle fatigue.[39]
- The current density is increased until a visible contraction is obtained, and then the application is continued at this mA intensity.
- Monopolar technique is used for isolated muscle stimulation, bipolar technique is used to stimulate several muscles at the same time or to stimulate deep muscle groups.
- Regardless of the technique used, it is recommended to stimulate the muscles for 30-60 min 5 days a week.

Consequently, 2 types of current are commonly used to stimulate denervated muscles. These currents are direct current or alternating current. Both currents are modulated by interrupting. The pulse duration for both currents is over 10 ms, and the first choice waveform is often the rectangular type. The main differences of these currents are that in direct current the electron flow is unidirectional (monophasic), while in alternating current it is bidirectional (biphasic). In an alternating current, electron flow can be visualized in sine wave form, and a pulse can be symmetrical or asymmetrical. The direct current causes chemical changes under the electrodes. Where there is a change in direction in an alternating current, no chemical change is expected where current passes.[29]

It should be noted that electrotherapy should be combined with exercise to increase its beneficial effects on denervated muscle stimulation.

There is no standard denervated muscle protocol for the most common pathologies in the clinic. Additionally, commercially accessible devices do not currently have the ES properties used by devices in research reporting successful outcomes. Therefore, there is a need for studies with a high level of evidence (randomized controlled studies) in the future to investigate which stimulation parameter is more effective than the other for denervated muscle and to prescribe a standard treatment protocol in the latest model electrotherapy devices.

References

1. Xu J, Tu Y, Gu Y. Effect of electric stimulation on denervated skeletal muscle atrophy. [Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi.] Chinese. 2003;17(5):396-9. PMID:14551939.
2. Chiaramonte R, Pavone V, Testa G, Pesce I, Scaturro D, Musumeci G, et al. The role of physical exercise and rehabilitative implications in the process of nerve repair in peripheral neuropathies: A systematic review. Diagnostics. 2023;13(3):364. doi:10.3390/diagnostics13030364.
3. Gordon T, English AW. Strategies to promote peripheral nerve regeneration: Electrical stimulation and/or exercise. Eur J Neurosci. 2016;43(3):336-50. doi:10.1111/ejn.13005.
4. Dow DE, Cederna PS, Hassett CA, Kostrominova TY, Faulkner JA, Dennis RG. Number of contractions to maintain mass and force of a denervated rat muscle. Muscle Nerve. 2004;30(1):77-86. doi:10.1002/mus.20054.
5. GigoBenato D, Russo TL, Geuna S, Domingues NRSR, Salvini TF, Parizotto NA. Electrical stimulation impairs early functional recovery and accentuates skeletal muscle atrophy after sciatic nerve crush injury in rats. Muscle Nerve. 2010;41(5):685-93. doi:10.1002/mus.21549.
6. Piccinini G, Cuccagna C, Caliandro P, Coraci D, Germanotta M, Pecchioli C, et al. Efficacy of electrical stimulation of denervated muscle: A multicenter, double blind, randomized clinical trial. Muscle Nerve. 2020;61(6):773-8. doi:10.1002/mus.26880.
7. Arakawa T, Katada A, Shigyo H, Kishibe K, Adachi M, Nonaka S, et al. Electrical stimulation prevents apoptosis in denervated skeletal muscle. NeuroRehabilitation. 2010;27(2):147-54. doi:10.3233/NRE-2010-0591.
8. Zealear DL, Mainthia R, Li Y, Kunibe I, Katada A, Billante C, et al. Stimulation of denervated muscle promotes selective reinnervation, prevents synkinesis, and restores function. Laryngoscope. 2014;124(5):E180-E7. doi:10.1002/lary.24454.
9. Jagmohan S. (2011), Low frequency currents. In S. Jagmohan (Ed.), Manual of practical electrotherapy (pp. 8-71). New Delhi: Jaypee Brothers Publishers. ISBN:9350258307.
10. Gordon T. Peripheral nerve regeneration and muscle reinnervation. Int J Mol Sci. 2020;21(22):8652. doi:10.3390/ijms21228652.
11. Carlson BM. The biology of long-term denervated skeletal muscle. Eur J Transl Myol. 2014;24(1):3293. doi:10.4081/ejtm.2014.3293.
12. Ceylan O, Seyfettinoğlu F, Dülgeroğlu AM, Avcı A, Bayram B, Bora OA. Histomorphological comparison of immobilization and denervation atrophies. Acta Orthop Traumatol Turc. 2014;48(3):320-5. doi:10.3944/AOTT.2014.2993.
13. Boncompagni S, Kern H, Rossini K, Hofer C, Mayr W, Carraro U, et al. Structural differentiation of skeletal muscle fibers in the absence of innervation in humans. Proc Natl Acad Sci USA. 2007;104(49):19339-44. doi:10.1073/pnas.0709061104.
14. Mödlin M, Forstner C, Hofer C, Mayr W, Richter W, Carraro U, et al. Electrical stimulation of denervated muscles: First results of a clinical study. Artif Organs. 2005;29(3):203-6. doi:10.1111/j.1525-1594.2005.29035.x.
15. Carraro U, Rossini K, Mayr W, Kern H. Muscle fiber regeneration in human permanent lower motoneuron denervation: Relevance to safety and effectiveness of FES-training, which induces muscle recovery in SCI subjects. Artif Organs. 2005;29(3):187-91. doi:10.1111/j.1525-1594.2005.29032.x.
16. Jin H, Wu Z, Tian T, Gu Y. Apoptosis in atrophic skeletal muscle induced by brachial plexus injury in rats. J Trauma. 2001;50(1):31-5. doi:10.1097/00005373-200101000-00005.

17. Jejurikar SS, Marcelo CL, Kuzon Jr WM. Skeletal muscle denervation increases satellite cell susceptibility to apoptosis. Plast Reconst Surg. 2002;110(1):160-8. doi:10.1097/00006534-200207000-00027.
18. Tomori K, Ohta Y, Nishizawa T, Tamaki H, Takekura H. Low-intensity electrical stimulation ameliorates disruption of transverse tubules and neuromuscular junctional architecture in denervated rat skeletal muscle fibers. Muscle Res Cell Motil. 2010;31:195-205. doi:10.1007/s10974-010-9223-8.
19. Willand MP, Holmes M, Bain JR, Fahnestock M, De Bruin H. Electrical muscle stimulation after immediate nerve repair reduces muscle atrophy without affecting reinnervation. Muscle Nerve. 2013;48(2):219-25. doi:10.1002/mus.23726.
20. Kurz A, Volk GF, Arnold D, Schneider-Stickler B, Mayr W, Guntinas-Lichius O. Selective electrical surface stimulation to support functional recovery in the early phase after unilateral acute facial nerve or vocal fold paralysis. Front Neurol. 2022;13:869900. doi:10.3389/fneur.2022.869900.
21. Low J, Reed A. (2006), Production of currents for electrotherapy. In J. Low, A. Reed (Eds.), Electrotherapy explained: Principles and practice (pp. 114-131). London: Elsevier Health Sciences. ISBN: 0750688432.
22. Forster A, Palastanga N. (2006), Electrical stimulation of nerve and muscle. In A. Forster, N. Palastanga (Eds.), Clayton's electrotherapy: Theory and practice (pp. 55-111). London: Baillife Tindall. ISBN:0702011002.
23. Mitra PK. (2006), Therapeutic electrical stimulation. In PK Mitra (Ed.), Handbook of practical electrotherapy (pp. 15-21). New Delhi: Jaypee Brothers Publishers. ISBN:8180616207.
24. Mokrusch T, Engelhardt A, Eichhorn KF, Prischenk G, Prischenk H, Sack G, et al. Effects of long-impulse electrical stimulation on atrophy and fibre type composition of chronically denervated fast rabbit muscle. J Neurol. 1990;237(1):29-34. doi:10.1007/BF00319664.
25. Arnold D, Thielker J, Klingner CM, Puls WC, Misikire W, Guntinas-Lichius O, et al. Selective surface electrostimulation of the denervated zygomaticus muscle. Diagnostics. 2021;11(2):188. doi:10.3390/diagnostics11020188.
26. Husain S, Sadoughi B, Mor N, Sulica L. Time course of recovery of iatrogenic vocal fold paralysis. Laryngoscope. 2019;129(5):1159-63. doi:10.1002/lary.27572.
27. Seifpanahi S, Izadi F, Jamshidi A-A, Shirmohammadi N. Effects of transcutaneous electrical stimulation on vocal folds adduction. Eur Arch Otorhinolaryngol. 2017;274:3423-8. doi:10.1007/s00405-017-4619-3.
28. Zuo KJ, Gordon T, Chan KM, Borschel GH. Electrical stimulation to enhance peripheral nerve regeneration: Update in molecular investigations and clinical translation. Exp Neurol. 2020;332:113397. doi:10.1007/s00405-017-4619-3.
29. Chandrasekaran S, Davis J, Bersch I, Goldberg G, Gorgey AS. Electrical stimulation and denervated muscles after spinal cord injury. Neural Regen Res. 2020;15(8):1397. doi:10.4103/1673-5374.274326.
30. Cole BG, Gardiner PF. Does electrical stimulation of denervated muscle, continued after reinnervation, influence recovery of contractile function? Exp Neurol. 1984;85(1):52-62. doi:10.1016/0014-4886(84)90159-6.
31. Tuncay F, Borman P, Taşer B, Ünlü İ, Samim E. Role of electrical stimulation added to conventional therapy in patients with idiopathic facial (Bell) palsy. Am J Phys Med Rehabil. 2015;94(3):222-8. doi:10.1097/PHM.0000000000000171.
32. Ohtake PJ, Zafron ML, Poranki LG, Fish DR. Does electrical stimulation improve motor recovery in patients with idiopathic facial (Bell) palsy? Phys Ther. 2006;86(11):1558-64. doi:10.2522/ptj.20060005.
33. Ashley Z, Sutherland H, Lanmuller H, Unger E, Li F, Mayr W, et al. Determination of the chronaxie and rheobase of denervated limb muscles in conscious rabbits. Artif Organs. 2005;29(3):212-215. doi:10.1111/j.1525-1594.2005.29037.x
34. Kern H, Hofer C, Mödlin M, Forstner C, Raschka-Högler D, Mayr W, et al. Denervated muscles in humans: Limitations and problems of currently used functional electrical stimulation training protocols. Artif Organs. 2002;26(3):216-8. doi:10.1046/j.1525-1594.2002.06933.x
35. Gargiulo P, Reynisson PJ, Helgason B, Kern H, Mayr W, Ingvarsson P, et al. Muscle, tendons, and bone: structural changes during denervation and FES treatment. Neurol Res. 2011;33(7):750-8. doi:10.1179/1743132811Y.0000000007.
36. Kern H, Hofer C, Strohhofer M, Mayr W, Richter W, Stöhr H. Standing up with denervated muscles in humans using functional electrical stimulation. Artif Organs. 1999;23(5):447-52. doi:10.1046/j.1525-1594.1999.06376.x.
37. Chu X-L, Song X-Z, Li Q, Li Y-R, He F, Gu X-S, et al. Basic mechanisms of peripheral nerve injury and treatment via electrical stimulation. Neural Regen Res. 2022;17(10):2185. doi:10.4103/1673-5374.335823.
38. Hussain G, Wang J, Rasul A, Anwar H, Qasim M, Zafar S, et al. Current status of therapeutic approaches against peripheral nerve injuries: A detailed story from injury to recovery. Int J Biol Sci. 2020;16(1):116. doi:10.7150/ijbs.35653.
39. Gorgey AS, Black CD, Elder CP, Dudley GA. Effects of electrical stimulation parameters on fatigue in skeletal muscle. J Orthop Sports Phys Ther. 2009;39(9):684-92. doi:10.2519/jospt.2009.3045.

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Neuropraxia

ZELIHA OZLEM YURUK

Introduction

Peripheral Nerve Injury

The peripheral nervous system consists of cranial, spinal, and autonomic nerves. The system connects the central nervous system to the limbs and organs. Peripheral nerve injury (PNI) is a type of motor, sensory, and autonomic disorder caused by damage to the structure of peripheral nerves. The incidence of PNI caused by trauma is approximately 5%, including brachial plexus and root injuries.[1]

After PNI, varying degrees of damage occur in the peripheral nerves.[2] The Seddon and Sunderland classification systems are widely used to define PNIs. Seddon classified PNIs as neuropraxia, axonotmesis, and neurotmesis. Sunderland made a more detailed classification and divided PNIs into 5 stages (Table 27.1).[2]

Grade I injury is the least severe injury. It is defined as focal demyelination (neuropraxia) of the nerves with no axon loss.[3] Additional axon loss (axonotmesis) in grade II lesions are the only differen-

Table 27.1 Seddon and Sunderland classification systems.[2]

Seddon	Sunderland	Injury	Spontaneous recovery	Nerve conduction study	Electromyography
Neuropraxia	Grade I	Focal segmental demyelination	Yes	Partial/complete conduction block proximally. Preserved conduction block distally even after 2 weeks	Normal morphology and poor MUAP recruitment. Abnormal activity (If the demyelination prolonged)
Axonotmesis	Grade II	Damaged axon with intact endoneurium	Yes, slower than neuropraxia	Partial/complete conduction block proximally. Preserved conduction block distally until Wallerian denervation sets in.	Abnormal activity
Axonotmesis	Grade III	Damaged axon and endoneurium with intact perineurium	Not very likely, surgical intervention may be needed		
Axonotmesis	Grade IV	Damaged axons, endoneurium, and perineurium with intact epineurium	Highly unlikely, surgical intervention is necessary		
Neurotmesis	Grade V	Complete nerve transection (disruption of myelin sheath, axon, endoneurium, perineurium and epineurium)	No, surgical intervention is necessary	Complete conduction block	Abnormal activity

tiator from grade I lesions, but both will most likely achieve full recovery. Injuries of the grade III-V are characterized by additional loss of adjacent connective tissue layers from inner to outermost. The damage of the endoneurium in grade III injury disrupts the scaffold, by which axons elongate for regeneration and causes neuroma formation. Variable outcomes were seen in the following grade III lesions. Neuroma formation and inhibited regeneration occur in grade IV injuries. Recovery is poor due to perineurial damage. However, the epineurium remains intact in grade IV injury. Grade V injury is characterized by complete nerve transection and discontinuity.[3]

Many variables affect recovery after PNI. Surgical repair is essential for promoting regeneration in neuromas (grade III-IV) and complete transection (grade V).[3]

Factors that affect re-innervation are the:[4]

- Injury type,
- Distance of the de-innervated muscle,
- Age,
- Time elapsed after injury,
- General health status,
- Genetic factors.

Complete or partial loss of motor functions (loss of voluntary and reflex contraction of the muscle and progressive muscle atrophy), loss of sensory functions (muscle spindle atrophies, Meissner, Pacinian and Merkel atrophy, some other receptors are lost), autonomic loss, and cortex plasticity are seen after PNI.[1,5]

De-innervated muscle fibers are biochemically, mechanically, and electrically different from healthy muscle. Morphological and physiological changes seen in de-innervated muscles are the:[4]

- Muscle atrophy,
- Venous stasis and edema,
- Acetylcholine (ACh) hypersensitivity,
- Loss of muscle weight,
- Loss of sarcoplasm,
- Decreased resting potential of fibers and increased transmembrane resistance,
- Increased connective tissue and fibrosis,
- Fibrillation and fasciculation potential,
- Increased chronaxie.

As can be seen, many problems appear after PNI. Conservative treatment, surgical procedures, or both are applied to reduce the unfavorable effects of de-innervation, support re-innervation, and nerve regeneration. Physiotherapy and rehabilitation play an essential role in PNI. Physiotherapy can protect and maintain motor, sensory, autonomic, and cortical functions during re-innervation. The treatment program should be individualized according to the patient's assessment. The main goals of physiotherapy and rehabilitation are to:[6]

- Give education to the patient and family,
- Protect the de-innervated muscle and prevent repetitive injury,
- Maintain the relationship between the cortex and peripheral organs,
- Enhance the sensory inputs,
- Control the venous stasis and edema,
- Maintain the joint range of motion,
- Maintain muscle strength,
- Minimize secondary complications,
- Limit the pain.

Physiotherapy and rehabilitation approaches for PNI are the:[3,6]

- Sensory re-education, skin protection,
- Therapeutic massage, joint and nerve mobilization,
- Orthotic approaches,
- Electrical stimulation (ES),
- Stretching, strengthening, and range of motion exercises,
- EMG-Biofeedback,
- Activities of daily living training.

Neuropraxia (Sunderland I)

Nerve conduction block occurs due to mechanical trauma, prolonged compression, or traction. Sports injuries, bone fractures, ligament and tendon injuries, dental work, or surgeries can cause neuropraxia. Bell's Palsy, Gullian-Barre Syndrome, and Carpal Tunnel Syndrome are the examples of neuropraxia. The lesion is localized in the myelin sheath. The axon continuity is preserved. Wallerian degeneration does not occur in the nerve. Fibril-

lation and de-innervation changes are not observed in the muscles. There is conduction above and below the lesion. The complete or partial loss of motor function and paralysis becomes. Sensory loss may also be seen. Schwann cells provide re-myelination. Recovery takes 3-4 months. But some people, especially older adults, may take longer to heal.[3,5]

Patient Evaluation

Before the clinical decision-making for the physiotherapy and rehabilitation program and ES, a detailed patient assessment is essential. Physiotherapists do sensory and electrodiagnostic functionality tests and evaluate muscle strength, range of motion, anthropometric properties, posture, viscoelastic (tone, elasticity, thixotropy) properties of the muscles, pain, and autonomic functions in patients with PNI.[6]

If the duration of re-innervation prolongs and the de-innervation continues, detailed evaluation techniques such as ultrasound and magnetic resonance imaging are required. Thus, the response of the muscle to the physiotherapy and rehabilitation program can be predicted.[7-9]

Electrical Stimulation for Neuropraxia

The Aim and Effects of Electrical Stimulation in Neuropraxia

The ES was initially conducted and propagated by Reid.[5] The ES was broadly used on many patients with PNI after the World Wars. The ES prevents atrophy and keeps the muscle as healthy as possible until re-innervation. The denervated muscle is neither voluntary nor reflexively active because it has atrophied and weakened. However, with an appropriate ES protocol, contraction of the de-innervated muscle can be achieved and prevent the decrement associated with de-innervation.[10,11]

The aims of the ES in neuropraxia are to:[4,5,12,13]

- Keep the muscle active while waiting for regeneration,
- Delay atrophy,
- Activate the muscle spindles and maintain sensory input,
- Improve blood flow.

Many studies have shown that skeletal muscle ES is effective for motor function.[14,15] Muscle stem cells, such as satellite cells, are responsible for the growth and repair of skeletal muscle. Myogenic precursor cells (MPCs) activate muscle stem cells and promote muscle regeneration. De Filippo et al. revealed that ES could increase the fusion of adult stem cells with the existing myofibers by increasing cytoplasmic free calcium (Ca^{+2}) concentration and the gene expression of skeletal muscle-specific factors.[16] The regenerative capacity of skeletal muscle was affected by MPC proliferation. The researchers found that ES tended to reduce the superoxide dismutase activity. Thus, ES promoted muscle regeneration by decreasing the oxidative status in the satellite cells of healthy older adults.

Increased glucose consumption and reduced acetyl carnitine bundles observed after ES indicated that ES could enhance the changes in glycolytic and fatty acid metabolic processes.[17] Because ES increased the transport of glucose transporter type 4 (GLUT-4) to the plasma membrane. Muscle contractions activate adenosine monophosphate-activated protein kinase (AMPK), which increases glucose uptake.[18] Thus, ES may trigger the phosphorylation of AMPK, increasing GLUT-4 protein levels. Studies found that ES released adenosine triphosphate (ATP) and increased GLUT-4 transmission.[19,20] Although ES increases the consumption of ATP, like exercise, it does not increase oxidative stress in muscle. However, the relationship between inflammation and ES is still unclear. Lambernd et al. found that ES decreased some protein levels, implying an anti-inflammatory effect.[21] Time may be the major influential factor. Mancinelli et al. demonstrated that oxidative stress and inflammation began immediately after PNI and ended after three days.[22] Therefore, the application of ES may be optimal 3 days after PNI.

