Ref: Ro J Neurol. 2024;23(1)
DOI: 10.37897/RJN.2024.1.5

Role of BoNT-A in patient with post COVID-19 spasticity, assessed by H-reflex

Safa Muntadher Fawzi[1], Israa F. Jaafar[2], Islam Muntadher Fawzi[3]

[1]Al-Karkh Sector of Health, Medical City, Baghdad, Iraq
[2]Dentistry College Baghdad, Al-Esraa University, Baghdad, Iraq
[3]Al-Rasafa Sector of Health, Baghdad, Iraq

ABSTRACT

Background. COVID-19 is a pandemic disease due to viral infection. It spread throughout the world, and the association of COVID-19 with neuroendocrine system is a well-known fact especially while the connection between the endocrine and immune system neuroinflammation play a crucial role in pathophysiology. Therapeutic indication of Botulinum-neurotoxin-A (BoNT-A) is used in the treatment of focal post-stroke spasticity (PSS) and in re-habilitation which is regarded as a safe and effective type of treatment.

Objective. To assess spasticity after COVID-19 infection.

Methods. Thirty patients diagnosed as post-COVID-19 stroke spasticity were enrolled, their age ranged from (30-60 years). They had focal spasticity of lower extremities. BoNT-A was given in day 0 and 4 weeks later, in the gastrocnemius and soleus muscle. H-reflex was recorded from soleus muscles at 1st presentation and 4 weeks after injection of BoNT-A. Muscle power was assessed by Medical Research Council scale (MRC) and MAS.

Results. The amplitude and latency of H-reflex record from soleus muscles and the H/M ratio showed a statistically significant difference between pre- and post-therapy with BoNT-A injection in cases with post COVID-19 spasticity. There was a significant increase in MRC scale but, MAS scale showed a significant reduction after injection of BoNT-A.

Conclusion. Post COVID spasticity is a well-known complication after COVID-19 infection, there was clinical improvement in PSS post BoNT-A injections, which was assessed clinically by MAS and MRC scale, neurophysiological the H-reflex was correlated negatively regarding latency, while there was no correlation regarding H-reflex amplitude or Hmax/Mmax ratio and MAS.

Keywords: COVID-19, post COVID spasticity, H-reflex, BoTN-A, MRC scale

INTRODUCTION

COVID-19 pandemic is an infectious illness that spread throughout globally, which caused massive health problems [1]. The association with neuroendocrine system is a well-known fact especially the connection with endocrine and immune system neuroinflammation play a crucial role in the pathophysiology, different neurological complications occur after COVID infection with 28-38% spasticity post-stroke prevalence [2].

Stroke is one of the post COVID-19 complications, and elderly stroke is one of the reasons for disability and mortality. Spasticity as a squally in those patients can be managed regardless of the cause [3].

Patients with (PSS) frequently suffer from pain, stiffness of joint, soft tissue that leads to contracture with abnormal posture of extremities [4]. Limitation in joint movement was estimated to occur after stroke within 3-6 weeks [3].

Early diagnosis and treatment of PSS would reduce the complications, improve functions of joints muscles and extremities with better life style for such patients [5,6].

The BoNT-A injections are used clinically for treatment due to its safety and effectiveness for patients with spasticity [7,8]. They reduce spasticity which improves muscle function, and range of movement in the lower extremities [9,10]. The actions of BoNT-A injection are inhibition of exocyto-

Corresponding author:
Israa Faeck Jaafar
E-mail: medicalresearch68@yahoo.com

Article History:
Received: 20 January 2024
Accepted: 30 March 2024

sis of acetylcholine (Ach) from presynaptic nerves terminals on the neuro-muscular junctions [11]. It acts by inhibition of selective reversible muscle contraction with no undetectable general weakness and sedation lasting for three to four months [12].

