EMG-TRIGGERED NEUROMUSCULAR ELECTRICAL STIMULATION FOR MUSCULOSKELETAL REHABILITATION OF STROKE

Pratiwi NMD[1], Tedyanto EH[1], Arimbawa IK[1], Mintarjo JA[2], and Widyadharma IPE[1].
[1]Department of Neurology, Faculty of Medicine, Universitas Udayana, 80234 Denpasar, Bali, Indonesia.
[2]Faculty of Medicine, Hang Tuah University, Surabaya, East Java, Indonesia.

Correspondence:
Ni Made Dwita Pratiwi,
Department of Neurology,
Faculty of Medicine,
Universitas Udayana, 80234 Denpasar,
Bali, Indonesia,
Email: dwtpratiwi@gmail.com

Abstract

A decline in stroke-related mortality has led to an increased prevalence of post-stroke complications, globally. One of the most significant clinical effects of stroke are musculoskeletal problems. Musculoskeletal issues are typically induced by hemiplegia and they occur on the affected side. They also may not appear for weeks or months after a stroke. The most frequent musculoskeletal complications of stroke include motor loss, spasticity, shoulder discomfort, and wrist flexion contracture. Neuromuscular electrical stimulation (NMES) is a rehabilitation technique advised for stroke patients. NMES contracts muscles innervated by an external electrical stimulus, with or without patient participation (active or passive). There is evidence that NMES can strengthen muscles, reduce spasticity, increase corticospinal neural circuit excitability, and improve neuroplasticity. Electromyogram (EMG)-triggered NMES is a device that identifies subtle electrical EMG signals that remain discernible in paralyzed muscles after a stroke and utilizes these signals to trigger electrical stimulation impulses to the same paralyzed muscles, resulting in muscle movement. A study found that EMG-triggered NMES was superior to cyclic-NMES for increasing wrist extension and grip strength following the intervention.

Keywords: Electromyography, Electromyogram-triggered, Musculoskeletal Rehabilitation, Neuromuscular Electrical Stimulation, Stroke

Introduction

The incidence of post-stroke complications worldwide is increasing due to the decline in stroke-related fatalities. Many stroke survivors experience some long-term complications, including musculoskeletal complications. Primary care physicians are on the front line to optimize the management of chronic sequelae and outcomes of stroke. Thus, early diagnosis and adequate management are crucial (1).

Neuromuscular electrical stimulation (NMES) is a device that is used for post-stroke rehabilitation therapy, especially in musculoskeletal rehabilitation. NMES stimulates muscle by applying an electrical patch, with or without patient participation (active or passive). The latter is classified as passive because no effort is required to maintain muscular contraction. This is the basis of cyclic-NMES (2-4). On the other hand, electromyogram (EMG)-triggered NMES requires active participation of muscular contraction. In this technique, target muscles are stimulated directly by voluntary EMG activity from the same muscle. EMG-triggered NMES requires an active participant to induce electrical stimulation and activate the related NMES-induced muscle contractions. It can increase a patient's range of motion, reduce spasticity due to decreased muscle tone, and improve neural circuits after stroke (5-7). Herein, we provide a literature review about the musculoskeletal complications of stroke, the type of NMES, and the benefits of EMG-triggered NMES for post-stroke rehabilitation.

Musculoskeletal complications of stroke

Many stroke survivors experience post-stroke complications, such as musculoskeletal manifestations. Musculoskeletal complications are most often caused by hemiplegia, and they manifest on the hemiplegic side. Motor deficits, spasticity, shoulder pain, and wrist flexion contractures are the most common musculoskeletal complications of stroke (1). These musculoskeletal complications may not manifest for weeks or months after a stroke. About 80% of stroke patients experience hemiparesis, with more

than 40% chronically. It is caused by a lack of motor signal transmission from the brain's motor cortex to the muscles due to neuronal loss. This pathological process may cause muscle weakness or contractures, muscle tone changes, and motor control impairments (8, 9).