Studies that investigated the effects of muscle ES on nerve regeneration are controversial. Some authors stated that ES was effective,[23,24] others ar-

gued that it had a detrimental effect on nerve regeneration.[25] Might ES be harmful for remyelination in neuropraxia? Segmental demyelination occurs in neuropraxia. The remyelination is rapid in neuropraxia. Most people with neuropraxia recover fully. Thus, ES during the period of re-innervation has no negative impact on remyelination.[23]

Because the treatment duration is so long, skin irritation and contact eczema can be seen with ES. If these side effects occur, the physiotherapist gives a break to the treatment. Contraindications for ES of denervated muscle are the same as for NMES.[13]

Electrical Stimulation Protocol for Neuropraxia

The Faradic Excitability Test shows nerve excitability and neuropraxia. The Faradic current is an alternating biphasic current with a short pulse duration. So, it cannot be effective in complete de-innervation. However, in the case of neuropraxia, the nerve gives a contraction response to the Faradic current because there is no degeneration in the nerve. ES with low-frequency alternating current has higher conductivity than the Direct current. Therefore, alternating currents can stimulate deep muscles of the limbs and trunk.[26]

Alternating currents are comfortable for the patients and can elicit greater muscle torque. Tanaka et al. suggested that ES using alternating current has the potential to become an effective therapeutic intervention to prevent deep muscle atrophy.[27] The frequency and pulse duration of the ES should be determined according to the fiber type distribution of the muscle. If it is a slow-twitch muscle, a frequency below 40 Hertz (Hz) should be applied. If it is a fast-twitch muscle 50-70 Hz should be chosen. In neuropraxia, there is no need for a longer pulse duration. The pulse duration of the Faradic current is 0.1-1 millisecond (ms). This value is equivalent to chronaxie.[4,13]

The Faradic current duty cycle is 1:9. It is also recommended that the current be on time for 2-5 seconds. The off period should be adjusted at least 2-5 times the on time. It is recommended that the ramp-up time should be at least 3 times the ramp-down time to elicit an isolated muscle contraction and increase patient comfort.

High Voltage Pulsed Galvanic Stimulation (HVPGS) can also be used to elicit contraction. HVPGS is a monophasic pulsed electric current with a frequency of 1-120 Hz, consisting of double peak impulses [5-200 microseconds (μs)] and high voltage [up to 500 Volt (V)]. HVPGS, like most monophasic pulsed currents, have such short pulse durations and long interpulse intervals that any charge deposited at the electrode-skin interface dissipates before causing permanent reverse polar effects.[4,13]

It is recommended that the current amplitude be as high as is tolerable and capable of stimulating a tetanic contraction of the target muscle. The atrophied and de-innervated muscles are vulnerable to trauma. Excessive ES of the muscles can cause trauma. Higher current amplitude elicits strong and deep muscle contractions. However, higher amplitudes also cause trauma. The long pulse duration and high current amplitude can be painful if the sensation is intact. However, the goal is to maximize the contraction response while minimizing the pain.

Physiotherapists should avoid fatigue when using ES. In order not to create oxidative stress in the muscle, the application should be stopped when signs of fatigue are seen.[28] The 200 muscle contractions per day are sufficient to prevent muscle fiber atrophy. However, to prevent fatigue, 90 contractions of each muscle should be performed as 3 sets of 30-30-30 or 2 sets of 45-45 contractions. The treatment sessions are planned 3-5 times/week for approximately 8 weeks. The ES should be started as soon as possible after PNI. ES should be terminated after active movement has begun.[29,30]

The electrode size depends on the size of the muscle to be stimulated and the intensity of the contraction to be elicited. Small electrodes may be used to localize stimulation to small muscles. Larger electrodes are needed to stimulate larger muscles and muscle groups. One electrode may be placed over the most excitable part of a muscle. The second electrode is placed at a convenient location near to the muscle being treated. The other

Table 27.2 Parameter settings for ES in neuropraxia.[4,5,13]

Current type/waveform	Pulsed alternating current-Faradic current Asymmetric biphasic High Voltage Pulsed Galvanic Current (HVPGS)
Pulse/cycle duration	0.1-1ms (Faradic current) 100-600 µs (HVPGS)
Amplitude	Optimal tolerated contraction
Pulse rate (frequency)	<40 Hz for slow-twitch muscles 50-70 Hz for fast-twitch muscles
Ramp up/ramp down	1 /3 seconds (s)
On time (duty cycle)/ Off time	1:9 s (%10) 2-5 s/2-25s
Modulation	None
Treatment duration	3 sets of 30-30-30 or 2 sets of 45–45 contractions <30s
Frequency of sessions	3-5 times/week, approximately 8 weeks
Polarity	None
Electrode placement	Bipolar or monopolar technique Parallel to fibers

option is that both electrodes are placed close to the origin and insertion of the muscle.

Prior to the treatment, the skin should be cleaned with an alcohol-based wipe to remove skin debris, sweat, and dirt. It is necessary to do this in order to facilitate good contact between the electrode and the skin and thus reduce the electrical resistance of the interface.[31]

Clinical Evidence of ES in Neuropraxia

Bell's Palsy

Bell's Palsy is an acute disorder of the facial nerve that produces full or partial loss of movement on one side of the face. Bell's Palsy gets completely better without treatment in most, but not all people. Physiotherapy is used to improve facial function and minimize sequelae. While some studies support the use of ES in the literature, the other studies did not show the effects of ES.[32-35]

Tuncay et al. investigated the effect of ES and conventional physiotherapy and rehabilitation in an early phase of Bell's Palsy.[32] In the study, the authors divided 60 patients into two groups. 57.1% of patients had no axonal degeneration. Group 1 received conventional physiotherapy and rehabilitation program (superficial heat, therapeutic massage, and exercise), whereas Group 2 received ES in addition to the conventional physiotherapy and rehabilitation program for 5 days per week for 3 weeks. Outcome measures included the House-Brackmann Scale and Facial Disability Index scores, as well as facial nerve latencies and amplitudes of compound muscle action potentials derived from the Frontalis and Orbicularis Oris muscles. The study found that ES improved functional facial movements and electrophysiologic outcome measures at the 3-month follow-up in Bell's Palsy patients.

A meta-analysis indicated that medical treatment plus ES had the lowest rate of sequelae but was more likely to lead to mild adverse events. The most seen adverse events are pain and contact dermatitis. The meta-analysis also concluded that the role of ES in Bell's Palsy treatment is still controversial due to the unstandardized parameters of frequency, intensity, pulse duration, treatment time, and the number of contractions.[33]

Alakram et al. investigated the effects of ES on facial muscles during the early phase of Bell's Palsy.[34] Sixteen patients were allocated to the control and experimental groups. Both groups were treated with heat, massage, exercises, and a home pro-

gram. The experimental group also received ES. The authors used 10 Hz frequency and 10 μs pulse duration HVPGS with optimal contraction level for 30 min. The results showed that ES during the acute phase of Bell's Palsy is safe but may not have added value over spontaneous recovery and multimodal physiotherapy.

A Cochrane review found that ES produced no benefit over a placebo after 6 months of Bell's Palsy. Low-quality comparisons of ES with medical treatment or the addition of ES to hot packs, massage, and facial exercises reported no significant differences.[35]

Gullian-Barre Syndrome

Guillain-Barré Syndrome (GBS) is an acute polyradiculoneuropathy with subacute progressive muscle weakness, sensory symptoms, and pain. ES might be considered in the acute, subacute, and even chronic phases of GBS.[36]

Harbo et al. conducted a pilot study of ES to evaluate the feasibility, safety, and effect on muscle wasting in the early phase of GBS.[37] Seventeen patients were randomized to receive ES for the right or left Quadriceps Femoris muscle. The untreated side was the control. The cross-sectional area of the muscle measured by ultrasound and isometric knee extensor strength were the primary and secondary outcome measures. In this pilot study, none of the primary or secondary efficacy parameters reached statistical significance. However, the authors concluded that ES was a safe and feasible supportive therapy in the acute and subacute phases of GBS.

In a case report, ES was applied bilaterally to improve hand closure and pinch grip in a 78-year-old male patient with GBS. The HVPGS was used for treatment. The ES protocol was 300 μs pulse duration with an amplitude between 20-30 mA and a frequency of 35 Hz, 3 s ramp up, 6 s plateau, and 3 s ramp down followed by a pause of 12 s. The stimulation sessions were carried out simultaneously for both hands for 16 weeks. After 16 weeks of daily stimulation, hand closure could be voluntarily performed. Regained opposition of the thumb to the index finger enabled improved individually defined fine motor control. The restored function remained unchanged in the follow-up at 6 months without ES.[38]

Summary

In this chapter, the purpose and effects of ES, stimulation parameters, and clinical evidence are discussed in neuropraxia. De-innervation changes are not observed in the muscles. However, complete or partial loss of motor function, paralysis, and sensory loss can be seen. ES can keep the muscles active, delay atrophy, improve blood flow, and activate sensory inputs while waiting for re-myelination. Although beneficial effects of ES were reported in some studies, some researchers thought that ES is not required for neuropraxia. The role of ES in neuropraxia is still controversial due to unstandardized parameters such as frequency, intensity, pulse duration, treatment time, and number of contractions. Considering current knowledge, it may be possible to use ES combined with other conservative treatment methods for a short period. Further studies should be planned on neuropraxia to determine the effects and optimal stimulation parameters of ES.

References

1. Robinson LR. Traumatic injury to peripheral nerves. Muscle Nerve. 2022; 66(6):661-70. doi:10.1002/mus.27706.
2. Chhabra A, Ahlawat S, Belzberg A, Andreseik G. Peripheral Nerve Injury Grading Simplified on MR neurography: As referenced to Seddon and Sunderland classifications. Indian J Radiol Imaging. 2014;24(3):217-24. doi:10.4103/0971-3026.137025.
3. Ransom SC, Shahrestani S, Lien BV, Tafreshi AR, Brown NJ, Hanst B, et al. Translational approaches to electrical stimulation for peripheral nerve regeneration. Neurorehabil Neural Repair. 2020; 34(11):979-85. doi:10.1177/1545968320962508.
4. Kırdı N. (2016), Elektroterapide temel prensipler ve klinik uygulamalar. 2nd ed. Ankara: Hipokrat Kitabevi. ISBN:978-605-9160-03-2.
5. Nelson RM, Currier DP. (1991), Clinical electrotherapy. 2nd ed. USA: Appleton&Lange. ISBN:0-8385-1334-1334.
6. de Santana Chagas AC, Wanderley D, de Oliveira Ferro JK, Alves de Moraes A, Morais de Souza FH, da Silva Tenório A, et al. Physical therapeutic treatment for traumatic brachial plexus injury in adults: A scoping review. PMR. 2022;14(1):120-50. doi:10.1002/pmrj.12566.
7. Viddeleer AR, Sijens PE, van Ooyen PMA, Kuypers PDL, Hovius SER, Oudkerk M. Sequential MR imaging of denervated and reinnervated skeletal muscle as correlated to functional outcome. Radiology. 2012;264(2):522-30. doi:10.1148/radiol.12111915.

8. Kim SJ, Hong SH, Jun WS, Choi JY, Myung JS, Jacobson JA, Lee JW, Choi JA, Kang HS. MR imaging mapping of skeletal muscle denervation in entrapment and compressive neuropathies. Radiographics. 2011;31(2):319-32. doi:10.1148/rg.312105122.
9. Kim JS, Seok HY, Kim BJ. The Significance of muscle echo intensity on ultrasound for focal neuropathy: The median- to ulnar-innervated muscle echo intensity ratio in carpal tunnel syndrome. Clin Neurophysiol. 2016;127(1):880-5. doi:10.1016/j.clinph.2015.04.055.
10. Arakawa T, Katada A, Shigyo H, Kishibe K, Adachi M, Nonaka S, et al. Electrical stimulation prevents apoptosis in denervated skeletal muscle. NeuroRehabilitation. 2010;27(2):147-54. doi:10.3233/NRE-2010-0591.
11. Tomori K, Ohta Y, Nishizawa T, Tamaki H, Takekura H. Low-Intensity electrical stimulation ameliorates disruption of transverse tubules and neuromuscular junctional architecture in denervated rat skeletal muscle fibers. J Muscle Res Cell Motil. 2010;31(3):195-205. doi:10.1007/s10974-010-9223-8.
12. Kahn J. (2000), Principles and practice of electrotherapy. 4th ed. Philadelphia, Pennsylvania: Churchill Livingstone. ISBN:0443065535.
13. Cameron MH. (1999), Physical agents in rehabilitation: from research to practice. 3rd ed. Philadelphia, USA: WB Saunders Company. ISBN:0-7216-6244-7.
14. Willand MP, Rosa E, Michalski B, Zhang JJ, Gordon T, Fahnestock M, et al. Electrical muscle stimulation elevates intramuscular BDNF and GDNF mRNA following peripheral nerve injury and repair in rats. Neuroscience. 2016;334:93-104. doi:10.1016/j.neuroscience.2016.07.040.
15. Fu T, Jiang L, Peng Y, Li Z, Liu S, Lu J, et al. Electrical muscle stimulation accelerates functional recovery after nerve injury. Neuroscience. 2020;426:179-88. doi:10.1016/j.neuroscience.2019.10.052.
16. Di Filippo ES, Mancinelli R, Marrone M, Doria C, Verratti V, Toniolo L, et al. Neuromuscular electrical stimulation improves skeletal muscle regeneration through satellite cell fusion with myofibers in healthy elderly subjects. J Appl Physiol (1985). 2017;123:501-12. doi:10.1152/japplphysiol.00855.2016.
17. Khodabukus A, Madden L, Prabhu NK, Koves TR, Jackman CP, Muoio DM, et al. Electrical stimulation increases hypertrophy and metabolic flux in tissue-engineered human skeletal muscle. Biomaterials. 2019;198:259-69. doi:10.1016/j.biomaterials.2018.08.058.
18. Nedachi T, Fujita H, Kanzaki M. Contractile C2C12 myotube model for studying exercise-inducible responses in skeletal muscle. Am J Physiol Endocrinol Metab. 2008;295:E1191-1204. doi:10.1152/ajpendo.90280.2008.
19. Christensen CS, Christensen DP, Lundh M, Dahllof MS, Haase TN, Velasquez JM, et al. Skeletal muscle to pancreatic beta-cell cross-talk: the effect of humoral mediators liberated by muscle contraction and acute exercise on beta-cell apoptosis. J Clin Endocrinol Metab. 2015;100:E1289-E98. doi:10.1210/jc.2014-4506.
20. Osorio-Fuentealba C, Contreras-Ferrat AE, Altamirano F, Espinosa A, Li Q, Niu W, et al. Electrical stimuli release ATP to increase GLUT4 translocation and glucose uptake via PI3Kgamma-Akt-AS160 in skeletal muscle cells. Diabetes. 2013;62:1519-26. doi:10.2337/db12-1066.
21. Lambernd S, Taube A, Schober A, Platzbecker B, Gorgens SW, Schlich R, et al. Contractile activity of human skeletal muscle cells prevents insulin resistance by inhibiting pro-inflammatory signaling pathways. Diabetologia. 2012;55:1128-39. doi:10.1007/s00125-012-2454-z.
22. Mancinelli R, Toniolo L, Di Filippo ES, Doria C, Marrone M, Maroni CR, et al. Neuromuscular electrical stimulation induces skeletal muscle fiber remodeling and specific gene expression profile in healthy elderly. Front Physiol. 2019;10:1459. doi:10.3389/fphys.2019.01459.
23. Wiland MP, Nguyen MA, Borschel GH, Gordon T. Electrical stimulation to promote peripheral nerve regeneration. Neurorehabil Neural Repair. 2016;30(5):490-6. doi:10.1177/1545968315604399.
24. Chu XL, Song XZ, Li Q, Li YR, He F, Gu XS, et al. Basic mechanisms of peripheral nerve injury and treatment via electrical stimulation. Neural Regen Res. 2022;17(10):2185-93. doi:10.4103/1673-5374.335823.
25. Tam SL, Archibald V, Jassar B, Tyreman N, Gordon T. Increased neuromuscular activity reduces sprouting in partially denervated muscles. J. Neurosci. 2002;21(2):654-67. doi:10.1523/JNEUROSCI.21-02-00654.2001.
26. Petrofsky J. The Effect of the subcutaneous adipose on the transfer of current through skin and into muscle. Med Eng Phys. 2008;30:1168-76. doi:10.1016/j.medengphy.2008.02.009.
27. Tanaka M, Hirayama Y, Fujita N, Fujino H. Electrical stimulation using sine waveform prevents unloading-induced muscle atrophy in the deep calf muscles of rat. Acta Histochem. 2014;116(7):1192-8. doi:10.1016/j.acthis.2014.06.009.
28. Griffin JE, Karselis TC. (1982), Physical agents for physical therapists. USA: Thomas Publisher. ISBN:0398053847.
29. Gordon T. Electrical stimulation to enhance axon regeneration after peripheral nerve injuries in animal models and humans. Neurotherapeutics. 2016;13(2):295-310. doi:10.1007/s13311-015-0415-1.
30. Yeh CC, Tsai FJ, Huang CY, Yao CH, Chen YS. Timing of applying electrical stimulation is an important factor deciding the success rate and maturity of regenerating rat sciatic nerves. Neurorehabil Neural Repair. 2010;24(8):730-5. doi:10.1177/1545968310376758.
31. Kitchen S, Bazin S. (2002), Electrotherapy evidence-based practice. 11th ed. Edinburgh, New York: Churchill Livingstone. ISBN:0443072167.
32. Tuncay F, Borman P, Taşer B, Ünlü İ, Samim E. Role of electrical stimulation added to conventional therapy in patients with idiopathic facial (Bell) palsy. Am J Phys Med Rehabil. 2015;94(3):222-8. doi:10.1097/PHM.0000000000000171.
33. Shi J, Lu D, Chen H, Shu M, Xu Y, Qian J, et al. efficacy and safety of pharmacological and physical therapies for Bell's Palsy: A bayesian network meta-analysis. Front Neurol. 2022;13:868121. doi:10.3389/fneur.2022.868121.
34. Alakram P, Puckree T. Effects of Electrical stimulation on house-brackmann scores in early Bell's Palsy. Physiother Theory Prac. 2010;26(3):160-6. doi:10.3109/09593980902886339.
35. Teixeira LJ, Valbuza JS, Prado GF. Physical therapy for Bell's Palsy (idiopathic facial paralysis). Cochrane Database Syst Rev. 2011;12:CD006283. doi:10.1002/14651858.CD006283.pub3.
36. Khan F, Amatya B. Rehabilitation interventions in patients with acute demyelinating inflammatory polyneuropathy: A systematic review. Eur J Phys Rehabil Med. 2012;48(3):507-22. PMID:22820829.
37. Harbo T, Markvardsen LK, Hellfritzsch MB, Severinsen K, Nielsen JF, Andersen H. Neuromuscular electrical stimulation in early rehabilitation of Guillain-Barré syndrome: A pilot study. Muscle Nerve. 2019;59(4):481-4. doi:10.1002/mus.26396.
38. Bersch I, Fridén J. Long-term effect of task-oriented functional electrical stimulation in chronic Guillain Barré syndrome-a single-subject study. Spinal Cord Ser Cases. 2021;7(1):53. doi:10.1038/s41394-021-00419-0.