The H-reflex is used to study neuro-motor control processes and clarifying neuromotor deficits [13,14]. Previous work revealed that patients suffering from spasticity had a larger amplitude of H-reflex and Hmax/Mmax ratio than normal subjects or the un-diseased side of patients at resting position [15], which means spasticity at rest is due to motor neurons hyper excitability of spinal circuits. The measurements H-reflex gives a clue of how effective the therapeutic interventions are (botulinum toxin) on reflex pathways [16].

This study aims to explore H-reflex changes in survivors with post covid spasticity and the effect of BoNT-A on PSS, and to assess the correlations if there are any regarding the changes in H-reflex with (MAS) Scale and (MRC) scale after treatment with BoNT-A injections.

METHODS

A cohort prospective research, which was carried out at the Clinical Neurophysiology Unit, Emamein Kadhimein Medical City from January to August 2023. Each patient of the study had signed a consent for participation.

The study involves 30 patients of both sexes, age ranged from 30 – 60 years. The 14 males and 16 females were referred by a specialist Neurologist.

Patients diagnosed with COVID-19 complicated by stroke had post stroke spasticity. They were referred from the specialist after a thorough clinical and neurological examination with assessment of muscle tone of ankle joints by the use of modified Ashworth Scale (MAS) [17,18], muscle power of the lower extremities was tested according to the Medical Research Council (MRC) scale [20], the examination was done at day zero then 3-4 weeks later. The diagnosis was confirmed by CT scan.

Exclusion criteria of patients were: Any neurological or neurodegenerative disease, orthopedic or musculoskeletal disorder, any disease or medications (like muscle relaxant) that affect the tests of nerve conduction, lastly patients in whom BoNT-A is contraindicated.

Patients were received in the early morning, H-reflex testing was done at day zero and then it was repeated 3-4 weeks later, the test was done by EMG/EP machine (Medtronic Keypoint, Denmark). The temperature of the room was monitored around 25º C to 28° C through the test procedures, the temperature of skin was measured by skin thermometer to keep it between 32 – 34° C.

H- reflex was recorded from the soleus muscles. The onset of M-latency and H-reflex were calculated from the starting point of stimulus artifacts to the first deflection from the baselines. The amplitudes of H-reflex, M-wave were measured as peak-to-peak value. Post recording of the H-wave then stimulus strength was adjusted to find Hmax and Mmax slowly, and the Hmax/Mmax ratio were measured (the maximum amplitudes ratio of the two action potentials) [19].

All patients involved in the study received an injection of BoNT-A toxin at: day zero then 3-4 weeks later. The vial of BoNT contains 100U which was diluted according to the method of El-Tamawy et al. [20]. All patients were injected with (100 U/session). The target muscles injected were gastrocnemius, soleus according to palpation/anatomic landmarks of International Movement Disorder Society guidelines [21].

Results are expressed as mean standard deviation using Microsoft Excel 2016 and IBM SPSS version 26. Continuous pre- and post-treatment results were tested by paired student (t) test, while median and range was used for Non-continuous variables using the Wilcoxon test for comparison. A p-value < 0.05 was considered significant.

RESULTS

The mean age was 47.70±6.87 years (range of thirty to sixty years). Cases were divided into 14 (46.6%) male and 16 (53.3%) females.

Table 1 shows: The MRC scale scoring was; 4 patients grade I, 14 cases grade II, while 12 cases were grade III and zero patient grade IV (Before treatment), while After treatment it was:0,1,9 and 20 respectively with a significant (P= 0.001).

Regarding MAS scale Score; 16 of patients had score 4, 8 of them had 3 score, while 5 patients scored 2, lastly one of them had a score of 5.

There was significant increase in MRC scale score (p<0.001) post-treatment compared to pre-treatment value, in contrary there was significant reduction in MAS scale after treatment with Bot-A with a (p <0.001), Table 1.