Hemiplegic shoulder pain (HSP) is frequent. Approximately 9–40% of hemiplegic stroke cases experience HSP 2–3 months after the onset of a stroke. HSP can be divided into four categories. First, misaligned joint due to hemiplegia, producing sharp joint pain. Second, spasticity causing muscle pain (dull pain). Spasticity is an inappropriate involuntary muscle that can cause pain, stiffness, and immobilization, affecting approximately 60% of stroke survivors. The worst outcome of spasticity is that it may produce contractures that lead to pressure ulcers (10, 11). Third, central post-stroke pain causes diffuse pain. Fourth, reflex sympathetic dystrophy affects the entire limb and shoulder (12-14). Hand and wrist flexion contractures may also develop in hemiplegic patients. Permanent contracture of the hand impedes hand function rehabilitation (15).

Neuromuscular electrical stimulation (NMES)

Neuromuscular electrical stimulation (NMES) is a technique that stimulates lower motor neurons to induce muscle contractions. NMES is applied transcutaneously or intramuscularly. There are two types of NMES are available: (i) in cyclic NMES, the muscle is stimulated repeatedly at almost near maximum contraction, with no voluntary effort required (also called passive NMES), and (ii) in EMG-triggered NMES, the muscle is triggered or controlled by electrical activity from the target muscle to elicit the desired stimulation. EMG-triggered NMES detects the residual electrical activity of the muscle and uses these signals to trigger electrical stimulation impulses to the same muscles, resulting in muscle movement (16, 17).

NMES is a therapeutic method developed to stimulate motor rehabilitation. This technique produces muscle contractions using electrical impulses. The impulse produced by NMES is delivered through electrodes placed on the skin and then continues to the specific muscle group to be stimulated. Impulses from NMES mimic action potentials generated by the central nervous system (CNS) that cause muscle contraction. Normal electrical excitation occurs regularly in lower motor neurons and the muscles they innervate, allowing NMES to be utilized to activate neuromuscular activity of paretic limbs following a stroke (18, 19).

Physiotherapists have long used NMES to artificially produce muscle contractions caused by abnormal muscles/nerves or injuries. NMES is used to re-educate muscle function, assist muscle contraction, strengthen muscles, maintain muscle mass, and prevent atrophy and muscle weakness, especially in post-stroke patients. The use of NMES for healthy individuals and competitive sportsmen is common across various sports such as basketball, football, ice hockey, and other sports to strengthen the abdominal wall muscles (20). EMG-triggered NMES was developed because movement time demands synchronization with motor intent. This method uses EMG to trigger electrical stimulation of the affected limb (21).

EMG-triggered NMES

EMG-triggered NMES is a system that detects any minimal electrical EMG signals in paralyzed muscles following a stroke and uses these signals to trigger electrical stimulation impulses to the same muscles, resulting in genuine muscle movement. EMG-triggered NMES demands patients' active participation in the training through cognitive intent to initiate electrical stimulation and activate the associated NMES-induced muscle contraction. This is also known as active NMES (5, 22). EMG-triggered NMES is based on the sensorimotor integration hypothesis, in which healthy neurons may be recruited and trained to plan more efficient movements. EMG-NEMS involves initiating a voluntary contraction until the electrical activity of the muscle reaches a threshold. Only then can electrical assistive stimulation be launched (23, 24).

EMG-triggered NMES has been hypothesized to produce cortical functional reorganization by inducing long-term potentiation in the sensorimotor cortex. It has been shown to increase metabolic activity in the supplementary motor area of the contralateral side of the lesion, the primary motor cortex, and the primary somatosensory cortex. Using infrared spectroscopy, it was noted that patients treated with EMG-triggered NMES exhibited cortical perfusion in the ipsilesional sensorimotor cortex compared to patients treated with cyclic NMES (25-27).