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Axonotmesis

ZELIHA OZLEM YURUK

Introduction

Axonotmesis is a term that describes the range of peripheral nerve injuries (PNI) that are more severe than neurapraxia and less severe than the transection of the nerve, as observed in neurotmesis.[1] This injury can be caused by blunt injury, fractures, dislocations, contusions, or stretch or crush injuries.[2]

Axonotmesis was classified into 3 stages according to Sunderland.[3] Axon loss is seen in grade II lesions. However, the endoneurium is intact and recovery is slower in grade II lesions. Injuries of the grade III-IV are characterized by additional loss of adjacent connective tissue layers from inner to outermost. The damage of the endoneurium in grade III injury disrupts the scaffold by which axons elongate for regeneration and causes neuroma formation. Variable outcomes were seen in the grade III lesions. Neuroma formation and inhibited regeneration occur in grade IV injuries. Recovery is poor due to perineurial damage. However, the epineurium remains intact in grade IV injury. Surgical repair is required for promoting regeneration in neuromas (grade III-IV).[4]

In axonotmesis, severe damage to the axons and Wallerian Degeneration occurs. Conduction block occurs immediately at the nerve injury site, followed by an irreversible loss of excitability, first at the neuromuscular junction and then at the distal nerve segment. The conduction distal to the lesion disappears after 24-72 hours. During Wallerian Degeneration, both injured ends retract with the proximal end, generally proceeding with degeneration to the closest node of Ranvier. However, the distal end degenerates completely. Following the degeneration of the proximal stump, the Schwann cell converts to a regenerative phenotype and releases growth factors. An axonal growth cone begins to develop at the distal end of the proximal stump and is distally guided by actin and myosin. The optimal outcome is to contact the endoneurial conduit of the degenerated distal nerve segment and grow along the original trajectory to re-innervate the end organs. The growth of a proximally damaged nerve is 2-3 mm/day and 1-2 mm/day for distal segments.[5]

The prognosis of axonotmesis relies on the underlying condition of the patient and the nature of the injury. In the best circumstances, the nerve can regenerate by axonal branching or through the expansion of the proximal segment of the damaged nerve. Nerve regeneration becomes more likely with limited damage to axons and structural units of the neural trunk. Spontaneous regeneration is still possible with axonotmesis if the perineurium and epineurium provide an intact tubule. Distal lesions have a better prognosis. However, nerve regeneration does not equate to functional recovery. The function also depends on achieving the regenerated axons with the end organ. Muscle architecture and motor endplates are considered viable for up to 1-year post-injury.[2,6,7]

Prognostic factors for regain of function include a patient's baseline health, the mechanism of injury, the degree of injury, the length of the nerve

gap, the type of injury, the nerve(s) involved (the spinal accessory nerve is most robust), the location of injury along the nerve (distal injuries have a better prognosis), concomitant injuries, the timing to surgery, the type of surgery, and the patient's age.[8,9]

Complete or partial loss of motor functions (loss of voluntary and reflex contraction of the muscle and progressive muscle atrophy), loss of sensory functions (muscle spindle atrophies, Meissner, Pacinian, and Merkel atrophy, some other receptors are lost), autonomic loss, and cortex plasticity occur after axonotmesis.[10] Positive sharp waves are seen after 1-2 weeks, and fibrillation potentials are also seen after 2-3 weeks of axonotmesis in electromyographic (EMG) evaluation.[11]

Patient Evaluation

Before the clinical decision-making for the physiotherapy and rehabilitation program and ES physical examination is essential. Physiotherapists perform electrodiagnostic tests and evaluate muscle strength, range of motion, dermatome, anthropometric properties, posture, viscoelastic (tone, elasticity, thixotropy) properties of the muscles, pain, and autonomic functions in patients with PNI.[12] The Faradic Excitability Test should be routinely performed for follow-up of the recovery process.[13]

Technology is helpful in screening nerve injuries. Nerve conduction studies help to determine the location, severity, and progression of nerve injury via motor and sensory conduction studies. However, electrodiagnostic studies may have normal results 2-3 days post-injury and may not reveal the full extent of the injury until 2-3 weeks post-injury. Additional diagnostic techniques such as ultrasound, magnetic resonance myelography, myelography, and magnetic resonance neurography are needed for detailed assessment by clinicians.[2]

Electrical Stimulation (ES) for Axonotmesis

The Effects of ES in Axonotmesis

The effects of ES on axonotmesis should be considered in terms of muscle and nerve recovery.

The Effects of ES on De-Innervated Muscles

De-innervation atrophy is a much more complex condition than atrophy due to inactivity. Muscle plasticity is affected by many neural factors. The de-innervated muscle is neither voluntary nor reflexively active because it has atrophied and weakened. However, an appropriate ES protocol can achieve contractions of the de-innervated muscle and prevent the decrement associated with de-innervation. In axonotmesis, the muscle is stimulated by the sarcolemma, not by the neurolemma. This method is called Electrical Muscle Stimulation (EMS).[13] The EMS prevents atrophy and keeps the muscle as healthy as possible until re-innervation.[14,15]

In an animal study, de-innervated muscles were stimulated with 600 contractions for 5 days a week after nerve injury and repair. The study showed that the stimulated muscles had a higher motor unit number. It was determined that muscle-derived neurotrophic factors [Brain-Derived Neurotrophic Factor (BDNF), Glial Cell Line-Derived Neurotropic Factor (GDNF)] and messenger ribonucleic acid (mRNA) levels were high in stimulated muscles. The authors concluded that the EMS of de-innervated muscles could delay atrophy and promote re-innervation following nerve damage.[16]

Wiland et al. evaluated the efficacy of EMS over 6 months following Tibial nerve transection and immediate repair.[17] Rats were divided into 6 groups based on treatment (EMS or no treatment) and duration (1, 2, or 3 months). In the EMS group, Gastrocnemius muscle was electrically stimulated with 600 contractions per day 5 days a week. Daily stimulated muscles had significantly greater numbers of re-innervated motor units with smaller average motor unit sizes. Most of the muscle endplates were reinnervated by a single axon arising from a nerve trunk with significantly fewer numbers of terminal sprouts in the EMS group, the numbers being small. Although muscle mass and force were unchanged, EMS improved behavioral outcomes. They demonstrated that EMS using a moderate stimulation paradigm immediately following nerve transection and repair enhances electrophysiological and behavioral recovery.

An experimental study from Ashley et al. showed that the size and function of de-innervated muscles could be restored partially by an intensive daily regime of EMS for 6-10 weeks, initiated at the earliest possible stage after post-axon damage injury in rabbits.[18] Clinical experience has shown that whenever stimulation has been discontinued, the muscles quickly revert to their former wasted condition. They found no evidence of stimulation-induced damage, even after stimulating for 6-10 weeks.

A controlled experimental study investigated the features of apoptosis during de-innervation and re-innervation after experimental nerve injury and identified the effect of EMS on skeletal muscle morphology and apoptosis-related factors. In the study, rat sciatic nerves were de-innervated completely or partially, and EMS was applied to the Gastrocnemius muscle for 2 weeks. The stimulation parameters were as follows: 1 Hertz (Hz) frequency biphasic triangular impulses, 10 milliseconds (ms) stimulation duration, 5 milliamperes (mA) stimulus intensity, and for 30 minutes (min)/day for 14 sessions. In conclusion, apoptosis in completely de-innervated muscles was greater than that in partially de-innervated muscles 4 weeks after injury. The apoptotic activity decreased during re-innervation. EMS can delay muscle atrophy and reduce apoptosis after partially de-innervated.[19]

The Effects of ES on Regeneration of the Nerves

Experimental studies have demonstrated ES to be a promising adjunctive therapy to enhance axonal regeneration and functional recovery following decompression, direct neurorrhaphy, and repair using grafts. ES acts through retrograde action potentials to increase cyclic adenosine monophosphate (cAMP) levels in the soma, which drives the increased expression of BDNF. Although the exact mechanism is not completely clear, ES promotes axonal outgrowth and survival.[20] Distance from the injury to the original target, slow regeneration of axons across the injury site, progressive decline in the regenerative capacity of axotomized neurons, failure of chronically de-innervated Schwann cells to support axonal regeneration, and muscle atrophy are considered factors limiting recovery.[21]

Extensive animal studies have reported the ability of brief intraoperative ES to enhance functional regeneration after PNI. The 1 hour, 20 Hz ES of the nerve after nerve repair enhances the early expression of BDNF and pro-regenerative associated genes and facilitates that sensory and motor axons grow faster across the suture site after transection of the Femoral nerve in rats.[22,23] In a recent animal study, the effects of ES on Wallerian Degeneration were investigated. It used a rat model of Sciatic nerve transection and provided ES at the distal stump of the injured nerve. ES was applied immediately after Sciatic nerve clipping, and two hooked titanium wire electrodes were hooked tensionless on the distal end of the injured nerve. Biphasic current [20 Hz, 100 microseconds (μs)] for 1 hour was used. The current intensity for each rat was adjusted to just above that required to induce a visible Gastrocnemius muscle twitch. The results showed that ES significantly promoted the degeneration and clearance of axons and the dedifferentiation of Schwann cells. It upregulated the expression of BDNF and Nerve Growth Factor (NGF) and increased the number of monocytes and macrophages. Evaluation of nerves bridged using silicone tubing after transection showed that ES accelerated early axonal and vascular regeneration while delaying Gastrocnemius muscle atrophy.[24]

In addition to recent studies supporting the encouraging effects of ES on nerve regeneration, some studies showed that the increased neural activity on sprouting remains unclear and controversial. In an experimental study, Tam et al. used 20 Hz frequency ES for 8 hours daily on the Tibialis Anterior, medial Gastrocnemius, Plantaris, and Soleus muscles.[25] The neural activity reduced motor unit enlargement. The authors indicated that increased neuromuscular activity was not recommended for rehabilitation immediately after motoneuron injury or in the early stages of motoneuron disease.

Pinheiro-Dardis et al. investigated the effects of ES on neuromuscular recovery after nerve crush injury in rats.[26] The authors showed that the ES impaired neuromuscular recovery at 14 days post-de-

nervation. Muscle hypo-excitability was accentuated by ES at 6- and 14-days post-denervation. Although ES reduced the accumulation of atrogin-1, muscle RING-finger protein-1 (MuRF1), and myoblast determination protein (myoD) mRNAs, it increased muscle atrophy. The gene expression of neural cell adhesive molecules (N-CAM) protein was altered by ES. The authors concluded that ES could delay the re-innervation process by modulating factors related to neuromuscular junction stability and organization and inducing dysfunction, hypo-excitability, and muscle atrophy. There were also claims that ES reduced acetylcholine (ACH) sensitivity because ES mimics physiological contractions. The number of contractions per day is insufficient. Only superficial fibers are stimulated by ES. High current intensity is needed to activate deep fibers.[11] The advantages and disadvantages of ES on de-innervated muscles and regeneration of the nerve are summarized in Table 28.1.

Table 28.1 Advantages and disadvantages of ES on re-innervation.[11,17,21,24-27]

Advantages of Electrical Stimulation	Disadvantages of Electrical Stimulation
Reduces venous stasis and edema	Causes trauma to de-innervated muscles (overstimulation)
Increases muscle-derived neurotrophic factors (BDNF, GDNF, NGF)	Decreases production of neural cell adhesive molecules (N-CAM) and acetylcholine (ACH) sensitivity
Delays atrophy and fibrosis	Delays or inhibits collateral sprouting and re-innervation
Keeps the muscle active while waiting for regeneration	Mimics the voluntary contraction however not has the same physiological mechanism of exercise
Maintains the joint range of motion	No added benefit for trophic condition
Enhances the sensory inputs and maintains the relationship between the cortex and peripheral organs	The number of contractions per day is insufficient.
Reduces the scar formation	Only superficial fibers are stimulated by ES. High current intensity is needed to stimulate deep fibers.

ES Protocol for Axonotmesis

Two ES techniques are used for axonotmesis: EMS or intraoperative brief ES on the injury site.[18,21] Intraoperative brief ES is a recent technique that has been shown to be effective in studies. Biphasic current (20 Hz, 100 μs) for 1 hour with implanted electrodes is used.[24] Although the technique seems effective for regeneration, it is not practical for physiotherapists because ES is used only after nerve repair and is an invasive technique.

As mentioned before, if the muscle is de-innervated, it is stimulated via sarcolemma. This is called EMS. The EMS is a traditional technique for PNI. It can be used for completely and partially de-innervated muscles. Because of the physiological changes of completely de-innervated muscles, only modified Galvanic current can elicit a contraction response. The pulse duration should be above 100 ms (300-600 ms) and the pulse interval should be two times of pulse duration (200-1000 ms).[11,13]

If re-innervation begins, the muscles can respond to the Faradic current. The Faradic Excitability Test should be routinely performed for re-innervation. The Faradic current is an alternating biphasic current with a short pulse duration. Therefore, it cannot be effective in complete de-innervation. If the muscle does not give a contraction response for the Faradic Excitability Test, the Galvanic current should be used for EMS. In partial de-innervation the Faradic current can also be used. Alternating currents are comfortable for patients and can elicit greater muscle torque. Tanaka et al. suggested that ES using alternating current has the potential to become an effective therapeutic intervention to prevent deeper muscle atrophy.[28] The frequency and pulse duration of the EMS should be determined according to the fiber type distribution of the muscle. If it is a slow-twitch muscle, a frequency below 40 Hz should be applied. If it is a fast-twitch muscle 50-70 Hz should be chosen. The pulse duration of the Faradic current is 0.1-1 ms. This value is equivalent to chronaxie.[11,13]

There are points to be considered in practice. Due to the elongated sarcomere length of the de-innervated muscle, the length of the muscle should be shortened while performing EMS. In addition, the patient should monitor muscle contractions so that the stimulation of the somatosensory field is strengthened. Applications should not be too long due to the low oxidative energy mechanism and should be done 3 days a week for maximum 8 weeks.[29-32] It is recommended that the current amplitude be as high as is tolerable and capable of stimulating tetanic contraction of the target muscle. The atrophied and de-innervated muscles are vulnerable to trauma. Excessive EMS can cause trauma. Higher current amplitude elicits strong and deep muscle contractions. However, higher amplitudes also cause trauma. The long pulse duration and high current amplitude can be painful if the sensation is intact. However, the goal is to maximize the contraction response while minimizing pain.

Physiotherapists should avoid fatigue when using EMS. In order not to create oxidative stress in the muscle, the application should be stopped when signs of fatigue are seen.[33] The 200 muscle contractions per day are sufficient to prevent muscle fiber atrophy. However, to prevent fatigue, 90 contractions of each muscle should be performed as 3 sets of 30-30-30 or 2 sets of 45–45 contractions. The treatment sessions are planned 3-5 times/week for approximately 8 weeks. The EMS should be started after nerve re-innervation begins and should be terminated when active movement begins.[34,35]

The electrode size and type depend on the size of the muscle to be stimulated and the intensity of the contraction to be elicited. Small or pen electrodes can be used to localize stimulation to small muscles. Larger electrodes are needed to stimulate larger muscles and muscle groups. One electrode may be placed over the most excitable part of a muscle. The second electrode is placed at a convenient location near the muscle being treated. EMS should be performed carefully if there is a co-contraction. The antagonist should not contract simultaneously.[11,13]

Table 28.2 Parameter settings for EMS in axonotmesis.[11,13,36]

Current type/ waveform	Modified Galvanic current (monophasic rectangular or triangular) Pulsed alternating current (asymmetric biphasic)
Pulse/cycle duration	>100 ms (Modified Galvanic current) 0.1-1 ms (Faradic current)
Amplitude	Optimal tolerated contraction
Pulse rate (Frequency)	None (Modified Galvanic current) <40 Hz for slow-twitch muscles (Alternating current) 50-70 Hz for fast-twitch muscles
Ramp up/ramp down	None (Modified Galvanic current) 1/3 seconds (s) (Alternating current)
On time (Duty cycle)/ Off time	1:2 (Modified Galvanic current) 1:9 s (%10) (Alternating current) 2-5 s/2-25s
Modulation	None
Treatment duration	3 sets of 30-30-30 or 2 sets of 45–45 contractions <30s
Frequency of sessions	3-5 times/week, approximately 8 weeks
Polarity	Cathode (Modified Galvanic current) None (Alternating current)
Electrode placement	Bipolar or monopolar technique Parallel to fibers

Before the treatment, the skin should be cleaned with an alcohol-based wipe to remove skin debris, sweat, and dirt. Because the treatment duration is so long, skin irritation and contact eczema can be seen with ES. If these side effects occur, the physiotherapist gives a break to the treatment. Contraindications for EMS of denervated muscle are the same as for NMES.[36]

Clinical Evidence of ES in Axonotmesis

Obstetric Brachial Plexus Palsy (OBPP)

EMS has been used for many years to excite paretic muscle groups of the extremity affected by OBPP. One reported benefit of EMS is that the infant becomes more aware of the extremity affected by the OBPP. Because EMS can activate the muscle spindles and maintain sensory input.[37] It also keeps the muscle active while waiting for regeneration and improves blood flow. However, some studies con-

cluded that the increased neuromuscular activity should not be recommended immediately after motor neuron injury or in the early stages of motor neuron diseases. The key is the time frame in which to apply activity or stimulation. Certainly, EMS should not be applied to muscles that are not demonstrating muscle motor function, nor should this technique be utilized during the initial/acute phase of the OBPP. When muscles demonstrate re-innervation, there may be an indication for EMS.[25,38]

Although EMS applications are recommended for muscles with innervation in the treatment of OBBP, the age at which the application will be performed, the method of application, and the current parameters have not been clarified. More studies are needed in the pediatric patient group to clarify the application method and current parameters.[39] Elnaggar et al. evaluated the effects of ES during weight-bearing exercises on shoulder function and bone mineral density in children with OBPP aged between 3 and 5 years.[40] In the randomized controlled trial, 42 children with OBPP were recruited. They were randomly assigned either to the control group (received an exercise program) or the study group (exercise program and EMS during weight bearing). One channel was used to stimulate shoulder flexion, elbow extension, and wrist and finger extension (one electrode was placed on the anterior fiber of the Deltoideus muscle and the other electrode was attached to the common extensor origin at the lateral epicondyle of the elbow joint. An alternating symmetrical biphasic current with 10 Hz was used. When the tapping sensation was tolerated, the frequency was increased to 30 Hz to produce the muscle contraction. The intensity was increased gradually and very slowly according to each child's tolerance only when the current was on. The duty cycle (on/off time) was initially set for 10 s on and 20 s off, and the cycle was set at 15 s on and 15 s off, when the previous setting was comfortable and showed no signs of fatigue, EMS was applied for a total of 15 min. It was found that EMS during weight-bearing exercises is an effective and simple method to improve shoulder function and bone mineral density in children with OBPP.

Cauda Equina Injury

Mödlin et al. evaluated the effects of EMS on de-innervated muscles in spinal cord-injured humans.[41] In the clinical study, 27 individuals with cauda equina lesions were included. After initial examinations, patients started their EMS treatment for Quadriceps Femoris muscle, Gluteal muscle, and Gastrocnemius muscles bilaterally. The EMS was applied by a specially developed stimulator with large electrodes (~200 cm^2) in sponge bags which were placed over the muscles. After 4-6 months, when the skin had adapted to EMS, the electrodes on the thighs were applied directly to the skin with gel. Patients were controlled every 4-8 weeks, and the stimulation protocol was adapted. Biphasic rectangular impulses with 2 Hz, 120-150 ms pulse duration, 5 s on, and 2 s off were used. The training was performed once a day for 15 min in the beginning and then extended to 20-30 min. After some months of regular stimulation, it was possible to reduce the pulse duration to 70 ms (5 Hz) and 40 ms. With a 40 ms impulse duration and a pulse duration of 10 ms (20 Hz) and bursts of 2 s (2 s pause), tetanic contractions could be elicited. A marked increase in muscle mass and quality was observed. The trophic situation of the de-innervated lower limbs improved obviously.

Kern et al. investigated the effects of EMS in a patient with long-standing Quadriceps Femoris muscle denervation.[42] Stimulation started 18 months after injury. The authors stimulated the Quadriceps Femoris muscle with biphasic rectangular current (Pulse duration of 40-120 ms, frequency of 20 Hz, and 2 s on, 2 s off). The treatment was done for 15 min per day, 5 days per week. Biopsies revealed evidence of both growth and regeneration of myofibers. The results suggest that EMS may offer a route to the future development of mobility aids in patients with lower motor neuron lesions.