TABLE 1. Muscle strength and tone scoring according to MRC scale and MAS of the studied group (n=30)

Clinical scale	BoNT-A injections		P value
	Before	Mean ±SD	
Medical Research Council (Grade)			
I	4(8%)	0	
II	14(48%)	1(2%)	**0.001**
III	12(44%)	9(18%)	
IV	0	20(80%)	
Total score	2.37±0.62	3.80±0.48	**<0.001**
Modified Ashford (Grade)			
I	0	5(10%)	**<0.001**
II	5(10%)	12(64%)	
III	8(36%)	13(26%)	
IV	16(52%)	0	
V	1(2%)	0	
Total score	3.47±0.70	2.2±0.60	**<0.001**

TABLE 2. H-reflex data before and after treatment with-BoNT-A

Lower limb	M wave		H wave		Hmax/Mmax ratio
	Latency in ms	Amplitude in µV	Latency in ms	Amplitude in µV	
p-value	0.675	0.310	**<0.001**	**<0.005**	**0.005**
Rt. LL (n =15) pretreatment Post treatment	 1.02±0.95 0.97±0.99	 2.72±0.68 2.79±0.52	 17.9 (7.2-27.07) 22.99 (8.7-29.3)	 1.49 (0.2-2.19) 1.1 (0.12-1.79)	 0.57 (0.07-0.74) 0.38 (0.04-0.55)
p-value	<0.05	0.38	**<0.005**	**<0.005**	**<0.005**
Lt. LL (n =15) pretreatment Post treatment	 1.1 (0.8-2) 0.99 (0.69-2.01)	 2.7 (1.4-4.2) 3.0 (1.5-5.39)	 17.9 (14.9-26.9) 23.5 (20.0 -29.9)	 1.6 (1.3-2.8) 1.05 (0.2-2.88)	 0.59 (0.33-0.74) 0.36 (0.11-0.57)
p-value	0.190	<0.05	**<0.001**	**<0.001**	**<0.001**

Data are presented (mean±SD / median and range); RT. = right; Lt. = left; LL = lower limb

The data of H-reflex in right and left sides of lower extremities: There was prolongation in latency while there was a decrease in amplitude and the H/M ratios after injections compared to patients before therapy (Table 2).

Following BoNT-A injection (Table 3) shown the duration of H-reflex was related negatively with MAS (r = -0.286; p = 0.044) as shown below.

TABLE 3. Findings of H-reflex correlation with; MRC, and MAS after BoNT-A treatment

	Significance	MRC	MAS
The latency of Mwave in ms	r	-0.149	-0.198
	p	0.359	0.168
The amplitude of Mwave in µV	r	-0.013	-0.264
	p	0.929	0.064
The latency of Hwave in ms	r	0.168	**-0.290**
	p	0.229	**0.045**
The amplitude of Hwave in µV	r	0.118	-0.155
	p	0.409	0.290
H_{max}/M_{max} ratio	r	0.156	-0.012
	p	0.282	0.929

The association between the H-reflex data and sex in Table 4; there was no significant association in different sex.

TABLE 4. Association between different sex (male and female) with the Data of H-waves and M-waves

Variables	Male (n=15)	Female (n=15)	p-value
M-latency (ms) **Mean±SD** *Range*	 0.99±0.1 0.7-1.2	 1.02±0.21 0.8-2	0.503
M-amplitude (µV) **Mean±SD** *Range*	 2.68±0.95 1.5-5.4	 2.62±0.92 1.4-5	0.822
H-latency (ms) **Mean±SD** *Median* *Range*	 17.24±8.11 11.25 8.9-30.1	 16.91±6.15 16.2 9.1-25.3	0.946
H-amplitude (µV) **Mean±SD** *Median* *Range*	 0.9±0.34 0.9 0.1-1.7	 1.08±0.54 1 0.2-1.9	0.238
H_{max}/M_{max} ratio) **Mean±SD** *Median* *Range*	 0.34±0.12 0.37 0.04-0.56	 0.41±0.16 0.44 0.12-0.73	0.084

DISCUSSION

In this study, treatment with the injections of BoNT was found to have the ability to reduce spasticity of paretic side. There was a decrease in MAS scores in all cases with variable degrees that indicated that BoNT was effective in reducing spasticity and which dose was adequate for these subjects. Similar results were found by Lopez et al in 2019 [22]. The effects of Botulinum toxins are related to the inhibition of Ach releasing at the neuro-muscular junctions [23], leading to a local neuromuscular block at site of injection, this resulted in paresis of the targeted spastic muscles, so it will reduce spasticity in the injected muscle with BoNT.