Electrodes are placed transcutaneously to detect electrical activity signals when the muscle contracts. When the signal reaches a threshold, electrical stimulation is initiated to cause muscle contraction. Subsequently, the patient is asked to contract the muscle again to repeat EMG-triggered NMES cycles. Repetitive stimulation provides feedback on each movement, which is important for motor learning. A disadvantage of this procedure is that it may not be applicable for severely paralyzed muscles as it requires voluntary contraction. When used on severely paralyzed muscle, cyclic-NMES may be indicated. A study revealed that EMG-triggered NMES was better than cyclic-NMES in improving wrist extension and grip strength after intervention. However, further studies are needed to substantiate this finding (28-30).

Molecular mechanism

The metabolic basis for changes in muscle mass is net muscle protein balance, i.e., the balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB). Muscle atrophy can be averted through protein consumption and exercise, while muscle mass is maintained via low-volume exercises, highlighting the potential of NMES as an interventional therapy. Five days of bed rest with NMES and protein supplementation did not significantly reduce muscle mass in healthy patients. Similarly, Guo et al. identified the efficacy of NMES in

conjunction with nocturnal protein consumption for treating MPS in aged adults. Prior to the administration of 20g of protein, 70 minutes of unilateral NMES on the lower extremity and 4-hour muscle biopsies revealed no significant differences in myofibrillar MPS between stimulated and control legs (31).

The Krebs cycle is the most extensive enzymatic cycle in humans, with citrate synthase (CS) being an essential enzyme. Four investigations employing low-frequency NMES for 4-10 weeks demonstrated increased CS activity ranging from 9 to 31%. In addition, NMES interventions resulted in increased levels of CS activity levels after four weeks but remained unchanged after a further four weeks. Similarly, after eight weeks of high-frequency NMES, isocitrate dehydrogenase (IDH), another enzyme implicated in the Krebs cycle, was also elevated. After several weeks of NMES, the levels of succinate dehydrogenase, cytochrome c oxidase, and pyruvate dehydrogenase increased relative to other oxidative enzymes (32).

With the participation of both efferent and afferent pathways, NMES-induced involuntary muscle contractions can prevent the loss of muscle mass caused by denervation and preserve muscle function. NMES-evoked depolarization of motor axons that transmit descending signals directly to motor endplates. Simultaneously, sensory neurons depolarize and transmit signals derived from direct depolarization, muscle spindles, Golgi tendon organs, and cutaneous receptors to the spinal cord. Repetitive afferent activation generates somatosensory input, resulting in central and peripheral involvement. Neuromuscular junction (NMJ) homeostatic plasticity is crucial for successful nerve regeneration and muscle reinnervation following NMES. Neurotrophic factors, including brain-derived neurotropic factor (BDNF), glial-derived neurotrophic factor (GDNF), and neuro growth factor (NGF), contribute to axonal regeneration following NMES. BDNF is the most prevalent neurotrophic factor involved in axonal regeneration, and its expression has been shown to increase following NMES. Increased BDNF expression can promote axonal growth via the tropomyosin receptor kinase B (trkB) signaling pathway, followed by the activation of downstream signaling pathways, such as the BDNF-PLC/Ras-PI3K/MEX pathway. Subsequently, once axonal sprouting reaches the muscle fibers, the formation of intact muscle is complete. BDNF is also able to bind to p75 receptors on nerve terminals to inhibit continued axonal growth and reestablish functional connections in the NMJ (33, 34).

EMG-triggered NMES for musculoskeletal rehabilitation

There is evidence that NMES can strengthen muscles, decrease spasticity, improve corticospinal neural circuit excitation, and enhance neuroplasticity. In addition, when NMES has been shown to be more effective in developing functional motor abilities than voluntary contractions performed simultaneously with stimulation when tested on normal individuals after voluntary contractions (e.g., EMG-triggered NMES) (35).

Hemiplegic shoulder pain

After a stroke, shoulder pain is a common complication in the hemiparetic upper extremity, including adhesive capsulitis, shoulder impingement, complex regional pain syndrome, brachial plexopathy, and subluxations. This condition can cause pain directly or place the capsule and extracapsular soft tissue at risk for both micro- and macro trauma, resulting in inflammation, immobility, and pain. Given the significance of functional and repetitive limb use for motor recuperation, immobility exacerbates paretic muscle conditions. The cycle repeats with the condition deteriorating. Numerous treatment methods have been reported, but their effectiveness are limited. Currently under investigation are transcutaneous and intramuscular NMES of the supraspinatus, trapezius, and deltoid muscles to minimize subluxations, enhance biomechanical integrity, and ultimately reduce pain (36).