Nerve Compression

Carpal tunnel syndrome (CTS) is the most prevalent compression lesion and initially presents as recurrent nocturnal paresthesia and dysesthesia. The progression of CTS may cause loss of sen-

sation, and ultimately, thenar motor function in moderate to severe cases. For a CTS patient with mild symptoms and no axonal loss, nonsurgical treatment options are standard. In later stages, CTS symptoms of axonal loss are present, thus necessitating the surgical release of the transverse carpal ligament. Carpal tunnel release surgery is known to be highly effective, but lack of symptom improvement and prolonged recovery may occur due to extensive axonal loss before treatment. Therapeutic strategies to accelerate or increase Median nerve regeneration in chronic CTS would undoubtedly have profound implications.[4]

Some studies used ES during surgical repair for one time with an external stimulator. The results showed that ES applied to injured peripheral nerves during surgical repair can enhance nerve recovery-both sensory and motor functions. However, it is not practical to use the technique.[43,44] In 2010, Gordon et al. investigated ES as a surgical adjunct in a randomized controlled trial of patients who underwent carpal tunnel release surgery.[43] Patients with chronic Median nerve compression neuropathy, evidenced by clinical signs of thenar muscle atrophy and at least 50% axonal loss on motor unit number estimation (MUNE), were enrolled. Median nerve ES was delivered with wire electrodes within 15 min of carpal tunnel release (Median nerve decompression) for 1 hour at maximal patient tolerance (20 Hz, 4–6 Volts). Compared to the 10 control subjects without significant increases in MUNE until 12 months post-surgery, the 11 subjects who received median nerve ES had significantly increased MUNE by 6–8 months post-surgery and achieved normal MUNE by 12 months post-surgery. The use of Median nerve ES enabled all motor neurons to regenerate and achieve thenar muscle re-innervation more rapidly following Median nerve decompression. ES reduced terminal motor latency by 3 months, whereas no significant reduction was seen in control subjects following surgery. Sensory nerve action potential (SNAP) amplitude of Median nerves increased by 6–8 months with ES but required 12 months for the control nerves, and SNAP conduction velocity increased by 3 months in ES patients versus 6–8 months in the control nerves. Despite study limitations such as a small sample size, lack of blinding, and no sham negative control, this pioneering study provided proof of principle that a single session of ES for 1 hour at 20 Hz was clinically translatable and accelerated target re-innervation in chronic compression neuropathy.

In 2015, ES was investigated in a double-blinded, randomized controlled trial of 31 patients with transected digital nerves who underwent epineural repair and immediate ES in the recovery room. Compared to sham stimulation, patients who received digital nerve ES for 1 hour (20 Hz, up to 30 Volt) had significantly more rapid recovery of multimodal sensory function. After 6 months, cold and warmth detection thresholds, static 2-point discrimination, and Semmes Weinstein monofilament testing all reached normal thresholds in ES patients, whereas patients with sham-stimulated digital nerves still had abnormal values. No statistically significant differences in functional measures were detected, with both groups of patients demonstrating comparable improvement in the functionality. This study demonstrated that ES accelerates sensory recovery after neurotmetic (nerve transection) injury. The authors emphasized the translatability of ES into the clinical realm of peripheral nerve surgery and highlighted the cost savings benefits of a single session of ES versus long-term pharmacologic treatments and prolonged rehabilitation. Limitations of this study included the lack of objective evaluation measures such as nerve conduction studies, several follow-up times (60 days) within each follow-up period, and an early study endpoint inadequate to ascertain final between-group differences, as functional recovery may require more than 6 months in the sham ES control patients.[45] These prospective, randomized clinical trials represent Level I evidence for the benefit of a single session of low-frequency perioperative ES for PNI in humans requiring surgical treatment and demonstrate the logistical feasibility of administering ES perioperatively or immediately postoperatively in the recovery room.[43,44]

Summary

In this chapter, the purpose and effects of ES, stimulation parameters, and clinical evidence in axonotmesis are discussed. Two ES techniques are used for axonotmesis: EMS or intraoperative brief ES on the injury site.[18,21] Clinical evidence suggests that 1 hour of 20 Hz ES applied intraoperatively following repair can improve patient recovery.[24] Although the technique seems effective for regeneration, it is not practical for physiotherapists because the ES is used only after nerve repair and is an invasive technique. The other technique is EMS. There are experimental and clinical studies on EMS in the literature. Although past studies have shown the harmful effects of EMS, recent studies have supported the EMS. The EMS should be started after nerve re-innervation begins and should be terminated when active movement begins.[34,35] First of all, alternating currents should be preferred. If no contraction response is obtained from the muscle, a modified Galvanic current should be preferred. The patient's tolerance and the amount of treatment should also be considered. Further studies should be planned on axonotmesis to determine the optimal stimulation parameters of ES. Shorter application times, more convenient devices, and other indications could be evaluated. Thus, continued research efforts are ongoing to provide evidence to identify optimal ES delivery paradigms. Additionally, novel biocompatible and bioresorbable devices with ES capabilities may be available in the near future and provide new perspectives on the long-term application of ES.[20]

References

1. Wade SM, Nesti LJ, Cook GA, Bresner JS, Happel JP, Villahermosa AJ, et al. Managing complex peripheral nerve injuries within the military health system: A multidisciplinary approach to treatment, education, and research at Walter Reed national military medical center. Mil Med. 2020;185(5-6):e825-e830. doi:10.1093/milmed/usz415.
2. Smith BW, Sakamuri S, Spain DA, Joseph JR, Yang LJ, Wilson TJ. An update on the management of adult traumatic nerve injuries-replacing old paradigms: A review. J Trauma Acute Care Surg. 2019;86(2):299-306. doi:10.1097/TA.0000000000002081.
3. Chhabra A, Ahlawat S, Belzberg A, Andreseik G. Peripheral nerve injury grading simplified on MR neurography: As referenced to Seddon and Sunderland classifications. Indian J Radiol Imaging. 2014;24(3):217-24. doi:10.4103/0971-3026.137025.
4. Ransom SC, Shahrestani S, Lien BV, Tafreshi AR, Brown NJ, Hanst B, et al. Translational approaches to electrical stimulation for peripheral nerve regeneration. Neurorehabil Neural Repair. 2020; 34(11):979-85. doi:10.1177/1545968320962508.
5. Girouard MP, Bueno M, Julian V, Drake S, Byrne AB, Fournier AE. The molecular interplay between axon degeneration and regeneration. Dev Neurobiol. 2018;78(10):978-90. doi:10.1002/dneu.22627.
6. Kamble N, Shukla D, Bhat D. Peripheral nerve injuries: Electrophysiology for the neurosurgeon. Neurol India. 2019;67(6):1419-22. doi:10.4103/0028-3886.273626.
7. Menorca RM, Fussell TS, Elfar JC. Nerve physiology: mechanisms of injury and recovery. Hand Clin. 2013;29(3):317-30. doi:10.1016/j.hcl.2013.04.002.
8. Rasulić L, Savić A, Vitošević F, Samardžić M, Živković B, Mićović M, et al. Iatrogenic peripheral nerve injuries-surgical treatment and outcome: 10 years' experience. World Neurosurg. 2017;103:841-51.e6. doi:10.1016/j.wneu.2017.04.099.
9. Bhandari PS. Management of peripheral nerve injury. J Clin Orthop Trauma. 2019;10(5):862-6. doi:10.1016/j.jcot.2019.08.003.
10. Robinson LR. Traumatic injury to peripheral nerves. Muscle Nerve. 2022;66(6):661-70. doi:10.1002/mus.27706.
11. Nelson RM, Currier DP. (1991), Clinical electrotherapy. 2nd ed. USA: Appleton&Lange. ISBN:0-8385-1334-1334.
12. de Santana Chagas AC, Wanderley D, de Oliveira Ferro JK, Alves de Moraes A, Morais de Souza FH, da Silva Tenório A, et al. Physical therapeutic treatment for traumatic brachial plexus injury in adults: A scoping review. PMR. 2022;14(1):120-50. doi:10.1002/pmrj.12566.
13. Kırdı N. (2016), Elektroterapide temel prensipler ve klinik uygulamalar. 2nd ed. Ankara: Hipokrat Kitabevi. ISBN:978-605-9160-03-2.
14. Arakawa T, Katada A, Shigyo H, Kishibe K, Adachi M, Nonaka S, et al. Electrical stimulation prevents apoptosis in denervated skeletal muscle. NeuroRehabilitation. 2010;27(2):147-54. doi:10.3233/NRE-2010-0591.
15. Tomori K, Ohta Y, Nishizawa T, Tamaki H, Takekura H. Low-intensity electrical stimulation ameliorates disruption of transverse tubules and neuromuscular junctional architecture in denervated rat skeletal muscle fibers. J Muscle Res Cell Motil. 2010;31(3):195-205. doi:10.1007/s10974-010-9223-8.
16. Willand MP, Rosa E, Michalski B, Zhang JJ, Gordon T, Fahnestock M, et al. Electrical muscle stimulation elevates intramuscular BDNF and GDNF mRNA following peripheral nerve injury and repair in rats. Neuroscience. 2016;334:93-104. doi:10.1016/j.neuroscience.2016.07.040.
17. Wiland MP, Chiang CD, Zhang JJ, Stephen WP, Kemp SWP, Borschel GH, et al. Daily electrical muscle stimulation enhances functional recovery following nerve transection and repair in rats. Neurorehabil Neural Rep. 2015;29(7):690-700. doi:10.1177/1545968314562117.
18. Ashley Z, Sutherland H, Russold MF, Lanmüller H, Mayr W, Jarvis JC, et al. Therapeutic stimulation of denervated muscles: The influence of pattern. Muscle Nerve. 2008;38:875-86. doi:10.1002/mus.21020.
19. Lim JY, Ryo T. Effect of electromyostimulation on apoptosis-related factors in denervation and re-innervation of rat skeletal muscles. Muscle Nerve. 2010;42:422-30. doi:10.1002/mus.21719.
20. Juckett L, Saffari TM, Ormseth B, Senger JL, Moore AM. The effect of electrical stimulation on nerve regeneration following peripheral nerve injury. Biomolecules. 2022;12:1856. doi:10.3390/biom12121856.

21. Gordon T, Brushart TM, Amirjani N, Chan KM. he potential of electrical stimulation to promote functional recovery after peripheral nerve injury-comparisons between rats and humans. Acta Neurochir. 2007;100:3-11. doi:10.1007/978-3-211-72958-8_1.
22. Geremia NM, Gordon T, Brushart TM, Al-Majed AA, Verge VM. Electrical stimulation promotes sensory neuron regeneration and growth-associated gene expression. Exp. Neurol. 2007;205:347-59. doi:10.1016/j.expneurol.2007.01.040.
23. Al-Majed AA, Tam SL, Gordon T. Electrical stimulation accelerates and enhances expression of regeneration-associated genes in regenerating rat femoral motoneurons. Cell. Mol. Neurobiol. 2004;24:379-402. doi:10.1023/b:cemn.0000022770.66463.f7.
24. Li X, Zhang T, Li C, Xu W, Guan Y, Li X, et al. Electrical stimulation accelerates Wallerian degeneration and promotes nerve regeneration after sciatic nerve injury. Glia. 2023;71(3):758-74. doi:10.1002/glia.24309.
25. Tam SL, Archibald V, Jassar B, Tyreman N, Gordon T. Increased neuromuscular activity reduces sprouting in partially denervated muscles. J Neurosci. 2001;15;21(2):654-67. doi:10.1523/JNEUROSCI.21-02-00654.2001.
26. Pinheiro-Dardis CM, Erbereli BT, Gigo-Benato D, Castro PATS, Russo TL. Electrical stimulation delays re-innervation in denervated rat muscle. Muscle Nerve. 2017;56(6):E108-E118. doi:10.1002/mus.25589.
27. Dow DE, Cederna PS, Hassett CA, Dennis RG, Faulkner JA. Electrical stimulation prior to delayed re-innervation does not enhance recovery in muscles of rats. Restor Neurol Neurosci. 2007;25(5-6):601-10. PMID:18334775.
28. Tanaka M, Hirayama Y, Fujita N, Fujino H. Electrical stimulation using sine waveform prevents unloading-induced muscle atrophy in the deep calf muscles of rat. Acta Histochem. 2014;116(7):1192-8. doi:10.1016/j.acthis.2014.06.009.
29. Kern H, Salmons S, Mayr W, Rossini K, Carraro U. Recovery of long-term denervated human muscles induced by electrical stimulation. Muscle Nerve. 2005;31(1):98-101. doi:10.1002/mus.20149.
30. Qin L, Appell HJ, Chan KM, Maffulli N. Electrical stimulation prevents immobilization atrophy in skeletal muscle of rabbits. Arch Phys Med Rehabil. 1997;78(5):512-7. doi:10.1016/s0003-9993(97)90166-0.
31. Peviani SM, Russo TL, Durigan JL, Vieira BS, Pinheiro CM, Galassi MS, et al. Stretching and electrical stimulation regulate the metalloproteinase-2 in rat denervated skeletal muscle. Neurol Res. 2010;32(8):891-6. doi:10.1179/174313209X459093.
32. Gigo-Benato D, Russo TL, Geuna S, Domingues NR, Salvini TF, Parizotto NA. Electrical stimulation impairs early functional recovery and accentuates skeletal muscle atrophy after sciatic nerve crush injury in rats. Muscle Nerve. 2010;41(5):685-93. doi:10.1002/mus.21549.
33. Griffin JE, Karselis TC. (1982), Physical agents for physical therapists. USA: Charles C. Thomas Publisher. ISBN:0398053847.
34. Gordon T. Electrical stimulation to enhance axon regeneration after peripheral nerve injuries in animal models and humans. Neurotherapeutics. 2016;13(2):295-310. doi:10.1007/s13311-015-0415-1.
35. Yeh CC, Tsai FJ, Huang CY, Yao CH, Chen YS. Timing of applying electrical stimulation is an important factor deciding the success rate and maturity of regenerating rat sciatic nerves. Neurorehabil Neural Repair. 2010;24(8):730-5. doi:10.1177/1545968310376758.
36. Kitchen S, Bazin S. (2002), Electrotherapy evidence-based practice. 11th ed. Edinburgh, New York: Churchill Livingstone. ISBN:0443072167.
37. Okafor UA, Akinbo SR, Sokunbi OG, Okanlawon AO, Noronha CC. Comparison of electrical stimulation and conventional physiotherapy in functional rehabilitation in Erb's palsy. Nig Q J Hosp Med. 2008;18(4):202-5. doi:10.4314/nqjhm.v18i4.45029.
38. Shepherd RB. (1999), Brachial plexus injury. In: Campbell SK editor. Decision making in pediatric neurologic physical therapy. Philadelphia: Churchill Livingstone. ISBN:978-0443079238.
39. Ramos LE, Zell JP. Rehabilitation program for children with brachial plexus and peripheral nerve injury. Semin Pediatr Neurol. 2000;7(1):52-57. doi:10.1016/s1071-9091(00)80010-8.
40. Elnaggar RK. Shoulder function and bone mineralization in children with obstetric brachial plexus injury after neuromuscular electrical stimulation during weightbearing exercises. Am J Phys Med Rehabil. 2016;95:239-47. doi:10.1097/PHM.0000000000000449
41. Mödlin M, Forstner C, Hofer C, Mayr W, Richter W, Carraro U, Protasi F, Kern H. Electrical stimulation of denervated muscles: First results of a clinical study. Artif Organs. 2005;29(3):203-6. doi:10.1111/j.1525-1594.2005.29035.x.
42. Kern H, Salmons S, Mayr W, Rossini K, Carraro U. Recovery of long-term denervated human muscles induced by electrical stimulation. Muscle Nerve. 2005;31(1):98-101. doi:10.1002/mus.20149.
43. Gordon T, Amirjani N, Edwards DC, Chan KM. Brief post-surgical electrical stimulation accelerates axon regeneration and muscle re-innervation without affecting the functional measures in carpal tunnel syndrome patients. Exp Neurol. 2010;223:192-202. doi:10.1016/j.expneurol.2009.09.020.
44. Piccinini G, Cuccagna C, Caliandro P, Coraci D, Germanotta M, Pecchioli C, et al. Efficacy of electrical stimulation of denervated muscle: A multicenter, double-blind, randomized clinical trial. Muscle Nerve. 2020;61:773-8. doi:10.1002/mus.26880.
45. Wong JN, Olson JL, Morhart MJ, Chan KM. Electrical stimulation enhances sensory recovery: A randomized controlled trial. Ann Neurol. 2015;77(6):996-1006. doi:10.1002/ana.24397.

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Neurotmesis

ZELIHA OZLEM YURUK

Introduction

Neurotmesis is a complete transection of a peripheral nerve. Etiologies of traumatic peripheral nerve injury (PNI) include high-velocity trauma, lacerations, bone fractures, penetrating injury, crush, traction, ischemia, and less common mechanisms such as thermal, electric shock, and radiation.[1] Sunderland's fifth-degree injury corresponds to the definition of neurotmesis in Seddon's classification and represents the highest degree of nerve injury with a complete nerve defect.[2] In neurotmesis, the entire nerve, including the endoneurium, perineurium, and epineurium, is completely severed.[3]

After neurotmesis occurs, many cell signals and neurotrophic factors are involved, as seen in Wallerian Degeneration. Within 30 minutes (min) after injury, intracellular processes that promote repair and regeneration have already been activated. Schwann cells play an indispensable role in promoting regeneration by producing neurotrophic factors and increasing their synthesis of surface cell adhesion molecules.[4] Schwann cells adaptively respond to axonal interruption, switching from a highly myelinated state to a de-differentiated state. De-differentiated Schwann cells engulf debris and form a regeneration path for axon growth. Schwann cells also secrete a group of neurotrophic factors, including nerve growth factor, brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF), to encourage neuron survival and axon elongation.[5-7] Although the physiological recovery starts, surgical repair is required after neurotmesis. If surgery is not performed on time, degeneration of motor neurons and loss of axon regeneration can occur, leading to loss of function.[8] Complete loss of motor functions (loss of voluntary and reflex contraction of the muscle and progressive muscle atrophy), loss of sensory functions (muscle spindle atrophies, Meissner, Pacinian, and Merkel atrophy, some other receptors are lost), autonomic loss, and cortex plasticity occur after neurotmesis.[9]

Recovery is more difficult as there is complete motor and sensory loss. Muscle de-innervation continues for a long time. Additional time is required for functional recovery after re-innervation. Axons may be misdirected due to disruption of the continuity of the endoneurial tubule. Neuromas frequently occur and can be a source of pain. The degree of misdirection of re-innervation depends on the nerve fiber composition of the affected fascicle. It cannot be said that functional recovery will occur definitively after surgical repair. Nerve fibers that regenerate after re-anastomosis cannot regain the original number, even if their diameter increases for several years. The transmission rate increases slowly, reaching 60% of the normal value within 4 years.[4] Distal lesions have a better prognosis.[10]

Endoneurial tubules must be in contact with regenerating axons within 18 to 24 months after injury; otherwise, degeneration will occur. The

Schwann cells and endoneurial tubules remain viable for 18 to 24 months after injury. If they do not receive a regenerating axon within this period, the tubules degenerate. Target muscle atrophy becomes irreversible after 12 to 18 months of de-innervation, which limits the functional outcome of the repair.[11] Axon regrowth is 1 mm/day from the site of injury or surgical repair. When the regenerative distance exceeds 20 inches, even when the axons successfully reach their target, they are non-functional because de-innervated muscle fibers undergo fibrofatty degeneration at 20 to 24 months.[12,13]

Patient Evaluation

Physical examination of the involved extremity and the muscles innervated point toward a specific nerve involved. Before planning a physiotherapy and rehabilitation program, patient evaluation is essential. The sensory distribution of the nerve is tested. There is complete anesthesia of the sensory distribution of the nerve. All involved muscles show flaccid paralysis. Eliciting a Tinel sign is useful in following patients with a PNI to determine the regeneration of axons across the defect.[4]

Physiotherapists perform electrodiagnostic tests and evaluate muscle strength, range of motion, dermatome, anthropometric properties, posture, viscoelastic (tone, elasticity, thixotropy) properties of the muscles, pain, and autonomic functions in patients with PNI.[14] The Faradic Excitability Test should be routinely performed for follow-up of the recovery process.[15]

Technology is helpful in screening nerve injuries for clinicians. Differentiation of neurapraxia or axonotmesis from neurotmesis is done by observing nerve continuity and the demonstration of proximal and distal nerve stumps.[16] It also provides information on the presence and location of neuromas, the length of any gap, and anatomical continuity after nerve-grafting procedures. Magnetic resonance imaging (MRI), ultrasound, and electromyography (EMG) are the most useful screening techniques to differentiate between nerve axonotmesis and neurotmesis.[1,4,17]

Electrical Stimulation (ES) for Neurotmesis

Aim and Effects of ES in Neurotmesis

The aims of the ES in neurotmesis are to:[18,19]

- Keep the muscle active while waiting for regeneration,
- Delay atrophy and fibrosis,
- Stimulate re-innervation,
- Decrease pain.