There was a significant elevation in cumulative MRC score at 2nd visit post injection with BoNT-A; which means an increase in muscle strength [24].

Spasticity is a UMN positive sign; because there is increase in muscle tone and stretches reflex, while weakness and decrease in muscles strength are considered the "negative" UMN sign [25]. These cycles of positive and negative motor neuron lesions are one of clinical complains in the recovery period post-stroke [26,27]. Consequently, contracture resulted due to the weakness and spasticity leading to immobilizations of the joint at a shortened muscles length, these contractures will exacerbate spasticity in muscles. Such a vicious cycle continues and the patient's condition becomes worse unless treated effectively [28,29].

The decrease in spasticity of muscles is due to the reduction of reciprocal inhibitions from the antagonistic muscles post injections. Different studies have showed that injection can paralyze afferent fibers

[30,31], as well as the blockage of ACh release from pre-synaptic terminal at neuro-muscular junction.

There was a good degree of increment in muscle strength simultaneous with decreased spasticity as assessed by "MRC scale and MAC, respectively after BoNT-A injection were of value for those patients with PSS".

The values of H_{max}/M_{max} ratios were significantly greater in the affected limb of stroke cases before the injection of BoNT-A due to higher excitability of moto-neuron pool in such patients (Phadk CP 39). After BoNT-A injections, the amplitudes and Hmax/Mmax ratio were decreased in the limb with spasticity of stroke cases. This suggests a decline in the motoneuron pools of excitability.

Hyper-excitability of stretch reflexes are the pathophysiological changes that occur in spastic patients after stroke in patients with PSS, with alteration in the descending conductions pathway above the spine levels which may affect the excitability of alpha motor neurons [32]. The increased excitability of alpha-motor neurons may represent the severity of spasticity. The excitability of alpha motor neurons is detected in this study by using H-reflex; to reflect and to assess the peripheral sensory afferent or supra-spinal-descending conductions pathway in various aspects of human movements. Our patients with PSS had fewer latency of H-reflex. Joodaki et al., in 2001Cecen et al. in 2018 had similar observations [32,33]. After BoNT-A injections, our data showed prolongation in the latency of H-reflexes.

In this study, there were negative correlations between latency of H-reflex and MAS post injections of BoNT-A. These findings of the relation between H-reflex and MAS would make the H-reflex and MAS as clinical and neuro-physiological tools for assessment of muscle spasticity. The finding of no relation between MAS and H_{max}/M_{ma} might be related to the fact that Hmax/Mmax ratios reach the maximum between 8 weeks - 24 weeks and regardless weather H-reflex can be elicited as short as post the spinal cord injury [34]. So, it`s recommended to examine cases at least 6 months after the disorder process.

However, studies on post-stroke spasticity patients regarding neurophysiological examination had mainly focused chronic cases [35-37]. Since the average time for spasticity to occur is 1 month after the onset of stroke and abnormal neuroplasticity develops [38], early identification of spasticity is necessary for early and adequate treatment and hence there are better outcomes. In parallel with the neuro-physiological results, a recent meta-analysis suggested that post-stroke spasticity usually appeared or disappeared within one to three months post-stroke and remained stable beyond three months [39].

In this study, no correlation was found between the H_{max}/M_{ma} ratio and the MAS scores. This could be attributed to the mechanisms underlying spasticity where there are changes in spinal interneurons and motor neuron excitability or could be due to mistakes inherent to the MAS scale, which rely on the subjective judgment of the investigator, measuring the resistance to passive muscles stretching. This resistance often reflects the combination of spasticity, thixotropy and fixed muscle contractures. A recent study on the evolutional changes in neurophysiology of the spinal segmental circuitry has showed that the amplitudes of flexor reflexes may fall as spasticity becomes established [40-42].