The pathophysiology of HSP is not well known, but it is hypothesized that the etiology is multifactorial. Subluxation of the shoulder due to hemiplegia can lead to shoulder pain. A study by Chuang et al. revealed that 45% of stroke survivors had shoulder pain and shoulder subluxation (5) leading to limited use of the affected arm. Neuromuscular electrical stimulation (NMES. EMG-triggered NMES combined with bilateral arm training improved shoulder pain during shoulder movement and has superior pain reduction compared to transcutaneous electrical nerve stimulation (TENS). Patients treated with EMG-triggered NMES had significant reduction in pain scale (Faces Rating Scale) and intensity during active (2.94 point) and passive (3.53 point) shoulder movements compared to TENS with bilateral arm training ($p < 0.05$). The EMG-triggered NEMS group maintained the intervention effect at follow up (1 month after intervention), whereas the TENS group showed increased pain scale ($p = 0.01$). The EMG-triggered NMES group was also able to maintain pain reduction due to their active participation throughout the intervention, leading to increased motivation to continue using their paralyzed arm, resulting in long-lasting effects on pain reduction and pain-free passive shoulder movement (37).

Motor function

Additionally, evidence indicates that neuromuscular electrical stimulation (NMES) can elicit alterations within the brain. An example of this is the gradual elevation of surface quadriceps muscle surface NMES intensity from the sensory threshold to the maximum motor response, leading to a corresponding rise in cortical activity. This includes both the primary somatosensory and motor cortex (38). A recent study demonstrated that applying 25Hz stimulation to the common peroneal nerve with an intensity exceeding the motor park for 30 minutes, while maintaining a stationary seated position, resulted in a noteworthy increase in the motor-evoked potential (MEP) of the anterior tibialis muscle. Specifically, MEP

was elevated by 50% of the transcranial magnetic stimulation (TMS) intensity. This suggests that the TMS intensity used initially produced an MEP response that was only half the size of the maximum MEP response achievable. In other words, it was a submaximal TMS intensity, compared to NMES (39). The previous condition manifested itself following 10 minutes of stimulation and endured for a minimum of 30 minutes after the cessation of said stimulation. Subsequent experiments proved that heightened arousal does not transpire beyond the motor neuron level but at the cortical level. Research has shown that extended utilization of footdrop stimulators can lead to an augmentation in TMS-induced MEP and maximum voluntary contraction of the tibialis anterior among individuals who have suffered from a stroke. This proves that using stimulation devices significantly intensifies the activation of the cortical motor area and its remaining descending connections (16, 40).

EMG-triggered NMES effectively restores motor function by somatosensory and muscle contraction feedback via electrical stimulation (41). A study by Francisco et al. (42) found that EMG-triggered NMES significantly improved upper limb motor function compared to cyclic NMES. It affects brain plasticity and motor function recovery when the stimuli are used simultaneously rather than as a single stimuli. Thus far, no studies have established a set of criteria regarding stroke onset and degree of motor weakness that would have a higher chance of achieving optimal improvements in motor function with this treatment (43).

A case series of 69 stroke survivors reported an improvement in active range of motion in the wrist after using EMG-triggered NMES. Patients using EMG-triggered NMES more frequently showed increased extensor EMG amplitude (28). Another study using EMG-triggered NMES for paralyzed ankle dorsiflexion revealed that subjects had significantly improved active ankle flexion and extension after the intervention. EMG-triggered NMES positively affects ankle range of motion and strength. Sabut et al. (44) also revealed that EMG-triggered NMES can reduce the spasticity of plantar flexor muscles and increase the strength of dorsiflexor muscles in a patient with foot drop. The exact dose of EMG-triggered NMES is not well known, but 20 minutes per day is the minimum training dose that positively affects improvement in motor function and balance (28, 43-44).