The effects of ES on neurotmesis should be considered in terms of de-innervated muscle, nerve regeneration, and pain management. Electrical Muscle Stimulation (EMS), brief intraoperative ES, Magnetic Field Therapy, and Transcutaneous Electrical Nerve Stimulation (TENS) can be used for neurotmesis.[18-21]

The Effects of ES on De-Innervated Muscles

De-innervation atrophy is a much more complex condition than atrophy due to inactivity. Muscle plasticity is affected by many neural factors. The de-innervated muscle is neither voluntary nor reflexively active because it has atrophied and weakened. The treatment goals remain focused on providing innervation to the de-innervated muscle before irreversible muscle changes associated with de-innervation. ES provides an external source of stimulation to the muscle fibers. Studies have shown the benefit of ES on contractile properties of the muscles.[22] However, the efficacy of ES in prolonging the period before irreversible muscle atrophy and increasing the capacity for re-innervation remains unanswered. In neurotmesis, the muscle is stimulated by the sarcolemma, not by the neurolemma. This method is called EMS, as mentioned.[15]

A previous experimental study demonstrated that daily EMS increases re-innervation following nerve repair. Willand et al. provide a possible explanation of why re-innervation is increased following EMS using a rat model with a transected Tibial nerve and immediately repaired post-injury.[23] The rat model had intramuscular electrodes implanted in the Gastrocnemius muscle for ES.

The de-innervated muscle was stimulated with 600 contractions per day 5 days a week. GDNF mRNA levels of stimulated muscles were significantly upregulated compared with the no-stimulation groups. However, there was no difference in trophic factor mRNA levels in the distal stump compared to the non-stimulated rats, suggesting that EMS did not regulate Schwann cell derived GDNF transcription. The authors suggested that EMS upregulates intramuscular levels of GDNF mRNA. This increase in trophic factor diffused into the distal nerve stump provided the beneficial effects of axon regeneration at the growth cone facilitated nerve regeneration.[23]

Another study by Willand et al. evaluated the efficacy of EMS over 6 months following Tibial nerve transection and immediate repair.[24] Rats were divided into 6 groups based on treatment (EMS or no treatment) and duration (1, 2, or 3 months). In the EMS group, Gastrocnemius muscle was electrically stimulated with 600 contractions per day, 5 days a week. Daily stimulated muscles had significantly greater numbers of re-innervated motor units with smaller average motor unit sizes. Most of the muscle endplates were re-innervated by a single axon arising from a nerve trunk with significantly fewer numbers of terminal sprouts in the EMS group. Although muscle mass and force were unchanged, EMS improved electrophysiological outcomes.[24] Although recent studies showed the encouraging effects of ES on de-innervated muscles, some studies showed no benefit or harmful effects of EMS. In an experimental study, Tam et al. used 20 Hertz (Hz) frequency ES for 8 hours daily on the Tibialis Anterior, medial Gastrocnemius, Plantaris, and Soleus muscles.[25] The neural activity reduced motor unit enlargement. The authors indicated that increased neuromuscular activity was not recommended for rehabilitation immediately after motoneuron injury or in the early stages of motoneuron disease.

Many studies using nerve injury animal models used Galvanic Current EMS with implanted intramuscular wires, and some studies used implanted stimulators. Typically, in clinical practice, Galvanic EMS is applied via transcutaneous electrodes. In a review, the use of Galvanic EMS with transcutaneous electrodes did not reveal any efficacy in human de-innervated muscle. Given the lack of strong clinical evidence and the variation of the technique to apply the EMS in the clinical setting of patients with nerve injury, some authors did not advocate the use of Galvanic EMS in de-innervated muscle.[26] The potential therapeutic benefit of EMS in a facial nerve injury model has been assessed. The Vibrissal muscles of rats have been subjected to EMS or sham stimulation. One day after end-to-end suture, the Vibrissal muscles were exposed to EMS (rectangular shaped, 0.1 milliseconds (ms) of pulse duration, frequency of 5 Hz at established predefined threshold amplitude between 3.0 and 5.0 Volts) 3 times per week, each time for 5 min. Using video-based motion analysis, restoration of Vibrissal motor performance following ES or sham stimulation has been evaluated and correlated with the extent of collateral axonal branching at the lesion site and the number of motor end plates in the target musculature. The authors found that EMS did not improve functional outcomes.[27]

Pinheiro-Dardis et al. investigated the effects of EMS on neuromuscular recovery after nerve crush injury in rats.[28] The authors showed that EMS impaired neuromuscular recovery at 14 days post-denervation. Muscle hypo-excitability was accentuated by EMS at 6- and 14-days post-denervation. Although EMS reduced the accumulation of atrogin-1, Muscle Ring-Finger Protein-1 (MuRF1), and myoblast determination protein 1 (myoD) mRNAs, it increased muscle atrophy. The gene expression of neural cell adhesive molecules (N-CAM) protein was altered by EMS. The authors concluded that EMS could delay the re-innervation process by modulating factors related to neuromuscular junction stability and organization and inducing dysfunction, hypo-excitability, and muscle atrophy.

There were also claims that ES reduced acetylcholine (ACH) sensitivity because ES mimics physiological contractions. The number of contractions per day is insufficient. Only superficial fibers are stimulated by ES. High intensity is needed to activate deep fibers.[29]

The Effects of ES on Regeneration of the Nerves

ES has been demonstrated to augment nerve regeneration after PNI and repair in both animal models and humans.[30,31] Experimental studies have demonstrated ES to be a promising adjunctive therapy to enhance axonal regeneration and functional recovery following decompression, direct neurorrhaphy, and repair using grafts. ES acts through retrograde action potentials to increase cyclic adenosine monophosphate (cAMP) levels in the soma, which drives the increased expression of BDNF. Although the exact mechanism is not completely clear, ES promotes axonal outgrowth and survival.[19]

Extensive animal studies have reported the ability of brief intraoperative ES to enhance functional regeneration after PNI. The 1 hour, 20 Hz ES of the nerve after nerve repair enhances the early expression of BDNF and pro-regenerative associated genes and facilitates that sensory and motor axons grow faster across the suture site after transection of the Femoral nerve in rats.[32,33] Brushart et al. suggested that ES promotes the onset of axonal regeneration but did not increase regeneration speed.[34] Asensio-Pinilla et al. investigated the effects of ES and exercise on axon regeneration in rats.[35] Four groups of adult rats were subjected to Sciatic nerve transection and suture repair. Two groups received ES (3 Volts, 0.1 ms at 20 Hz) for 1 hour, immediately after the injury, or for 4 weeks. A third group received 1 hour ES and was submitted to treadmill running for 4 weeks (5 meters per min, 2 hours daily). A fourth group performed only exercise, whereas an untreated group served as the control. Groups that received acute ES, that were forced to exercise on the treadmill, or both showed higher levels of muscle re-innervation and increased numbers of regenerated myelinated axons compared with control animals or animals that received chronic ES. The authors demonstrated that acute ES could accelerate axonal regeneration and enhance muscle re-innervation after sciatic nerve injury.

Lu et al. determined the regenerating effects of ES with different current intensities during 6 weeks on the Sciatic nerves of rats.[36] The stimulation was applied to the animals for 15 min every other day beginning a week after the nerve repair with needle electrodes. The stimulating frequency was 2 Hz and the current intensity was 1 milliampere (mA), to produce a visual muscle contraction. Similarly, animals in the other groups received ES of 2 Hz at current intensities of 2 and 4 mA respectively. The group receiving ES, especially at 1 mA, had significantly shorter latency, larger area of the evoked muscle action potentials, and faster conduction velocity compared with the controls. However, ES at 4 mA provoked adverse responses to the function recovery of regenerated nerves in the kinematic gait analysis. This result reveals the importance of physical therapists using safe stimulus protocols for rehabilitation.[36] Another study investigated the effects of ES at different frequencies on the regeneration of transected Peripheral nerves in rats. Starting 1-week after transection, ES was applied at 1, 2, 20, or 200 Hz between the proximal and distal nerve stumps. The control group received no stimulation. The authors found that higher-frequency ES led to less regeneration compared to low-frequency ES.[37]

Insufficient recovery after neurotmesis is due to (1) inappropriate pathfinding because of axonal regrowth to inappropriate targets, (2) excessive collateral axonal branching at the lesion site, and (3) poly innervation of the neuromuscular junctions. In addition to recent studies supporting the encouraging effects of ES on nerve regeneration, some studies showed that increased neural activity on sprouting remains unclear and controversial. The ES of the Facial nerve did not improve the functional outcome nor reduce aberrant regeneration after Facial nerve reconstruction in rats. The only positive effect of this treatment on the Facial nerve was a transient improvement in protraction velocity between 1 and 3 months after surgical reconstruction.[38]

Pulsed electromagnetic magnetic fields (PEMF) have beneficial effects on nerve regeneration. The biological basis of magnetic stimulation mainly relies on protein synthesis, ion channel regulation, and growth factor secretion.[39] However, little re-

search has examined the nerve conduction characteristics of regenerating peripheral nerves under PEMF.[20] Bademoğlu et al. investigated the effects of PEMF on Sciatic nerve regeneration in the short- and long-term after crushing damage.[40] Twenty-four female Wistar-Albino rats were divided into 3 groups: sham, Sciatic nerve injury, Sciatic nerve injury and PEMF. The PEMF group was exposed to PEMF [4 hours/day, intensity; 0.3 milliTesla (mT), low-frequency:2 Hz] for 40 days. The results indicated PEMF was not effective in long-term. However, PEMF might be useful in the short term. More studies are needed to precisely evaluate and optimize the intensity and duration of the application in humans.

The Effects of ES on Pain

PNI can be associated with a combination of nociceptive, neuropathic, and complex regional pain syndromes. The incidence of neuropathic pain is high, reaching up to 95% of cases, especially if cervical root avulsion has occurred. Neuropathic pain results from damage to the somatosensory system, and its progression toward chronicity depends upon disruptions affecting both the peripheral and central nervous systems. Managing these painful conditions is complex.[41]

TENS can regulate neuromodulation based on Melzack and Wall's Gate Control Theory of pain. It has a very low rate of adverse effects and complications. Although an initial success with TENS could be observed in up to 60-65% of patients, such benefits often wane over time, with only 20-30% of patients reporting any meaningful analgesic effect after one or two months of treatment.[21,41]

The advantages and disadvantages of ES on de-innervated muscles and regeneration of the nerve are summarized in Table 29.1.

ES Protocol for Neurotmesis

Different ES techniques are used for neurotmesis: intraoperative brief ES on the injury site, EMS, PEMF, and TENS.[20,21,31,42]

Intraoperative Brief ES

Intraoperative brief ES is a recent technique that has been shown to be effective in studies. Biphasic current (20 Hz, 100 μs) for 1 hour with implanted electrodes is used.[43] Although the technique seems effective for regeneration, it is impractical for physiotherapists because ES is used only after nerve repair and is an invasive technique.

EMS

As mentioned before, if the muscle is de-innervated, it is stimulated via the sarcolemma. This is called EMS. The EMS is a traditional technique for PNI. It can be used for completely and partially de-innervated muscles. Because of the physiological changes of completely de-innervated muscles, only modified Galvanic current can elicit a contraction response. The pulse duration should be

Table 29.1 Advantages and disadvantages of ES on re-innervation.[22,23,25,26,29]

Advantages of Electrical Stimulation	Disadvantages of Electrical Stimulation
Reduces venous stasis and edema	Causes trauma to de-innervated muscles (overstimulation)
Increases muscle-derived neurotrophic factors (BDNF, GDNF, NGF)	Decreases production of neural cell adhesive molecules (N-CAM) and acetylcholine (ACH) sensitivity
Delays atrophy and fibrosis	Delays or inhibits collateral sprouting and re-innervation
Keeps the muscle active while waiting for regeneration	Mimics the voluntary contraction however not has the same physiological mechanism as exercise
Reduce pain	No added benefit for trophic condition
Enhances the sensory inputs and maintains the relationship between the cortex and peripheral organs	The number of contractions per day is insufficient.
Reduces scar formation	Only superficial fibers are stimulated by ES. High current intensity is needed to stimulate deep fibers.

above 100 ms (300-600 ms) and the pulse interval should be two times of pulse duration (200-1000 ms).[15,29]

If re-innervation begins, the muscles can respond to the Faradic current. The Faradic Excitability Test should be routinely performed for re-innervation. The Faradic current is an alternating biphasic current with a short pulse duration. Therefore, it cannot be effective in complete de-innervation. If the muscle does not give a contraction response for the Faradic Excitability Test, the Galvanic current should be used for EMS. In partial de-innervation, the Faradic current can also be used. Alternating currents are comfortable for the patients and can elicit greater muscle torque. Tanaka et al. suggested that ES using an alternating current can become an effective therapeutic intervention to prevent deeper muscle atrophy.[44] The frequency and pulse duration of the EMS should be determined according to the fiber type distribution of the muscle. If it is a slow-twitch muscle, a frequency below 40 Hz should be applied. If it is a fast-twitch muscle 50-70 Hz should be chosen. The pulse duration of the Faradic current is 0.1-1 ms. This value is equivalent to chronaxie. [15,29]

There are points to be considered in practice. Due to the elongated sarcomere length of the de-innervated muscle, the length of the muscle should be shortened while performing EMS. In addition, the patient should monitor muscle contractions so that the stimulation of the somatosensory field is strengthened. Applications should not be too long due to the low oxidative energy mechanism and should be done 3 days a week for maximum 8 weeks.[45-48] It is recommended that the current amplitude be as high as is tolerable and capable of stimulating tetanic contraction of the target muscle. The atrophied and de-innervated muscles are vulnerable to trauma. Excessive EMS can cause trauma. Higher current amplitude elicits strong and deep muscle contractions. However, higher amplitudes also cause trauma. The long pulse duration and high current amplitude can be painful if the sensation is intact. However, the goal is to maximize the contraction response while minimizing pain.[15,29]

Physiotherapists should avoid fatigue when using EMS. In order not to create oxidative stress in the muscle, the application should be stopped when signs of fatigue are seen. The 200 muscle contractions per day are sufficient to prevent muscle fiber atrophy. However, to prevent fatigue, 90 contractions of each muscle should be performed as 3 sets of 30-30-30 or 2 sets of 45–45 contractions. The treatment sessions are planned 3-5 times/week for approximately 8 weeks. The EMS should be started after nerve re-innervation begins and should be terminated when active movement begins.[49,50]

The electrode size and type depend on the size of the muscle to be stimulated and the intensity of the contraction to be elicited. Small or pen electrodes can be used to localize stimulation to small muscles. Larger electrodes are needed to stimulate larger muscles and muscle groups. One electrode may be placed over the most excitable part of a muscle. The second electrode was placed at a convenient location near the muscle being treated. EMS should be performed carefully if there is a co-contraction. The antagonist should not contract simultaneously.[15,29]

PEMF

Studies have investigated different magnetic field properties (static or pulsed magnetic field) and intensities, various magnetic nanoparticle-encapsulating cytokines based on super para-magnetism, magnetically functionalized nanofibers, and their relevant mechanisms and clinical applications. A suitable application of magnetic field or magnetic biomaterials can shorten the regeneration time of peripheral nerves and promote the release of growth factors.[51] The PMF parameter can be set at 0-20 mT and a frequency of 50-100 Hz.[52]

TENS

Neuromas frequently occur and can be a source of pain in neurotmesis. The pain is typically neuropathic, characterized by burning and dysesthesias.[4] TENS is a method of ES that aims to provide symptomatic pain relief by exciting sensory nerves and stimulating either the pain gate mechanism and/or the opioid system. The different methods of

Table 29.2 Parameter settings for EMS in neurotmesis.[15,29]

Current type/waveform	Modified Galvanic current (monophasic rectangular or triangular) Pulsed alternating current (asymmetric biphasic) after re-innervation
Pulse/cycle duration	>100 ms (Modified Galvanic current) 0.1-1 ms (Faradic current)
Amplitude	Optimal tolerated contraction
Pulse rate (Frequency)	None (Modified Galvanic current) <40 Hz for slow-twitch muscles (Alternating current) 50-70 Hz for fast-twitch muscles (Alternating current)
Ramp up/ramp down	None (Modified Galvanic current) 1/3 seconds (s) (Alternating current)
On time (Duty cycle)/ Off time	1:2 (Modified Galvanic current) 1:9 s (%10) (Alternating current) 2-5 s/2-25 s
Modulation	None
Treatment duration	3 sets of 30-30-30 or 2 sets of 45–45 contractions (Modified Galvanic current) <30 s (Alternating current)
Frequency of sessions	3-5 times/week, approximately 8 weeks
Polarity	Cathode (Modified Galvanic current) None (Alternating current)
Electrode placement	Bipolar or monopolar technique Parallel to fibers

applying TENS relate to these different physiological mechanisms. Conventional TENS (frequency 60-120 Hz, pulse duration 50-100 μs, intensity at sensory level, 20-30 min) or Acupuncture-type TENS on painful site (frequency 1-5 Hz, pulse duration 150-250 μs, maximum tolerable intensity that does not cause discomfort, 30 min) can be used for pain in PNI.[15,53]

Clinical Evidence of ES in Neurotmesis

Facial Nerve Injury

Although clinicians and researchers have tested the usefulness of ES applications for enhancement of peripheral nerve regeneration for more than a century, the efficacy of such treatment for Facial paralysis remains questionable. In a recent small but long prospective observational study, Arnold et al. included 3 patients with early onset (15 days to 3.5 months) of EMS of the Zygomatic muscle as home training after Facial nerve lesion during schwannoma surgery with spontaneous regeneration or after Facial nerve repair. Selective Zygomatic muscle response in the absence of discomfort was reproducibly obtained. The EMS parameters were 50 ms pulse duration and 7 Hz frequency of triangular single pulses. The required amplitude was remarkably lower with ≤ 5 mA in these patients early after the onset of the Facial nerve lesion, compared to other patients with long-term (4 months to 16 years) de-innervation (where amplitudes up to 15 mA were needed). The authors found that the ES parameter was not causing discomfort and unwanted unspecific reactions of other ipsilateral and/or contralateral Facial muscles.[54] Appropriate ES does not hinder the regeneration of the Facial nerve. It maintains muscle function between the onset of the lesion and spontaneous re-innervation or surgically induced re-innervation of the target muscles. It may also reduce synkinetic re-innervation although data are still rare to sparse to allow general conclusions.[55]

Cauda Equina Injury

Trauma to the spinal roots of the Brachial plexus and the Cauda Equina typically results in a lower motor neuron syndrome, with de-innervation of peripheral targets, sensory impairments from dorsal root injury, and pain. Historically, nerve

root injuries have been associated with an overall poor clinical outcome, as a successful repair strategy would also require axonal regeneration within both the central nervous system tissue of the spinal cord and the peripheral nervous system.[56] Kern et al. investigated the effects of EMS in a patient with long-standing Quadriceps Femoris muscle de-innervation.[45] Stimulation started 18 months after injury. The authors stimulated the Quadriceps Femoris muscle with biphasic rectangular current (pulse duration of 40-120 ms, frequency of 20 Hz, and 2 s on, 2 s off). The treatment was done for 15 min per day, 5 days per week. Biopsies revealed evidence of both growth and regeneration of myofibers. The results suggest that EMS may offer a route to the future development of mobility aids in patients with lower motor neuron lesions.[45] Albertin et al. used two years of home-based ES on severely atrophic Quadriceps Femoris muscles of 3 patients with complete conus and cauda equina lesions.[57] Muscle biopsies showed a 30% increase in the epidermis after two years of home-based ES. The authors found impressive improvements in the EMS-induced muscle strength and size of the muscle fibers after 2 years of EMS.