Here, there was exclusion of cases with clinically detectable fixed contracture, but it's not possible to exclude the changes which may occur in muscle fiber structures or the visico-elastic features.

This study has some limitations that need to be addressed. It examines the relationship between MAS and H-reflex parameters in a moderate sample size (n = 30). A great sample size is recommended to evaluate the changes in neuro-physiological tests. The duration of the study could be prolonged to evaluate the effects of BoNT-A injection on MAS and H reflex in chronic PSS patients.

CONCLUSION

This study provides evidence that patients with post COVID spasticity have clinical improvement after BoNT injections assessed by MAS and MRC scales, in addition to significant differences regarding the latency and amplitudes of H-reflex in those patients pre- and post-BoNT-A injection.

Acknowledgments:
We would like to thank everyone who participated in this work starting from patients, all the neurophysiology department in Al- Emamein Kadhimein Medical City including physicians, nurses and specialists.

Contribution of authors:
Dr. Safa has done the clinical examination of patients and performed the H- reflex test for them and the injection of BoNT-A, Dr. Israa has put the plan of the study, collected the data analyzed it, made the tables and wrote the article. Dr. Safa and Dr. Islam had collected the patients, Dr. Safa did the neurological tests, Dr. Israa had put the plan and wrote the paper.

Conflict of interest: none declared

Financial support: none declared

REFERENCES

1. Faeck Jaafar I, Ahmed Mehdi S, M Fawzi AH. Isolation insult during COVID-19 pandemic on the psychological status of medical students. *J Clin Lab Anal.* 2022 Oct;36(10):e24702. doi: 10.1002/jcla.24702.
2. 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 Jul-Sep;31(3):179-80. doi: 10.11138/fneur/2016.31.3.179.
3. Kuo C-L, Hu G-C. Post-stroke Spasticity: A Review of Epidemiology, Pathophysiology, and Treatments. *Int J Gerontol.* 2018;12(4):280-284.
4. Opheim A, Danielsson A, Alt Murphy M, Persson HC, Sunnerhagen KS. Upper-limb spasticity during the first year after stroke: stroke arm longitudinal study at the University of Gothenburg. *Am J Phys Med Rehabil.* 2014 Oct;93(10):884-96. doi: 10.1097/PHM.0000000000000157.
5. Wissel J, Schelosky LD, Scott J, Christe W, Faiss JH, Mueller J. Early development of spasticity following stroke: a prospective, observational trial. *J Neurol.* 2010 Jul;257(7):1067-72. doi: 10.1007/s00415-010-5463-1.
6. Lundström E, Smits A, Terént A, Borg J. Time-course and determinants of spasticity during the first six months following first-ever stroke. *J Rehabil Med.* 2010 Apr;42(4):296-301. doi: 10.2340/16501977-0509.
7. Dong Y, Wu T, Hu X, Wang T. Efficacy and safety of botulinum toxin type A for upper limb spasticity after stroke or traumatic brain injury: a systematic review with meta-analysis and trial sequential analysis. *Eur J Phys Rehabil Med.* 2017 Apr;53(2):256-267. doi: 10.23736/S1973-9087.16.04329-X.
8. Ghroubi S, Alila S, Elleuch W, Ayed HB, Mhiri C, Elleuch MH. Efficacy of botulinum toxin A for the treatment of hemiparesis in adults with chronic upper limb spasticity. *Pan Afr Med J.* 2020 Feb 25;35:55. doi: 10.11604/pamj.2020.35.55.16091.