Combination therapy

In previous trials, EMG-triggered NMES was used in combination with other training methods such as task-oriented training (TOT), mental imagery training (MIT), and bilateral arm training. It was revealed that the use of EMG-triggered NMES in combination with any of these training methods resulted in more significant effects than when used alone. EMG-triggered NMES combined with TOT (30 minutes/day, 5 times/week) for 4 weeks showed improvements in muscle activation and motor recovery of wrist and finger extensors compared to EMG-triggered NMES alone ($p < 0.05$) (45). Further research using a larger sample size is needed to investigate the neuroplasticity changes in the cerebral cortex.

EMG-triggered NMES combined with bilateral arm training can also result in significant reduction in pain scale (Faces Rating Scale) and intensity during active (2.94 point) and passive (3.53 point) shoulder movement ($p < 0.05$) (5). Patients undergoing EMG-triggered NEMS combined with bilateral arm training maintained the intervention effect at follow-up (1 month after intervention). Another study comparing the outcomes of EMG-triggered NMES combined with MIT vs. EMG-triggered NMES alone reported significant improvements in daily living activity and motor function in the group receiving the former (41, 42). This combination is an effective method for improving motor function in stroke survivors. The patients were asked to envision movement of the paralyzed muscle using performance memory and cognitive function. MIT was able to generate electrical signals and induce EMG even though the patients had minimal muscle electrical activity (46, 47).

Summary

Post-stroke patients can experience muscle weakness and spasticity, which can cause immobilization and pain in the shoulder. EMG-triggered NMES can improve motor function and pain in the shoulder by increasing BDNF, GDNF, and NGF expression. An illustrative diagram of the mechanism by which EMG-triggered NMES can improve motor function and shoulder pain is presented in Figure 1.

Conclusion

EMG-triggered NMES is an effective method to aid the recovery of motor function and hemiplegic shoulder pain in stroke survivors. EMG-triggered NMES showed better results when combined with other therapy, such as TOT, MIT, and bilateral arm training. Further research with larger sample size is needed to establish EMG-triggered NMES as an effective method for musculoskeletal rehabilitation in stroke patients.

Acknowledgement

The authors would like to thank the Department of Neurology, Faculty of Medicine, 80234 Universitas Udayana, Denpasar, Bali, Indonesia.

Competing interests

The authors declare that they have no competing interests.

Financial support

No funding was received for this work.

References

1. Chohan SA, Venkatesh PK, How CH. Long-term complications of stroke and secondary prevention: An overview for primary care physicians. Singapore Med J. 2019; 60(12):616-20.