In a European Union project, the effect of four years of home-based ES was investigated in patients with complete Conus and Cauda Equina syndrome. Quadriceps Femoris muscles were stimulated using a custom-designed stimulator, large surface electrodes, and customized progressive stimulation settings. Results from this study demonstrated that home-based ES induced a compliance-dependent recovery of muscle volume and size of muscle fibers, as evidenced by the gain and loss in muscle mass.[58]

Summary

In this chapter, the purpose and effects of ES, stimulation parameters, and clinical evidence in neurotmesis are discussed. Compared with axonotmesis the re-innervation is not completely successful in neurotmesis. Therefore, the efficacy of ES in prolonging the period before irreversible muscle atrophy and increasing the capacity for re-innervation remains unanswered. EMS, intraoperative brief ES, TENS, and PEMF can be used for neurotmesis.[18,21] Clinical evidence suggests that 1 hour of 20 Hz ES applied intraoperatively following repair can improve patient recovery. Although the technique seems effective for regeneration, it is impractical for physiotherapists because the ES is used only after nerve repair and is an invasive technique. The other technique is EMS. There are experimental and clinical studies on EMS in the literature. Although some studies have shown the harmful effects of EMS, recent studies have supported EMS. More studies are needed to precisely evaluate and optimize the intensity and duration of the PEMF and TENS application in humans. Different studies presented both positive and negative effects of ES. These negative effects may be due to a lack of stimulation intensity needed to reach deep muscle fibers when using surface electrodes, incorrect frequency selection for stimulation, or stimulation protocols with long periods of rest between stimuli. Nevertheless, ES has been shown to have beneficial effects in human subjects and thus is a worthwhile approach to maintaining muscle mass and force.[22,45]

References

1. Omejec G, Podnar S. Contribution of ultrasonography in evaluating traumatic lesions of the peripheral nerves. Neurophysiol Clin. 2020;50(2):93-101. doi:10.1016/j.neucli.2020.01.007.
2. Chhabra A, Ahlawat S, Belzberg A, Andreseik G. Peripheral nerve injury grading simplified on MR neurography: As referenced to Seddon and Sunderland classifications. Indian J Radiol Imaging. 2014;24(3):217-24. doi:10.4103/0971-3026.137025.
3. Kaya Y, Sarikcioglu L. Sir Herbert Seddon (1903-1977) and his classification scheme for peripheral nerve injury. Childs Nerv Syst. 2015;31(2):177-80. doi:10.1007/s00381-014-2560-y.
4. Campbell WW. Evaluation and management of peripheral nerve injury. Clin Neurophysiol. 2008;119(9):1951-65. doi:10.1016/j.clinph.2008.03.018.
5. Jessen KR, Mirsky R, Lloyd AC. Schwann cells: development and role in nerve repair. Cold Spring Harb Perspect Biol. 2015;7(7):a020487. doi:10.1101/cshperspect.a020487.
6. Madduri S, Gander B. Schwann cell delivery of neurotrophic factors for peripheral nerve regeneration. J Peripher Nerv Syst. 2010;15(2):93-103. doi:10.1111/j.1529-8027.2010.00257.x.
7. Yi S, Zhang Y, Gu X, Huang L, Zhang K, Qian T, Gu X. Application of stem cells in peripheral nerve regeneration. Burns Trauma. 2020;8:tkaa002. doi:10.1093/burnst/tkaa002.
8. Ransom SC, Shahrestani S, Lien BV, Tafreshi AR, Brown NJ, Hanst B, et al. Translational approaches to electrical stimulation for peripheral nerve regeneration. Neurorehabil Neural Repair. 2020;34(11):979-85. doi:10.1177/1545968320962508.

9. Robinson LR. Traumatic injury to peripheral nerves. Muscle Nerve. 2022;66(6):661-70. doi:10.1002/mus.27706.
10. Smith BW, Kamble N, Shukla D, Bhat D. Peripheral nerve injuries: electrophysiology for the neurosurgeon. Neurol India. 2019;67(6):1419-22. doi:10.4103/0028-3886.273626.
11. Siemionow M, Brzezicki G. Chapter 8: Current techniques and concepts in peripheral nerve repair. Int Rev Neurobiol. 2009;87:141-72. doi:10.1016/S0074-7742(09)87008-6.
12. Scarff JE. Peripheral nerve injuries: Principles of treatment. Med Clin North Am. 1958;42(3):611-40. doi:10.1016/s0025-7125(16)34269-9.
13. Menorca RM, Fussell TS, Elfar JC. Nerve physiology: Mechanisms of injury and recovery. Hand Clin. 2013;29(3):317-30. doi:10.1016/j.hcl.2013.04.002.
14. de Santana Chagas AC, Wanderley D, de Oliveira Ferro JK, Alves de Moraes A, Morais de Souza FH, da Silva Tenório A, et al. Physical therapeutic treatment for traumatic brachial plexus injury in adults: A scoping review. PMR. 2022;14(1):120-50. doi:10.1002/pmrj.12566.
15. Kırdı N. (2016), Elektroterapide temel prensipler ve klinik uygulamalar. 2nd ed. Ankara: Hipokrat Kitabevi. ISBN:978-605-9160-03-2.
16. Renna R, Coraci D, De Franco P, Erra C, Ceruso M, Padua L. Ultrasound study is useful to discriminate between axonotmesis and neurotmesis also in very small nerves: A case of sensory digital ulnar branch study. Med Ultrason. 2012;14(4):352-4. PMID:23243650.
17. Yang Z, Zheng C, Zhang F, Lin B, Cao M, Tian X, et al. Magnetic resonance imaging of enhanced nerve repair with mesenchymal stem cells combined with microenvironment immunomodulation in neurotmesis. Muscle Nerve. 2020;61(6):815-25. doi:10.1002/mus.26862.
18. Gordon T, Amirjani N, Edwards DC, Chan KM. Brief post-surgical electrical stimulation accelerates axon regeneration and muscle re-innervation without affecting the functional measures in carpal tunnel syndrome patients. Exp Neurol. 2010;223:192-202. doi:10.1016/j.expneurol.2009.09.020.
19. Juckett L, Saffari TM, Ormseth B, Senger JL, Moore AM. The effect of electrical stimulation on nerve regeneration following peripheral nerve injury. Biomolecules. 2022;12:1856. doi:10.3390/biom12121856.
20. Beck-Broichsitter BE, Lamia A, Geuna S, Fregnan F, Smeets R, Becker ST, et al. Does pulsed magnetic field therapy influence nerve regeneration in the median nerve model of the rat? BioMed Res Int. 2014:401760. doi:10.1155/2014/401760.
21. Carvalho GA, Nikkhah G, Samii M. Treatment of pain following traumatic lesions of the brachial plexus. Orthopäde. 1997;26:621-5. doi:10.1007/PL00003420.
22. Dow DE, Cederna PS, Hassett CA, Dennis RG, Faulkner JA. Electrical stimulation prior to delayed re-innervation does not enhance recovery in muscles of rats. Restor Neurol Neurosci. 2007;25(5-6):601-10. PMID:18334775.
23. Willand MP, Rosa E, Michalski B, Zhang JJ, Gordon T, Fahnestock M, et al. Electrical muscle stimulation elevates intramuscular BDNF and GDNF mRNA following peripheral nerve injury and repair in rats. Neuroscience. 2016;334:93-104. doi:10.1016/j.neuroscience.2016.07.040.
24. Willand MP, Chiang CD, Zhang JJ, Stephen WP, Kemp SWP, Borschel GH, et al. Daily electrical muscle stimulation enhances functional recovery following nerve transection and repair in rats. Neurorehabil Neural Rep. 2015;29(7):690-700. doi:10.1177/1545968314562117.
25. Tam SL, Archibald V, Jassar B, Tyreman N, Gordon T. Increased neuromuscular activity reduces sprouting in partially denervated muscles. J Neurosci. 2001;15;21(2):654-67. doi:10.1523/JNEUROSCI.21-02-00654.2001.
26. Novak CB, von der Heyde RL. Evidence and techniques in rehabilitation following nerve injuries. Hand Clin. 2013;29(3):383-92. doi:10.1016/j.hcl.2013.04.012.
27. Rink S, Bendella H, Akkin SM, Manthou M, Grosheva M, Angelov DN. Experimental studies on facial nerve regeneration. Anat Rec (Hoboken). 2019;302(8):1287-303. doi:10.1002/ar.24123.
28. Pinheiro-Dardis CM, Erbereli BT, Gigo-Benato D, Castro PATS, Russo TL. Electrical stimulation delays re-innervation in denervated rat muscle. Muscle Nerve. 2017;56(6):E108-E118. doi:10.1002/mus.25589.
29. Nelson RM, Currier DP. (1991), Clinical electrotherapy. 2nd ed. USA: Appleton&Lange. ISBN:0-8385-1334-1334.
30. Wong JN, Olson JL, Morhart MJ, Chan KM. Electrical stimulation enhances sensory recovery: A randomized controlled trial. Ann Neurol. 2015;77(6):996-1006. doi:10.1002/ana.24397.
31. Gordon T, Brushart TM, Amirjani N, Chan KM. The potential of electrical stimulation to promote functional recovery after PNI: Comparisons between rats and humans. Acta Neurochir Suppl 2007;100:3-11. doi:10.1007/978-3-211-72958-8_1.
32. Geremia NM, Gordon T, Brushart TM, Al-Majed AA, Verge VM. Electrical stimulation promotes sensory neuron regeneration and growth-associated gene expression. Exp. Neurol. 2007;205:347-59. doi:10.1016/j.expneurol.2007.01.040.
33. Al-Majed AA, Tam SL, Gordon T. Electrical stimulation accelerates and enhances expression of regeneration-associated genes in regenerating rat femoral motoneurons. Cell. Mol. Neurobiol. 2004;24:379-402. doi:10.1023/b:cemn.0000022770.66463.f7.
34. Brushart TM, Hoffman PN, Royall RM, Murinson BB, Witzel C, Gordon T. Electrical stimulation promotes motoneuron regeneration without increasing its speed or conditioning the neuron. J Neurosci 2002;22:6631-8. doi:10.1523/JNEUROSCI.22-15-06631.2002.
35. Asensio-Pinilla E, Udina E, Jaramillo J, Navarro X. Electrical stimulation combined with exercise increase axonal regeneration after PNI. Exp Neurol. 2009;219(1):258-65. doi:10.1016/j.expneurol.2009.05.034.
36. Lu MC, Tsai CC, Chen SC, Tsai FJ, Yao CH, Chen YS. Use of electrical stimulation at different current levels to promote recovery after peripheral nerve injury in rats. J Trauma. 2009;67(5):1066-72. doi:10.1097/TA.0b013e318182351a.
37. Lu MC, Ho CY, Hsu SF, Lee HC, Lin JH, Yao CH, et al. Effects of electrical stimulation at different frequencies on regeneration of transected peripheral nerve. Neurorehabil Neural Repair. 2008;22(4):367-73. doi:10.1177/1545968307313507.
38. Skouras E, Merkel D, Grosheva M, Angelova SK, Schiffer G, Thelen U, et al. Manual stimulation, but not acute electrical stimulation prior to reconstructive surgery, improves functional recovery after facial nerve injury in rats. Restor Neurol Neurosci. 2009;27:237-51. doi:10.3233/RNN-2009-0474.
39. Qian Y, Cheng Y, Cai J, Zhao X, Ouyang Y, Yuan WE, et al. Advances in electrical and magnetic stimulation on nerve regeneration. Regen Med. 2019;14(10):969-79. doi:10.2217/rme-2018-0079.
40. Bademoğlu G, Erdal N, Uzun C, Taşdelen B. The effects of pulsed electromagnetic field on experimentally induced sciatic nerve injury in rats. Electromagnet Biol Med. 2021;40(3):408-19. doi:10.1080/15368378.2021.1907403.
41. Lovaglio AC, Socolovsky M, Masi G, Bonilla G. Treatment of neuropathic pain after peripheral nerve and brachial plexus traumatic injury. Neurol India. 2019;67(Supplement):S32-S37. doi:10.4103/0028-3886.250699.
42. Ashley Z, Sutherland H, Russold MF, Lanmüller H, Mayr W, Jarvis JC, et al. Therapeutic stimulation of denervated muscles: The influence of pattern. Muscle Nerve. 2008;38:875-86. doi:10.1002/mus.21020.

43. Li X, Zhang T, Li C, Xu W, Guan Y, Li X, et al. Electrical stimulation accelerates Wallerian degeneration and promotes nerve regeneration after sciatic nerve injury. Glia. 2023;71(3):758-74. doi: 10.1002/glia.24309.
44. Tanaka M, Hirayama Y, Fujita N, Fujino H. Electrical stimulation using sine waveform prevents unloading-induced muscle atrophy in the deep calf muscles of rat. Acta Histochem. 2014;116(7):1192-8. doi:10.1016/j.acthis.2014.06.009.
45. Kern H, Salmons S, Mayr W, Rossini K, Carraro U. Recovery of long-term denervated human muscles induced by electrical stimulation. Muscle Nerve. 2005;31(1):98-101. doi: 10.1002/mus.20149.
46. Qin L, Appell HJ, Chan KM, Maffulli N. Electrical stimulation prevents immobilization atrophy in skeletal muscle of rabbits. Arch Phys Med Rehabil. 1997;78(5):512-7. doi:10.1016/s0003-9993(97)90166-0.
47. Peviani SM, Russo TL, Durigan JL, Vieira BS, Pinheiro CM, Galassi MS, et al. Stretching and electrical stimulation regulate the metalloproteinase-2 in rat denervated skeletal muscle. Neurol Res. 2010;32(8):891-6. doi:10.1179/174313209X459093.
48. Gigo-Benato D, Russo TL, Geuna S, Domingues NR, Salvini TF, Parizotto NA. Electrical stimulation impairs early functional recovery and accentuates skeletal muscle atrophy after sciatic nerve crush injury in rats. Muscle Nerve. 2010;41(5):685-93. doi:10.1002/mus.21549.
49. Gordon T. Electrical stimulation to enhance axon regeneration after peripheral nerve injuries in animal models and humans. Neurotherapeutics. 2016;13(2):295-310. doi:10.1007/s13311-015-0415-1.
50. Yeh CC, Tsai FJ, Huang CY, Yao CH, Chen YS. Timing of applying electrical stimulation is an important factor deciding the success rate and maturity of regenerating rat sciatic nerves. Neurorehabil Neural Repair. 2010;24(8):730-5. doi:10.1177/1545968310376758.
51. Fan Z, Wen X, Ding X, Wang Q, Wang S, Yu W. Advances in biotechnology and clinical therapy in the field of peripheral nerve regeneration based on magnetism. Front Neurol. 2023;14:1079757. doi:10.3389/fneur.2023.1079757.
52. Liu L, Liu Z, Huang L, Sun Z, Ma T, Zhu S, et al. Pulsed magnetic field promotes proliferation and neurotrophic genes expression in Schwann cells in vitro. Int J Clin Exp Pathol. 2015;8(3):2343-53. PMID:26045741.
53. Alarcón JB, Chuhuaicura PB, Sluka KA, Vance CGT, Fazan VPS, Godoy KA, et al. Transcutaneous electrical nerve stimulation in nerve regeneration: A systematic review of in vivo animal model studies. Neuromodulation. 2022;25(8):1248-58. doi:10.1016/j.neurom.2021.12.009.
54. Arnold D, Thielker J, Klingner CM, Puls WC, Misikire W, Guntinas-Lichius O, et al. Selective surface electrostimulation of the denervated zygomaticus muscle. Diagnostics (Basel). 2021;11:188. doi:10.3390/diagnostics11020188.
55. Kurz A, Volk GF, Arnold D, Schneider-Stickler B, Mayr W, Guntinas-Lichius O. Selective electrical surface stimulation to support functional recovery in the early phase after unilateral acute facial nerve or vocal fold paralysis. Front Neurol. 2022;13:869900. doi:10.3389/fneur.2022.869900.
56. Havton LA, Thomas Carlstedt T. Repair and rehabilitation of plexus and root avulsions in animal models and patients. Curr Opin Neurol. 2009;22(6):570-4. doi:10.1097/WCO.0b013e328331b63f.
57. Albertin G, Kern H, Hofer C, Guidolin D, Porzionato A, Rambaldo A, et al. Two years of functional electrical stimulation by large surface electrodes for denervated muscles improve skin epidermis in SCI. Eur J Transl Myol. 2018;28(1):7373. doi:10.4081/ejtm.2018.7373.
58. Carraro U, Edmunds KJ, Gargiulo P. 3d false color computed tomography for diagnosis and follow-up of permanent denervated human muscles submitted to home-based functional electrical stimulation. Eur J Transl Myol. 2015;25(2):5133. doi:10.4081/ejtm.2015.5133.

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Electrical Stimulation Approaches in the First 21 Days

FATMA NUR ALCIN • NILUFER CETISLI-KORKMAZ

First 21 Days

After the last fragments of the motor axon and the intramuscular nerve terminals disappear, the excitability of muscle fibers decreases, and degeneration and fibrosis of muscle fibers occur. Even when there is a reinnervation of a muscle that has reached this point, adequate contraction cannot be achieved. If the motor point of such a muscle is stimulated by an electric current mimicking a nerve impulse, regular contraction can be achieved, and atrophy could be prevented to some extent.[1] The amplitude and duration of the stimulation required to ensure the muscle fiber contraction should be increased as muscle excitability decreases. For fully denervated human muscle, the minimum pulse duration required to form a contraction is approximately 1 millisecond (ms).[2] Applications include Galvanic and Faradic currents to achieve the optimal clinical effect. The Galvanic current stimulates the denervated muscle, whereas the Faradic current stimulates the innervated muscle. In cases of axonotmesis and neurotmesis of motor nerves, muscles and nerves do not respond to Faradic current, but the response could be obtained in the first 14-21 days because the degeneration state is not complete. Then, the response is interrupted, and this period of non-response continues until regeneration. In neuropraxia cases, there is a response to Faradic current because there is no degeneration in the nerve, and Faradic current is applied until regeneration is completed in training the paralyzed muscles.[1] The stimulation should provide a moderately strong contraction without unnecessary discomfort for the patient and should resemble the normal activity of the motor neuron. Both currents were found to be maximally effective in the 2 weeks following denervation. On the other hand, electrode placement is advocated to be made on the nerve body in order to make a greater contribution to the ignition of the motor unit.[3,4] In addition, monopolar and bipolar electrode placement could be made. In monopolar stimulation, the active electrode is placed on the motor point of the muscle and the passive electrode is placed proximal region (Figure 30.1). In bipolar practice, electrodes are placed on the origin and insertion of the muscle group (Figure 30.2).

Hoffman, observed that following the ES application to the nerve roots, the re-innervation of the partially denervated muscle began with intramuscular axon sprouting on the third day after surgery in the research that is one of the first animal studies on the use of ES after peripheral nerve injury.[5] In another study, sinusoidal ES was given to the spinal cord or Sciatic nerve roots at 50-100 Hertz (Hz), 1-5 milliamperes (mA), 10 to 60 minutes (min) immediately after partial denervation of the Sciatic nerve, following cross-section of the L5 spinal cord root. It has been reported that this stimulation period significantly accelerates the onset of axonal sprouting.[6] It is stated in the literature that currents greater than 4 mA negatively affect regeneration, because excessive direct current can be inhibitory for growing fibers. ES at a low-frequency of 2

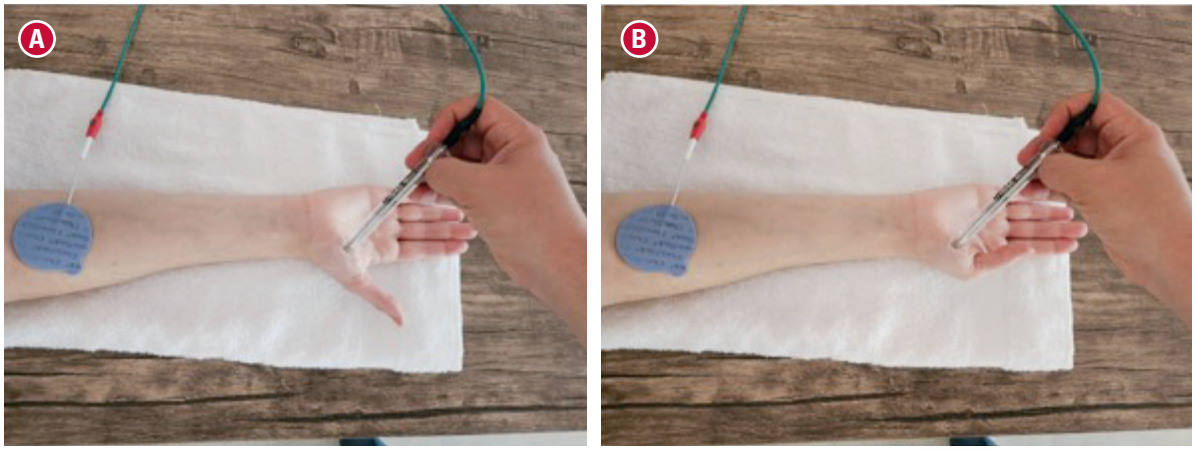

Figure 30.1 Monopolar application to Abductor Pollicis muscle: **A.** Starting position, **B.** During contraction.