9. Dashtipour K, Chen JJ, Walker HW, Lee MY. Systematic literature review of abobotulinumtoxinA in clinical trials for lower limb spasticity. *Medicine*. 2016;95:e2468. doi: 10.1097/MD.0000000000002468.
10. Gracies J-M, Esquenazi A, Brashear A, Banach M, Kocer S, Jech R, et al. Efficacy and safety of abobotulinumtoxinA in spastic lower limb: Randomized trial and extension. *Neurology*. 2017;89:2245–2253. doi: 10.1212/WNL.0000000000004687.
11. Simpson LL. Identification of the major steps in botulinum toxin action. *Annu Rev Pharmacol Toxicol.* 2004;44:167-93. doi: 10.1146/annurev.pharmtox.44.101802.121554.
12. Kheder A, Nair KP. Spasticity: pathophysiology, evaluation and management. *Pract Neurol.* 2012 Oct;12(5):289-98.doi:10.1136/practneurol-2011-000155.
13. Knikou M. The H-reflex as a probe: pathways and pitfalls. *J Neurosci Methods.* 2008 Jun 15;171(1):1-12. doi: 10.1016/j.jneumeth.2008.02.012.
14. Burke D. Clinical uses of H reflexes of upper and lower limb muscles. *Clin Neurophysiol Pract.* 2016 Apr 7;1:9-17. doi: 10.1016/j.cnp.2016.02.003.
15. Huang CY, Wang CH, Hwang IS. Characterization of the mechanical and neural components of spastic hypertonia with modified H reflex. *J Electromyogr Kinesiol*. 2006 Aug;16(4):384-91. doi: 10.1016/j.jelekin.2005.09.001.
16. Kerzoncuf M, Bensoussan L, Delarque A, Durand J, Viton JM, Rossi-Durand C. Plastic changes in spinal synaptic transmission following botulinum toxin A in patients with post-stroke spasticity. *J Rehabil Med.* 2015 Nov;47(10):910-6. doi: 10.2340/16501977-2014.
17. Ansari NN, Naghdi S, Arab TK, Jalaie S. The interrater and intrarater reliability of the Modified Ashworth Scale in the assessment of muscle spasticity: limb and muscle group effect. *NeuroRehabilitation.* 2008;23(3):231-7.
18. Ciesla N, Dinglas V, Fan E, Kho M, Kuramoto J, Needham D. Manual muscle testing: a method of measuring extremity muscle strength applied to critically ill patients. *J Vis Exp.* 2011 Apr 12;(50):2632. doi: 10.3791/2632.
19. Pensini M, Martin A. Effect of voluntary contraction intensity on the H-reflex and V-wave responses. *Neurosci Lett*. 2004 Sep 9;367(3):369-74. doi: 10.1016/j.neulet.2004.06.037.
20. El-Tamawy MS, Abdel-Kader A, Fathi S, Samir H, Noha A, El-Bahrawy MN, Darwish M. The role of botulinum toxin (type A) in the management of spastic stroke patients. *Egypt J Neurol Psychiat Neurosurg*. 2004;41(suppl. 3):903-911.
21. Wemove Worldwide Education and Awareness for Movement Disorders, 2001.
22. López de Munain L, Valls-Solé J, Garcia Pascual I, Maisonobe P; on behalf of the VALGAS investigators group. Botulinum Toxin type A improves function according to goal attainment in adults with poststroke lower limb spasticity in real life practice. *Eur Neurol.* 2019;82(1-3):1-8. doi: 10.1159/000503172.
23. Pirazzini M, Rossetto O, Eleopra R, Montecucco C. Botulinum neurotoxins: Biology, pharmacology, and toxicology. *Pharmacol. Rev.* 2017;9:200–235. doi: 10.1124/pr.116.012658.
24. Sarzyńska-Długosz I, Szczepańska-Szerej A, Drużdż A, Łukomski T, Ochudło S, Fabian A, et al.. Real-world effectiveness of abobotulinumtoxinA (Dysport®) in adults with upper limb spasticity in routine clinical practice: an observational study. *Neurologia i Neurochirurgia Polska.* 2020;54(1):90-99. doi: 10.5603/PJNNS.a2020.0004.