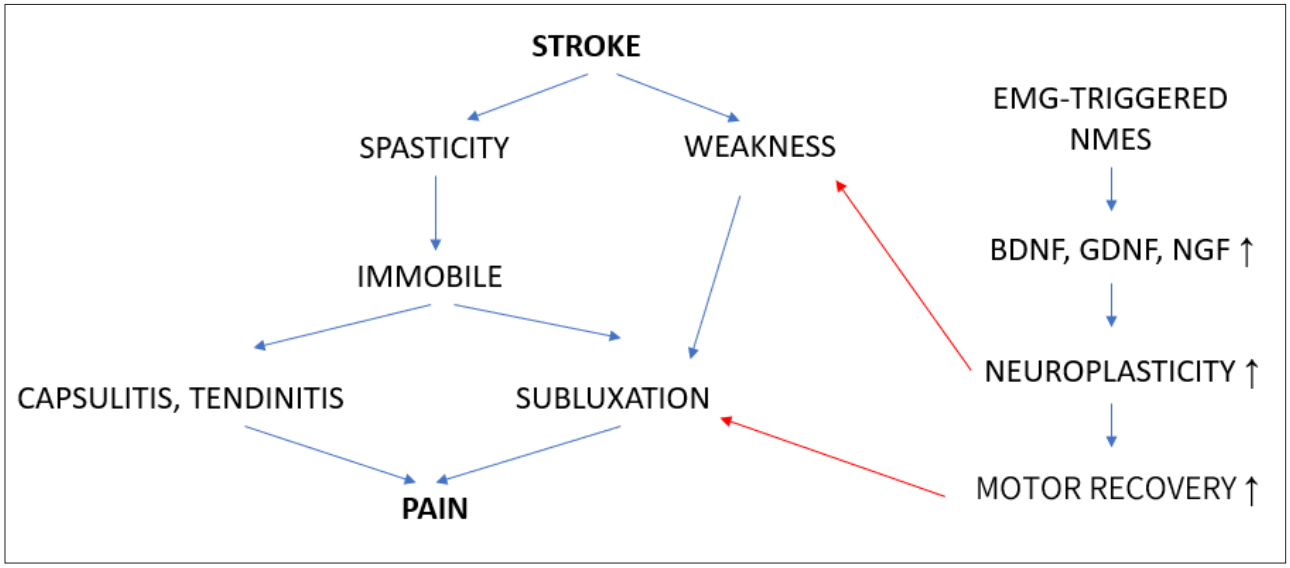

Figure 1: Illustrative diagram of the mechanism by which EMG-triggered NMES can improve motor function and shoulder pain. The red arrow indicates inhibit whilst the blue arrow indicates improve.

2. Monte-Silva K, Piscitelli D, Norouzi-Gheidari N, Batalla MAP, Archambault P, Levin MF. Electromyogram-related neuromuscular electrical stimulation for restoring wrist and hand movement in poststroke hemiplegia: a systematic review and meta-analysis. Neurorehabil Neural Repair. 2019; 33(2):96-111.
3. Takeda K, Tanino G, Miyasaka H. Review of devices used in neuromuscular electrical stimulation for stroke rehabilitation. Med Devices (Auckl). 2017; 10:207-13.
4. Nussbaum EL, Houghton P, Anthony J, Rennie S, Shay BL, Hoens AM. Neuromuscular electrical stimulation for treatment of muscle impairment: Critical review and recommendations for clinical practice. Physiother Can. 2017; 69(5):1-76.
5. Chuang LL, Chen YL, Chen CC, Li YC, Wong AMK, Hsu AL, *et al*. Effect of EMG-triggered neuromuscular electrical stimulation with bilateral arm training on hemiplegic shoulder pain and arm function after stroke: a randomized controlled trial. J Neuroeng Rehabil. 2017; 14(1):122.
6. Cauraugh JH, Kim S. Two coupled motor recovery protocols are better than one: Electromyogram-triggered neuromuscular stimulation and bilateral movements. Stroke. 2002; 33(6):1589-94.
7. de Kroon JR, IJzerman MJ, Chae J, Lankhorst GJ, Zilvold G. Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. J Rehabil Med. 2005; 37(2):65-74.
8. Raghavan P. Upper limb motor impairment after stroke. Phys Med Rehabil Clin N Am. 2015; 26(4):599-610.
9. Hatem SM, Saussez G, della Faille M, Prist V, Zhang X, Dispa D, *et al*. Rehabilitation of motor function after stroke: a multiple systematic review focused on techniques to stimulate upper extremity recovery. Front Hum Neurosci. 2016; 10:442.
10. Zeng H, Chen J, Guo Y, Tan S. Prevalence and risk factors for spasticity after stroke: a systematic review and meta-analysis. Front Neurol. 2021;11:616097.
11. Baricich A, Picelli A, Molteni F, Guanziroli E, Santamato A. Post-stroke spasticity as a condition: a new perspective on patient evaluation. Funct Neurol. 2016; 31(3):179-80.
12. Zhu Y, Su B, Li N, Jin HZ. Pain management of hemiplegic shoulder pain post stroke in patients from Nanjing, China. Neural Regen Res. 2013;8(25):2389-98.
13. Turner-Stokes L, Jackson D. Shoulder pain after stroke: a review of the evidence base to inform the development of an integrated care pathway. Clin Rehabil. 2002; 16(3):276-98.
14. Benlidayi IC, Basaran S. Hemiplegic shoulder pain: a common clinical consequence of stroke. Pract Neurol. 2014; 14(2):88-91.
15. Plantin J, Pennati G V., Roca P, Baron JC, Laurencikas E, Weber K, *et al*. Quantitative assessment of hand spasticity after stroke: imaging correlates and impact on motor recovery. Front Neurol. 2019; 10:836.
16. Chae J, Sheffler L, Knutson J. Neuromuscular electrical stimulation for motor restoration in hemiplegia. Top Stroke Rehabil. 2008; 15(5):412-26.
17. Allen K, Goodman C. Using electrical stimulation: a guideline for allied health professionals. Sydney Local Health District and Royal Rehabilitation Centre; Sydney, Australia. 2014;1-11. Available at: https://www.alliedhealthsupport.com/wp-content/uploads/2019/03/Using-Electrical-Stimulation_A-guideline-for-allied-health-professionals-January-2014.pdf. Accessed 14 August 2022.