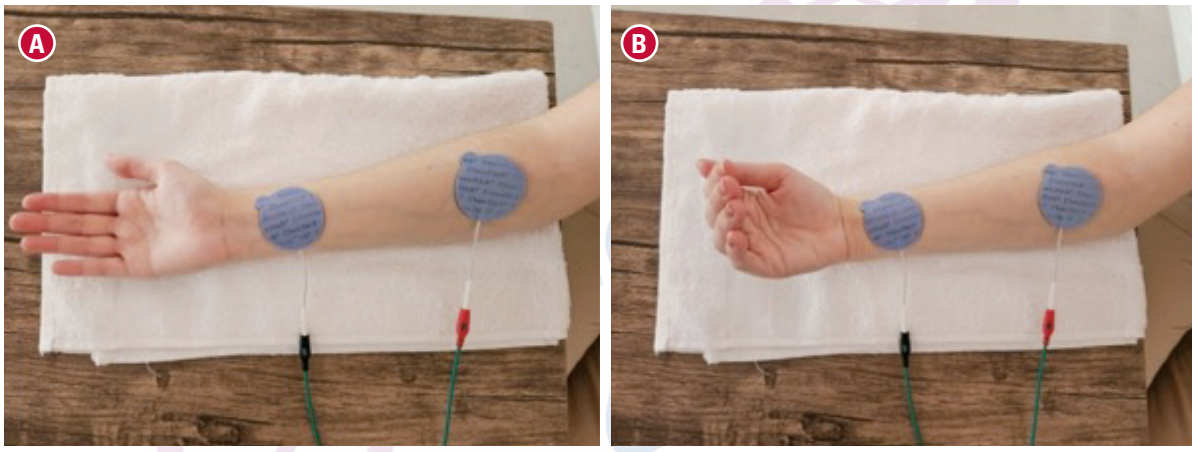

Figure 30.2 Bipolar application for forearm flexors. **A.** Starting position, **B.** During contraction.

Hz and a current of 1 mA indicates a more mature nerve regeneration.[7]

An example of important studies conducted in the following years is the study by Pocket & Gavin.[8] In this study, it was reported that ES given at 1 Hz for periods of 15 min, 30 min and 1 hour applied to the proximal of the crushed and impaired axonal continuity of the Sciatic nerve had a positive effect on earlier recovery of the toe extension reflex. In this study, it was evaluated that the ES of the crushed nerve has quite significant effects on the regeneration rate, although it does not affect the number of renewed axons. It has also been stated that the most effective time for stimulation is immediately after crushing (within about an hour).[8]

In another study conducted in the following years, repair was performed after Femoral nerve incision. Immediately after the repair, 20 Hz frequency stimulation was applied to the proximal nerve root with an implantable stimulator for 1 hour. The frequency used in the study was selected based on the average firing frequency of motor neurons in animals and humans. Continuous ES was applied for 1 hour, 24 hours, 1 week, or 2 weeks. As a result of the study, it was stated that axon growth from both sensory and motor neurons of stimulated nerves accelerated for all application periods, and the axons of all motor neurons regenerated within 21 days.[9] In these studies, the positive effects of short-term low-frequency ES on supporting nerve regeneration in animal models have been demonstrated. Subsequent studies have focused on elucidating the effects of short ES and the specific mechanisms responsible for axon

regeneration based on these studies. ES has also been shown to regulate cellular activities such as cell adhesion, cell proliferation, cell migration, and protein production.[10,11]

There are also animal studies conducted in the literature on the effect of ES combined with exercise on denervated muscles. In a study, it is aimed to clear the role of neuronal activity induced by ES and exercise, about promoting axonal regeneration and modulated plasticity in the spinal cord after nerve injury. The first group of the 4 adult rat groups received ES [3 Volts (V) at 20 Hz, 0.1 ms] for 1 hour per day immediately after the injury for 4 weeks, while the second group was subjected to treadmill exercise with a combined 1 hour ES (5 meters per min, 2 hours per day) for 4 weeks. The third group only exercised, whereas the control group received no treatment. The study indicated that acute ES, exercise, or both promote reinnervation of the muscle more but showed that the combination of ES and exercise has a more beneficial effect on the early stage of regeneration.[12]

There are also studies in the literature examining the effects of short-intensity-low-frequency ES on humans. Gordon et al. conducted a study on patients with severe carpal tunnel syndrome and thenar muscle denervation. In this randomized controlled clinical trial, ES was applied to the surgical decompression area of the subjects in the treatment group for 1 hour at 20 Hz using wire electrodes after surgical decompression of the carpal tunnel.[13] It was found that one year after the application, the stimulation group had a significantly higher number of motor units than the control group. Short-term low-frequency ES is effective in accelerating axonal regeneration in humans and enabling thenar muscle reinnervation to occur faster.[13]

In another double-blind, randomized controlled clinical trial involving 31 patients that have Digital nerve incision, ES up to 20 Hz and 30 V was applied to the Digital nerves for 1 hour after nerve transection. Significantly faster improvement in multimodal sensory functions was observed in patients receiving Digital nerve ES compared with patients receiving sham stimulation. After 6 months, it was observed that the cold and hot detection thresholds, static 2-point discrimination, and Semmes Weinstein monofilament tests of patients receiving stimulation reached normal thresholds, while there were still abnormal values in patients receiving sham stimulation.[14]

The first randomized controlled double-blind study showing improved functional results after ES was performed to treat traction injury of the Spinal Accessory nerve in 38 cancer patients who underwent neck dissection. While the patients were under general anesthesia, ES was given to the Spinal Accessory nerve for 1 hour (20 Hz, 3-5 V) before the wound closed, while the control group did not receive ES. After one year, the combined subjective and objective scores of shoulder function showed significantly greater improvement in patients receiving ES compared with control patients. At the same time, only 25% of the functional loss suffered by control patients was observed in this group.[15,16]

In an updated double-blind, randomized controlled clinical trial involving patients that have severe Cubital Tunnel Syndrome, ES was administered for a period of 1 hour (up to 20 Hz, 30 V) immediately after cubital tunnel decompression under general anesthesia. The control group was subjected to sham ES. In the results one year after surgery, it was stated that the patients in the ES group showed significant increases in the estimation of the number of motor units compared with the control group. Three years after surgery, it was found that the number of motor units of ES patients was more than doubled compared to sham stimulation control subjects. In addition to earlier muscle reinnervation in the ES group, the amplitudes of the compound muscle action potential also increased significantly at 3 years, and both grip and pinch strength improved significantly more in the ES group.[17] This study proves that ES is a promising adjunctive treatment option to peripheral nerve surgery to increase axonal regeneration and accelerate functional recovery.

In addition to the fact that 1 hour ES is effective in promoting motor axon regeneration, it has been stated that the same ES period is equally effective in supporting sensory axon regeneration.

ES was found to be ineffective in accelerating sensory nerve growth when the ES time period was extended from 1 hour to 14 days. The fact that sensory nerve regeneration is often lower than motor nerve regeneration, both in the absence and presence of ES, is effective in the formation of this condition.[10] These studies also show us the practicality of intraoperative ES application and the effect of 1 hour ES protocols. However, the application of 1-hour long-term ES through hooked or ringed nerve electrodes, which could only be used intraoperatively, is one of the important limitations of clinical use. It has been reported in the literature that the application of ES in the postoperative period with multi-day ES may have additional therapeutic benefits. Additionally, many studies in the literature concluded that long-term continuous ES may not improve regeneration. Whereas when nerves are stimulated intermittently with short ES, it may benefit regeneration and prevent neuronal damage due to excessive current.[7]

Table 30.1 Summary of studies applying ES for the first 21 days

Study	Parameters	Conclusion
Hoffman[5] (1952)	50-100 Hz 1-5 mA 10-60 min Sinusoidal ES	Significant acceleration of axonal sprouting initiation
Pocket and Gavin[8] (1985)	1 Hz 15 min, 30 min, and 1 hour	Positive effects on earlier recovery of the toe extension reflex
Al-Majed et al.[9] (2000)	20 Hz 1 hour, 24 hours, 1 week, and 2 weeks	Acceleration in axon growth from both sensory and motor neurons of stimulated nerves for all exposure times and regeneration of axons of all motor neurons within 21 days
Asensio-Pinilla et al.[12] (2009)	Group 1: 20 Hz, 3 V, 0,1 ms, 1 hour in a day x 4 weeks Group 2: 20 Hz, 3 V, 0,1 ms, 1 hour in a day x 4 weeks + 5 m/min, 2 hours in a day x 4 weeks exercise Group 3: 5 m/min, 2 hours in a day x 4 weeks exercise Group 4: Control (No treatment)	Acute ES and/or exercise promotes muscle reinnervation more, the combination of ES and exercise has a more beneficial effect in the early phase of regeneration
Gordon et al.[13] (2010)	20 Hz, 1 hour	Effective in accelerating axonal regeneration, faster thenar muscle reinnervation
Wong et al.[14] (2015)	20 Hz, 30 V, 1 hour	After 6 months, cold and hot detection thresholds, static two-point discrimination, and Semmes Weinstein monofilament tests of patients receiving ES reach normal thresholds
Barber et al.[16] (2018)	20 Hz, 3-5 V 1 hour	Combined subjective and objective scores for shoulder function after one year, significantly greater improvement in ES applied patients than in control patients
Power et al.[17] (2020)	20 Hz, 30 V 1 hour	A significant increase in motor unit number after one year, motor unit number of ES patients more than twice after three years compared to sham stimulation control subjects, significantly greater improvement in both grip and pinch strength
Javeed et al.[7] (2021)	2 Hz 1 mA	A more mature nerve regeneration

References

1. Tarakcı E. (2014), Faradik ve sinüzoidal akımlar. In: Özdinçler AR. (ed.) Fiziksel modaliteler ve elektroterapi. İstanbul, Türkiye: İstanbul Tıp Kitabevi, p. 105-108. ISBN:6054499807.
2. Eberstein A, Eberstein S. Electrical stimulation of denervated muscle: Is it worthwhile? Med Sci Sports Exerc. 1996;28(12):1463-9. doi:10.1097/00005768-199612000-00004.
3. Pieber K, Herceg M, Paternostro-Sluga T, Schuhfried O. Optimizing stimulation parameters in functional electrical stimulation of denervated muscles: A cross-sectional study. J Neuroeng Rehabil. 2015;12:51. doi:10.1186/s12984-015-0046-0.
4. Justice D, Awori J, Carlson S, Chang KW, Yang LJ. Use of neuromuscular electrical stimulation for treating neonatal brachial plexus palsy: A literature review. The Open Journal of Occupational Therapy. 2018;6(3):1-11. doi:10.15453/2168-6408.1431.
5. Hoffman H. Local re-innervation in partially denervated muscle: A histo-physiological study. Aust J Exp Biol Med Sci. 1950;28(4):383-98. doi:10.1038/icb.1950.39.
6. Hoffman H. Acceleration and retardation of the process of axon-sprouting in partially devervated muscles. Aust J Exp Biol Med Sci. 1952;30(6):541-66. doi: 10.1038/icb.1952.52.
7. Javeed S, Faraji AH, Dy C, Ray WZ, MacEwan MR. Application of electrical stimulation for peripheral nerve regeneration: Stimulation parameters and future horizons. Interdisciplinary Neurosurgery. 2021;24,101117. doi:10.1016/j.inat.2021.101117.
8. Pockett S, Gavin RM. Acceleration of peripheral nerve regeneration after crush injury in rat. Neurosci Lett. 1985;59(2):221-24. doi:10.1016/0304-3940(85)90203-4.
9. Al-Majed AA, Neumann CM, Brushart TM, Gordon T. Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration. J Neurosci. 2000;1;20(7):2602-8. doi:10.1523/JNEUROSCI.20-07-02602.2000.
10. Gordon T, English AW. Strategies to promote peripheral nerve regeneration: Electrical stimulation and/or exercise. Eur J Neurosci. 2015;43(3):336-50. doi:10.1111/ejn.13005.
11. Kubiak CA, Kung TA, Brown DL, Cederna PS, Kemp SWP. State-of-the-art techniques in treating peripheral nerve injury. Plast Reconst. 2018;141(3):702-10. doi:10.1097/prs.0000000000004121.
12. Asensio-Pinilla E, Udina E, Jaramillo J, Navarro X. Electrical stimulation combined with exercise increase axonal regeneration after peripheral nerve injury. Exp Neurol. 2009;219(1):258-65. doi:10.1016/j.expneurol.2009.05.0.
13. Gordon T, Amirjani N, Edwards DC, Chan KM. Brief post-surgical electrical stimulation accelerates axon regeneration and muscle reinnervation without affecting the functional measures in carpal tunnel syndrome patients. Exp Neurol. 2010;223(1):192-202. doi:10.1016/j.expneurol.2009.09.020.
14. Wong JN, Olson JL, Morhart MJ, Chan KM. Electrical stimulation enhances sensory recovery: A randomized controlled trial. Ann Neurol. 2015;77(6):996-1006. doi:10.1002/ana.24397.
15. Zuo KJ, Gordon T, Chan KM, Borschel GH. Electrical stimulation to enhance peripheral nerve regeneration: Update in molecular investigations and clinical translation. Exp Neurol. 2020;113397. doi:10.1016/j.expneurol.2020.113397.
16. Barber B, Seikaly H, Chan KM. Beaudry R. Intraoperative brief electrical stimulation of the spinal accessory nerve (BEST SPIN) for prevention of shoulder dysfunction after oncologic neck dissection: A double-blinded, randomized controlled trial. J Otolaryngol Head Neck Surg. 2018;47(1):7. doi:10.1186/s40463-017-0244-9.
17. Power HA, Morhart MJ, Olson JL, Chan KM. Postsurgical electrical stimulation enhances recovery following surgery for severe cubital tunnel syndrome: A double-blind randomized controlled trial. Neurosurgery. 2020;86:768-77. doi:10.1093/neuros/nyz322.

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Electrical Stimulation Approaches Between the First 21 Days and 3 Months

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Between the 21 Days-3 Months

Since time is required for degeneration to occur in the injured nerve, the degeneration reaction is determined by electrodiagnostic tests after the 14-21 days. In the presence of a partial degeneration reaction, the response to Faradic current in the nerve decreases. The response to Galvanic current is normal in muscle and nerve. The treatment is performed with Faradic current. In the presence of a complete degeneration reaction, there is no response to the Faradic current in the nerve. The treatment is performed with Galvanic current. In the presence of a definite degeneration reaction, there is no response to Faradic and Galvanic current in the nerve. The response to the Galvanic current is delayed in the muscle. The treatment is performed with Galvanic current until the response to Galvanic current is obtained.[1]

In the literature, it has been stated that the current to be applied should be an intermittent current of 10 milliseconds (ms) or longer, monophasic or biphasic form, in order to minimize denervation atrophy in denervated muscles.[2] In order for ES to be effective, it is necessary to stimulate all the muscle fibers in a muscle.[3] It was suggested that the application should be performed with surface electrode or implant electrodes to the midpoint or motor point of the muscle with a frequency of 2-4 pulses per second for slow-contracting muscles and 20-40 pulses per second for fast-contracting muscles.[2] Intermittent current does not physiologically stimulate muscle units in the application of NMES, and this primarily results in the triggering of muscles that are not resistant to fatigue. For this purpose, daily application of a progressive current with a deceleration of 2-3 seconds (s) for 15-20 minutes (min), and a duration of 50-150 ms is also the recommended protocols. Excessive stimulation of innervated muscle fibers is prevented with this application. It is argued that it is easier to select preferably denervated muscle fibers by gradually increasing the current. To cause contraction in denervated muscles, rectangular pulses with sufficient pulse duration (30 ms or more) or triangular pulses with long duration (100-500 ms) could be used. However, the use of rectangular pulses could cause excessive contraction of neighboring innervated muscles. Therefore, in clinical practice, triangular pulses with a pulse duration of 200 ms or 500 ms are mainly used, and in this way selective stimulation of the muscle is possible. The threshold current intensity can be significantly lower when stimulation is performed with 500 ms instead of 200 ms.[4] All stimulation patterns are not equally effective in terms of restoring the normal features of denervated muscles. For example, it has been shown that excitation by direct rectangular wave current with a duration of 25 ms at 20 Hertz (Hz) is better than pulses of 100 ms at 2 Hz or 0.2 ms at 20 Hz.[3] Even if stimulation started 28 days after denervation, ES is known to protect the muscle from atrophy at a level of 72-86%.[3]

A recent randomized controlled clinical trial demonstrated the benefit of ES administration

in addition to the use of steroids and acyclovir in the functional recovery of the Facial nerve. In the study, ES was applied to patients within 2 weeks after the onset of symptoms via surface electrodes placed as a cathode on the main branches of the Facial nerve and as anode on the mastoid process. The ES protocol was determined as below-threshold [1.4 milliamperes (mA), 10 ms) continuous daily stimulation at 20 Hz with a rectangular, monophasic pointed tip And this treatment was continued for 2 months (until the cessation of Wallerian Degeneration) (Figure 31.1). As a result, it has been reported that patients treated with ES have an earlier functional return within 3 months of the onset of symptoms.[5]

A study evaluated the effect of polarity and pulse duration on the stimulation intensity of triangular pulses in denervated muscles in patients with peripheral nerve lesions. Twenty-four patients who have denervated Extensor Digitorum Communis muscle, and 24 patients who have denervated Tibialis Anterior muscle due to peripheral nerve lesions is included in this study. Four different combinations of triangular pulses with various durations and polarity were tried and randomly transmitted to the denervated muscles. As a result of the study, ES of the denervated Tibialis Anterior muscle with a triangular current of 200 ms duration and a proximally applied cathode polarity was recommended.[4]

It was reported in a study by Ju et al. that 6-week ES showed rapid functional recovery and superior axonal regeneration.[6] However, this study also reported that invasive stimulation is more effective than non-invasive stimulation. Another double-blind randomized study in the literature examined 38 patients with traumatic peripheral nerve injury with axonal injury and clinical impairment of two muscles treated with real or sham ES. ES applied by using superficial electrodes consisted of triangular-rectangular stimuli with a duration of 150 ms and a frequency of 1 Hz, and the intensity used for each patient was 0.5 mA above the lowest intensity required to ensure muscle contraction. In this treatment, which was applied for 3 months, 3 weekly sessions consisting of 90 min each were applied to the patients. In this study, contrary to other studies, it was concluded that ES of the denervated muscle had no significant beneficial effect compared to sham therapy.[7] In another study, in a rat model with Sciatic nerve transection injury, rats were divided into two subgroups and nerve repair was performed 1 day, 1 week, 1 month, and 2 months after the injury. ES at a frequency of 20 Hz, a pulse width of 100 ms, and a direct current voltage of 3 Volts (V) was given to the rats in the experi-

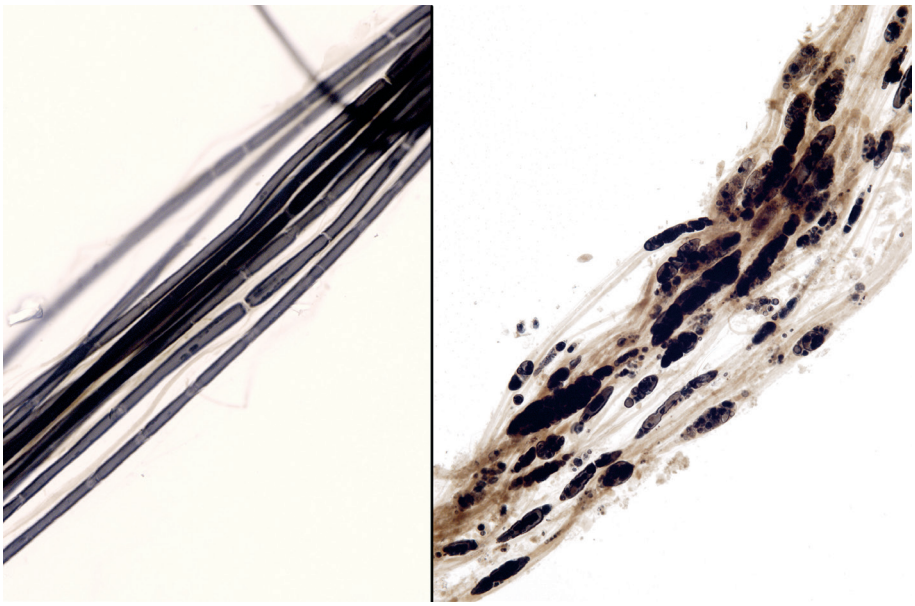

Figure 31.1 Myelinated nerve fibers and Wallerian Degeneration

mental group and the rats in the control group had not received any ES after the operation. The study results showed that the degree of fibrosis in the distal nerve tissue clearly increases as the repair time is prolonged, and ES after delayed repair does not provide positive results.[8] Another study aimed to determine whether ES still has any effect on nerve regeneration after sufficient time has passed. In the study, a delayed nerve repair model was designed in which rats received delayed nerve repair after 1 day, 1 week, 1 month, and 2 months. During all time periods, the nerve roots of the rats in the intervention group were bridged with an absorbable channel and given a weak ES for 1 hour, while the control group did not receive any treatment. All rats were given a recovery period for 6 weeks before the final functional test and tissue observation. The results of the study showed that after repair delays of 1 month and 2 months, there was more collagen tissue hyperplasia in the distal nerve in all rats. However, it has been confirmed that ES given within 1 month after the injury is effective in supporting nerve regeneration, but the intervention within 1 month after the injury is ineffective.[9]

Table 31.1 Summary of studies applying ES for the 21 days-3 months

Study	Parameters	Conclusion
Han et al.[8] (2015)	Direct current 20 Hz 100 ms, 3 V	As the repair time increases, the degree of fibrosis in the distal nerve tissue increases, and ES does not yield positive results after delayed repair
Kim and Choi[5] (2015)	Monophasic rectangle stimulus 20 Hz Mean amplitude 1.4 mA, 10 ms 2 months	Earlier functional return within 3 months of symptom onset in patients treated with ES
Piccini et al.[7] (2020)	Triangular-rectangular stimulus 1 Hz 0.5 mA, 150 ms 90 min/session x 3 days/week 3 months	No significant beneficial effect of ES of denervated muscles compared to sham therapy

References

1. Korkmaz NÇ, Kırdı N. (2016), Denerve kasın elektrik stimülasyonu. In: Kırdı N. (ed.) Elektroterapide Temel Prensipler ve Klinik Uygulamalar. Ankara, Türkiye: Hipokrat Kitabevi, p. 133-143. ISBN:978-605-9160-03-2.
2. Michlovitz SL. Is there a role for ultrasound and electrical stimulation following injury to tendon and nerve? J Hand Ther. 2005;18(2):292-6. doi:10.1197/j.jht.2005.02.013.
3. Eberstein A, Eberstein S. Electrical stimulation of denervated muscle: Is it worthwhile? Med Sci Sports Exerc. 1996;28(12):1463-9. doi:10.1097/00005768-199612000-00004.
4. Pieber K, Herceg M, Paternostro-Sluga T, Schuhfried O. Optimizing stimulation parameters in functional electrical stimulation of denervated muscles: A cross-sectional study. J Neuroeng Rehabil. 2015;12:51. doi:10.1186/s12984-015-0046-0.
5. Kim J, Choi JY. The effect of subthreshold continuous electrical stimulation on the facial function of patients with Bell's palsy. Acta Otolaryngol. 2015;136(1):100-5. doi:10.3109/00016489.2015.1083121.
6. Ju C, Park E, Kim T, Kim T, Kang M, Lee KS, et al. Effectiveness of electrical stimulation on nerve regeneration after crush injury: Comparison between invasive and non-invasive stimulation. PLoS One. 2020;15(5):e0233531. doi:10.1371/journal.pone.0233531
7. Piccinini G, Cuccagna C, Caliandro P, Coraci D, Germanotta M, Pecchioli C, et al. Efficacy of electrical stimulation of denervated muscle: A multicentre, double blind randomized clinical trial. Muscle Nerve. 2020. 61(6):773-8. doi:10.1002/mus.26880.
8. Han N, Xu C, Wang T, Kou Y, Yin X, Zhang P, et al. Electrical stimulation does not enhance nerve regeneration if delayed after sciatic nerve injury: The role of fibrosis. Neural Regen Res. 2015;10(1):90-4. doi:10.4103/1673-5374.150714.
9. Xu C, Kou Y, Zhang P, Han N, Yin X, Deng J, et al. Electrical stimulation promotes regeneration of defective peripheral nerves after delayed repair intervals lasting under one month. PLoS One. 2014;9:e105045. doi:10.1371/journal.pone.0105045.

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Electrical Stimulation Approaches After 3 Months

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After 3 Months

Denervated skeletal muscle experiences a rapid loss in both mass and contractile power. If the injury involves the lower motor neurons, this atrophy occurs much more severely. Muscle atrophy becomes more complicated with fibrosis within a few months after denervation.[1] In a study in the literature, it was stated that the endoneurium of distal nerve stumps that have been denervated for 1-2 months contains axonless Bungner bands (consisting of a column of overlapping Schwann cell cytoplasm processes, each surrounded by a permanent basal lamina). Distal nerve stumps that have been denervated for 4-6 months contain an increased amount of collagen and a relatively small number of Schwann cells.[2] The common belief is that due to atrophy, healing fails and denervated muscle fibers are replaced by fat and fibrosis.[3] The literature shows that it takes about 1 month for all motor nerve fibers to grow and cross the nerve suture region. During this time, the distal nerves and muscles are constantly degenerating, and the function of the Schwann cells at the distal end gradually weakens as the denervation period is prolonged and the Schwann cells become apoptotic.[4]

Although early denervation has been frequently addressed in both animal and human studies, studies on the long-term effects of denervation are still insufficient.[1] Studies in the literature indicate that nerve cell bodies in the spinal cord and dorsal root ganglia tend to die as the denervation time increases, Schwann cells become apoptotic, and axonal regeneration in the distal stump after prolonged denervation reacts only slightly to the signal expression. Therefore, some of the current studies have reported that ES applied after delayed repair of nerve damage in these conditions is unfavorable for nerve regeneration.[4] A study in which urgent 0 or 1, 3 or 6 months delayed repair was performed with a nerve graft after Sciatic nerve transection was applied to rats can be given as an example of studies that support this idea. Thirteen weeks after the repair, the regeneration of spinal motor neurons was evaluated. In the study, a dramatic decrease in the number of regenerated motor neurons and myelinated axons in the distal nerve stump was observed in the delayed groups of 3 and 6 months, whereas a progressive increase in fibrosis and proteoglycan scar markers in the distal nerve was detected with an increase in delayed repair time. This study has indicated that the critical time threshold at which the regeneration result becomes very poor appears to be 3 months.[5] However, the literature shows that although peripheral nerve regeneration progresses relatively slowly, the decrease in excitability also progresses very slowly. This also shows that a strong stimulus can still produce a response as long as some contractile tissue is present until 1-3 years after denervation.[1,3] Another study was designed to evaluate the effects of chronic denervation on the capacity of Schwann cells in the distal nerve stump to promote axonal regeneration and remyelinate regenerated axons. In this study, a delayed repair protocol was

applied in which the Peroneal nerve in the rat was denervated for 0-24 weeks before cross-stitching of newly axotomized Tibial and chronically denervated Peroneal nerve stumps. It has been found that short-term denervation of ≤4 weeks does not affect axonal regeneration, but longer-term denervation deeply reduces the number of motor neurons and axons in the distal nerve stump. However, the study also states that atrophic Schwann cells retain their capacity to re-myelinate renewed axons. These findings also show that chronically denervated Schwann cells show progressive inability to support axonal regeneration, despite which they have a constant capacity to re-myelinate renewed axons.[6] For this reason, electrodiagnostic tests should be repeated after the 3rd month of denervation and treatment should be continued with the appropriate current according to the type of degeneration reaction.

In the literature, it was also been proved that stimulation that starts after the 64th day of denervation increases tetanic tension 37 times for the rat Soleus muscle. Similar results were obtained with much longer period (between 4-10 months) denervation and stimulated in the last 3-8 weeks of denervation of the Soleus and Extensor Digitorum Longus muscles. Results in the literature support that the recovery of denervated muscle becomes more difficult as the interval between the onset of denervation and the onset of stimulation increases.[7] However, early nerve repair is not possible in cases where serious soft tissue trauma occurs with wound contamination. After most closed traction nerve damages, surgeons often postpone operative repair for 3-6 months to evaluate spontaneous regeneration in clinical evaluation. ES can still increase the regenerative capacity even after the repair of such chronic nerve lesions, but the functional recovery is weaker.[8,9] Studies in the literature show that the initial duration of NMES treatment varies between 3 weeks and 4.5 months. If the axon is intact, the injured nerve can be renewed at a rate of 1 inch per month. For these reasons, the first 3-6 months are critical for determining spontaneous recovery.[10]

In one of the current studies involved nine patients who had complete denervation of the Tibialis Anterior muscles and had undergone between 2 and 40 months after the lesion. The Tibialis Anterior muscle of the patients was stimulated with 20 milliseconds (ms) rectangular wave pulses at 25 Hertz (Hz) for 20 minutes (min), 2 times a day, 5 days a week, for a total of 3 weeks. It was stated that the level of foot dorsiflexion increases after treatment and the course of denervation atrophy is reversed.[11] In another study, the effects of ES on individuals with late-stage Facial nerve palsy were examined. In this study, individuals who were diagnosed with Facial nerve Palsy between 1 and 7 years ago were divided into two groups: those who underwent Facial nerve reconstruction surgery and those who did not. Both groups are divided into those who receive ES and those who do not. ES consisting of biphasic triangular stimuli was applied 2 times a day, 5 days a week, and for 10 min to prevent fatigue. The phase duration is set to 100-500 ms, and the amplitude is set to 5-27 milliamperes (mA). According to the results of the study, there was no difference in terms of the duration of reinnervation between the individuals who received and did not receive ES after Facial nerve reconstruction surgery, while less synkinesis was recorded with ES in the group who did not receive surgery.[12] In a case report in which the restorative potential of intense ES was investigated in a patient with long-term Quadriceps Femoris muscle denervation, there were none of the voluntary movements, sensations, and reflexes in the muscle and the condition was found to be consistent with total denervation. Eighteen months after the injury, two pairs of large electrodes were connected to the front surface of the thighs on proximal and distal portions, and ES therapy was started. The training was started with single twitches at 2 Hz and applied for 15 min a day and 5 days a week. After 4 months, the excitability of muscle fibers has improved enough for shorter duration pulses to be used. Therefore, the protocol is strengthened with an additional tetanic model consisting of 40 ms pulses transmitted at 20 Hz for 2 seconds (s) on and 2 s off for 15 min a day, 5 days a week. The total amount of stimulation was then applied for 30 min per day for each muscle. After 26 months of stimulation, the

patient's atrophy decreased, and the knee torque became sufficient to allow standing without upper limb support. This study shows that ES of muscles, which is tried with an extremely intensive protocol in patients with lower motor neuron lesions, can provide a significant functional return.[13]

There are findings in the literature that short-term low frequency ES accelerates axon growth and muscle reinnervation after emergency neurosurgery in rats and human patients. These findings suggest that ES improves regeneration after delayed nerve repair. To test this hypothesis in a study, rats' Common Peroneal nerves have been chronically axotomized and / or Tibial nerve Schwann cells and ankle extensor muscles have been chronically denervated with ligation and transection. After the neurosurgery was performed 3 months later, sham stimulation was given to one group, while 20 Hz ES was applied to the other group for 1 hour with wire electrodes. As a result of the study, it was concluded that ES significantly increases the number of both motor and sensory neurons that experience axonal regeneration and is effective in improving target reinnervation after delayed nerve repair.[14] Huang et al. also investigated the potential of short-term ES in enhancing functional recovery in delayed nerve damage repair.[15] In the study, the Sciatic nerve of rats was cut and the repair of nerve damage was delayed for 2, 4, 12, and 24 weeks. After these periods, one end of the wire electrodes was fixed in a ring around the nerve stump proximal to the lesion, and a sec-

Table 32.1 Summary of studies applying ES for after 3 months

Study	Parameters	Conclusion
Valencic et al.[11] (1986)	Square wave stimulus 25 Hz 20 ms 20 min/session 2 times x day 5 days/week 3 weeks	Increasing the level of foot dorsiflexion and reversing the course of denervation atrophy
Kern et al.[13] (2004)	First 4 months: 2 Hz 15 min/session 1 time x day 5 days/week After 4th months: 2 sec on, 2 sec off, 40 ms, 20 Hz 15 min/session 1 time x day 5 days/week Total 26 months	Decreased Quadriceps Femoris atrophy, with knee torque sufficient to stand up without upper extremity support
Huang et al.[15] (2013)	20 Hz 3 V 20 min	A significant increase in the diameter of the regenerated axons and the thickness of the myelin sheath, as well as the number of motor and sensory neurons. Increased amplitude of the compound muscle action potential and nerve conduction velocity in the Gastrocnemius muscle
Elzinga et al.[14] (2015)	20 Hz 1 hour	ES significantly increases the number of both motor and sensory neurons undergoing axonal regeneration and is effective in improving target reinnervation after delayed nerve repair
Puls et al.[12] (2020)	Biphasic triangle wave stimulus 10 min/session 2 times x day 5 days/week 100-500 ms 5-27 mA	No difference in reinnervation time between individuals who received and did not receive ES, less synkinesis with ES in the group that did not receive surgery

ond electrode used as an anode was placed on a muscle close to the nerve and a short depolarizing ES of 3 Volts (V), 20 Hz was applied for 20 min. As a result of the study, it was found that the diameter of the renewed axons and the thickness of the myelin sheath, as well as the number of motor and sensory neurons, significantly increased. However, it was found that the amplitude of the compound muscle action potential and nerve conduction velocity also increased in the Gastrocnemius muscle. This condition has shown that muscle atrophy is reversed partially. According to the study, the effectiveness of ES decelerated gradually with delays ranging from 2-24 weeks. These results prove that the application of ES after delays of up to 24 weeks can support nerve regeneration and increase functional recovery.[15] In a study with the opposite result, the Extensor Digitorum Longus muscle of rats was subjected to 3.5 months of denervation by Peroneal nerve axotomy. In the study, ES was applied to some rats during the denervation period. The results of the study revealed that ES applied during the denervation period did not improve muscle mass, strength, or motor function.[16] Although there are studies stating otherwise, in the light of many studies in the literature, it can be said that ES still has the potential to increase regeneration after chronic nerve injuries or delayed nerve repair, but early treatment gives better results.[9]

Conclusion

When the literature is examined, it is seen that the results of NMES in the treatment of completely denervated muscles are inconsistent.[10,17] It is thought that one of the reasons for the discrepancy in the results may be muscle damage and fatigue caused by the high electrical intensity used in some studies. Therefore, physiotherapists should take measures during to avoid overstimulating or exhausting the surrounding muscles in particular. In addition, although ES is not suitable for people with heart disease, pacemakers, risk of bleeding, and risk of thromboembolism, caution should also be exercised when using it on people who are pregnant or have epilepsy, sensory impairment, or joint replacements. ES should not be applied on the carotid sinus, through the thorax, on the diseased skin or in the laryngeal region.[10] In an article written on the use of ES for denervated muscle, it was stated that based on the results of animal experiments, solving the problem of using ES to benefit denervated muscle depends on the appropriate stimulation parameters, stimulation current and type, and correct placement of electrodes.[7] Clinical trials demonstrating the effects of ES on nerve regeneration are relatively new. In these studies, the inability to clearly understand the mechanisms by which functional recovery is performed, the inability to decently optimize stimulation settings, and the inability to characterize the effects on the cranial nerves could be cited as obstacles to the use of ES. Since the mechanism by which simulation affects the course of denervation atrophy is not clearly known, the selection of stimulation parameters and models used in studies is mostly done by trial-and-error methods. The lack of clarity in terms of application in these studies leads to continuing barriers to the use of ES in patients despite the positive effects proven in current studies.[7,18] Considering the important points in practice, it is important for physiotherapists using ES to further decipher the effectiveness of ES on nerve regeneration in the human population without ignoring the results of studies.

References

1. Carraro U, Rossini K, Mayr W, Kern H. Muscle fiber regeneration in human permanent lower motoneuron denervation: Relevance to safety and effectiveness of FES-training, which induces muscle recovery in SCI subjects. J Artif Organs. 2005;29(3):187–91. doi:10.1111/j.1525-1594.2005.29032.x.
2. Li H, Terenghi G, Hall SM. Effects of delayed re-innervation on the expression of c-erbB receptors by chronically denervated rat Schwann cells in vivo. Glia. 1997;20(4):333–47. doi:10.1002/(sici)1098-1136(199708)20:4<333::aid-glia6>3.0.co;2-6.
3. Gordon T, Brushart TM, Chan KM. Augmenting nerve regeneration with electrical stimulation. Neurol. Res. 2008;30(10):1012–22. doi:10.1179/174313208x362488 .
4. Han N, Xu C, Wang T, Kou Y, Yin X, Zhang P, Xue F. Electrical stimulation does not enhance nerve regeneration if delayed after sciatic nerve injury: The role of fibrosis. Neural Regen Res. 2015;10(1):90-4. doi:10.4103/1673-5374.150714.
5. Jonsson S, Wiberg R, McGrath AM, Novikov LN, Wiberg M, Novikova LN, et al. Effect of delayed peripheral nerve repair on nerve regeneration, schwann cell function and target muscle recovery. PLoS One. 2013;8(2):e56484. doi:10.1371/journal.pone.0056484.

6. Sulaiman OAR, Gordon T. Effects of short- and long-term Schwann cell denervation on peripheral nerve regeneration, myelination, and size. Glia. 2000;32(3):234–46. doi:10.1002/1098-1136(200012)32:3<234::aid-glia40>3.0.co;2-3.
7. Eberstein A, Eberstein S. Electrical stimulation of denervated muscle: Is it worthwhile? Med Sci Sports Exerc. 1996;28(12):1463-9. doi:10.1097/00005768-199612000-00004.
8. Gordon T, Wood P, Sulaiman OAR. Long-term denervated rat schwann cells retain their capacity to proliferate and to myelinate axons in vitro. Front Cell Neurosci. 2019;12:511. doi:10.3389/fncel.2018.00511.
9. Javeed S, Faraji AH, Dy C, Ray WZ, MacEwan MR. Application of electrical stimulation for peripheral nerve regeneration: Stimulation parameters and future horizons. Interdisciplinary Neurosurgery. 2021;24:101117. doi:10.1016/j.inat.2021.101117.
10. Justice D, Awori J, Carlson S, Chang KW, Yang LJ. Use of neuromuscular electrical stimulation for treating neonatal brachial plexus palsy: A literature review. OJOT. 2018;6(3). doi:10.15453/2168-6408.1431.
11. Valencic V, Vodovnik L, Stefancic M, Jelnikar T. Improved motor response due to chronic electrical stimulation of denervated tibialis anterior muscle in humans. Muscle Nerve. 1986;9(7):612-7. doi:10.1002/mus.880090706.
12. Puls WC, Jarvis JC, Ruck A, Lehmann T, Guntinas-Lichius O, Volk GF. Surface electrical stimulation for facial paralysis is not harmful. Muscle Nerve. 2020;61(3):347-53. doi:10.1002/mus.26784.
13. Kern H, Salmons S, Mayr W, Rossini K, Carraro U. Recovery of long-term denervated human muscles induced by electrical stimulation. Muscle Nerve. 2004;31(1):98-101. doi:10.1002/mus.20149.
14. Elzinga K, Tyreman N, Ladak A, Savaryn B, Olson J, Gordon T. Brief electrical stimulation improves nerve regeneration after delayed repair in Sprague Dawley rats. Exp Neurol. 2015;269:142-53. doi:10.1016/j.expneurol.2015.03.022.
15. 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. Eur J Neurosci. 2013;38(12):3691-701. doi:10.1111/ejn.12370.
16. Dow DE, Cederna PS, Hassett CA, Dennis RG, Faulkner JA. Electrical stimulation prior to delayed reinnervation does not enhance recovery in muscles of rats. Restor Neurol Neurosci. 2007;25(5-6):601-10. PMID:18334775.
17. Haastert-Talini K, Grothe C. Electrical stimulation for promoting peripheral nerve regeneration. Int Rev Neurobiol. 2013;109:111-24. doi:10.1016/B978-0-12-420045-6.00005-5.
18. Zuo KJ, Gordon T, Chan KM, Borschel GH. Electrical stimulation to enhance peripheral nerve regeneration: Update in molecular investigations and clinical translation. Exp Neurol. 2020;113397. doi:10.1016/j.expneurol.2020.113397.

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