18. Alawieh A, Zhao J, Feng W. Factors affecting post-stroke motor recovery: implications on neurotherapy after brain injury. Behav Brain Res. 2018; 340:94-101.
19. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol. 2009; 8(8):741-54.
20. Bodombossou-Djobo MMA, Zheng C, Chen S, Yang D. Neuromuscular electrical stimulation and biofeedback therapy may improve endometrial growth for patients with thin endometrium during frozen-thawed embryo transfer: a preliminary report. Reprod Biol Endocrinol. 2011; 9:122.
21. von Lewinski F, Hofer S, Kaus J, Merboldt KD, Rothkegel H, Schweizer R, *et al*. Efficacy of EMG-triggered electrical arm stimulation in chronic hemiparetic stroke patients. Restor Neurol Neurosci. 2009; 27(3):189-97.
22. Ijzerman MJ, Renzenbrink GJ, Geurts ACH. Neuromuscular stimulation after stroke: from technology to clinical deployment. Expert Rev Neurother. 2009; 9(4):541-52.
23. Krakauer JW. Motor learning: Its relevance to stroke recovery and neurorehabilitation. Curr Opin Neurol. 2006; 19(1):84-90.
24. Ambrosini E, Gasperini G, Zajc J, Immick N, Augsten A, Rossini M, *et al*. A robotic system with EMG-triggered functional electrical stimulation for restoring arm functions in stroke survivors. Neurorehabil Neural Repair. 2021; 35(4):334-45.
25. Hong IK, Choi JB, Lee JH. Cortical changes after mental imagery training combined with electromyography-triggered electrical stimulation in patients with chronic stroke. Stroke. 2012; 43(9):2506-9.
26. Hara Y, Obayashi S, Tsujiuchi K, Muraoka Y. The effects of electromyography-controlled functional electrical stimulation on upper extremity function and cortical perfusion in stroke patients. Clin Neurophysiol. 2013; 124(10):2008-15.
27. Shin HK, Cho SH, Jeon HS, Lee YH, Song JC, Jang SH, *et al*. Cortical effect and functional recovery by the electromyography-triggered neuromuscular stimulation in chronic stroke patients. Neurosci Lett. 2008; 442(3):174-9.
28. Knutson JS, Fu MJ, Sheffler LR, Chae J. Neuromuscular electrical stimulation for motor restoration in hemiplegia. Phys Med Rehabil Clin N Am. 2015; 26(4):729-45.
29. Meilink A, Hemmen B, Seelen HAM, Kwakkel G. Impact of EMG-triggered neuromuscular stimulation of the wrist and finger extensors of the paretic hand after stroke: a systematic review of the literature. Clin Rehabil. 2008; 22(4):291-305.
30. Boyaci A, Topuz O, Alkan H, Ozgen M, Sarsan A, Yildiz N, *et al*. Comparison of the effectiveness of active and passive neuromuscular electrical stimulation of hemiplegic upper extremities: a randomized, controlled trial. Int J Rehabil Res. 2013; 36(4):315-22.
31. Guo Y, Phillips BE, Atherton PJ, Piasecki M. Molecular and neural adaptations to neuromuscular electrical stimulation; implications for ageing muscle. Mech Ageing Dev. 2021; 193:111402.
32. Gondin J, Brocca L, Bellinzona E, D'Antona G, Maffiuletti NA, Miotti D, *et al*. Neuromuscular electrical stimulation training induces atypical adaptations of the human skeletal muscle phenotype: a functional and proteomic analysis. J Appl Physiol. 2011; 110(2):433-50.
33. 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.
34. Kern H, Hofer C, Loefler S, Zampieri S, Gargiulo P, Baba A, *et al*. Atrophy, ultra-structural disorders, severe atrophy and degeneration of denervated human muscle in SCI and aging. Implications for their recovery by functional electrical stimulation, updated 2017. Neurol Res. 2017; 39(7):660-6.
35. Kristensen MGH, Busk H, Wienecke T. Neuromuscular electrical stimulation improves activities of daily living post stroke: a systematic review and meta-analysis. Arch Rehabil Res Clin Transl. 2022; 4(1):100167.
36. Sheffler LR, Chae J. Neuromuscular electrical stimulation in neurorehabilitation. Muscle Nerve. 2007; 35(5):562-90.
37. Viana R, Pereira S, Mehta S, Miller T, Teasell R. Evidence for therapeutic interventions for hemiplegic shoulder pain during the chronic stage of stroke: a review. Top Stroke Rehabil. 2012; 19(6):514-22.
38. Smith G V., Alon G, Roys SR, Gullapalli RP. Functional MRI determination of a dose-response relationship to lower extremity neuromuscular electrical stimulation in healthy subjects. Exp Brain Res. 2003; 150(1):33-9.
39. Knash ME, Kido A, Gorassini M, Chan KM, Stein RB. Electrical stimulation of the human common peroneal nerve elicits lasting facilitation of cortical motor-evoked potentials. Exp Brain Res. 2003; 153(3):366-77.
40. Everaert DG, Thompson AK, Chong SL, Stein RB. Does functional electrical stimulation for foot drop strengthen corticospinal connections? Neurorehabil Neural Repair. 2010; 24(2):168-77.
41. Wilson RD, Page SJ, Delahanty M, Knutson JS, Gunzler DD, Sheffler LR, *et al*. Upper-limb recovery after stroke: A randomized controlled trial comparing EMG-triggered, cyclic, and sensory electrical stimulation. Neurorehabil Neural Repair. 2016; 30(10):978-87.
42. Francisco G, Chae J, Chawla H, Kirshblum S, Zorowitz R, Lewis G, *et al*. Electromyogram-triggered neuromuscular stimulation for improving the arm function of acute stroke survivors: a randomized pilot study. Arch Phys Med Rehabil. 1998; 79(5):570-5.
43. Barth E, Herrman V, Levine P, Dunning K, Page SJ. Low-dose, EMG-triggered electrical stimulation for balance and gait in chronic stroke. Top Stroke Rehabil. 2008; 15(5):451-5.
44. Sabut SK, Sikdar C, Kumar R, Mahadevappa M. Functional electrical stimulation of dorsiflexor

muscle: Effects on dorsiflexor strength, plantarflexor spasticity, and motor recovery in stroke patients. NeuroRehabilitation. 2011; 29(4):393-400.
45. Kim SH, Park JH, Jung MY, Yoo EY. Effects of task-oriented training as an added treatment to electromyogram-triggered neuromuscular stimulation on upper extremity function in chronic stroke patients. Occup Ther Int. 2016; 23(2):165-74.
46. Park JH. Effects of mental imagery training combined electromyogram-triggered neuromuscular electrical stimulation on upper limb function and activities of daily living in patients with chronic stroke: a randomized controlled trial. Disabil Rehabil. 2020; 42(20):2876-81.
47. Fu MJ, Knutson JS. Neuromuscular electrical stimulation and stroke recovery. In: Wilson R, Raghavan P. Stroke Rehabilitation. New York, USA: Elsevier. 2019;199-213.