25. Picelli A, Santamato A, Cosma M, Baricich A, Chisari C, Millevolte M,et al.. Early botulinum toxin type A injection for post-stroke spasticity: A longitudinal cohort study. *Toxins*. 2021;13:374. doi: 10.3390/toxins 13060374.
26. Mayer NH, Esquenazi A. Muscle overactivity and movement dysfunction in the upper motoneuron syndrome. *Phys Med Rehabil Clin N Am.* 2003;14:855-83. doi: 10.1016/S1047-9651(03)00093-7.
27. Gracies JM. Pathophysiology of spastic paresis. I: paresis and soft tissue changes. *Muscle Nerve.* 2005a;31:535-551. doi: 10.1002/mus.20284.
28. Gracies JM. Pathophysiology of spastic paresis. II: emergence of muscle overactivity. *Muscle Nerve.* 2005b;31:552-571. doi: 10.1002/mus.20285.
29. O'Dwyer N, Ada L, Neilson P. Spasticity and muscle contracture following stroke. *Brain*. 1996;119:1737-1749. doi: 10.1093/brain/119.5.1737.
30. Thibaut A, Chatelle C, Ziegler E, Bruno MA, Laureys S, Gosseries O. Spasticity after stroke: physiology, assessment and treatment. *Brain Injury.* 2013;27(10):1093-1105.
31. Li S. Spasticity, motor recovery, and neural plasticity after stroke. *Front Neurol.* 2017;8:120.
32. Cecen S, Niazi IK, Nedergaard RW, Cade A, Allen K, Holt K, et al. Posture modulates the sensitivity of the H-reflex. *Exp Brain Res*. 2018 Mar;236(3):829-835. doi: 10.1007/s00221-018-5182-x.
33. Joodaki MR, Olyaei GR, Bagheri H. The effects of electrical nerve stimulation of the lower extremity on H-reflex and F-wave parameters. *Electromyogr Clin Neurophysiol.* 2001 Jan-Feb;41(1):21-8.
34. Bakheit AM, Maynard VA, Curnow J, Hudson N, Kodapala S. The relation between Ashworth scale scores and the excitability of the alpha motor neurones in patients with post-stroke muscle spasticity. *J Neurol Neurosurg Psychiatry.* 2003 May;74(5):646-8. doi: 10.1136/jnnp.74.5.646.
35. Hiersemenzel LP, Curt A, Dietz V. From spinal shock to spasticity: neuronal adaptations to a spinal cord injury. *Neurology*. 2000 Apr 25;54(8):1574-82. doi: 10.1212/wnl.54.8.1574.
36. Ghotbi N, Olyaei GR, Hadian MR, Ansari NN, Bagheri H. Is there any relationship between the Modified Ashworth Scale scores and alpha motoneuron excitability indicators? *Electromyogr Clin Neurophysiol.* 2006 Sep;46(5):279-84.
37. Naghdi S, Ansari NN, Mansouri K, Asgari A, Olyaei GR, Kazemnejad A. Neurophysiological examination of the Modified Modified Ashworth Scale (MMAS) in patients with wrist flexor spasticity after stroke. *Electromyogr Clin Neurophysiol.* 2008;48:35-41.
38. Phadke CP, Robertson CT, Condliffe EG, Patten C. Upper-extremity H-reflex measurement post-stroke: reliability and inter-limb differences. *Clin Neurophysiol.* 2012 Aug;123(8):1606-15. doi: 10.1016/j.clinph.2011. 12.012.
39. Nam KE, Lim SH, Kim JS, Hong BY, Jung HY, Lee JK, et al. When does spasticity in the upper limb develop after a first stroke? A nationwide observational study on 861 stroke patients. *J Clin Neurosci.* 2019 Aug;66:144-148. doi: 10.1016/j.jocn.2019.04.034.
40. Dengler R, Kossev A, Wohlfahrt K, Schubert M, Elek J, Wolf W. F waves and motor unit size. *Muscle Nerve.* 1992 Oct;15(10):1138-42. doi: 10.1002/mus.880151013.
41. Vattanasilp W, Ada L, Crosbie J. Contribution of thixotropy, spasticity, and contracture to ankle stiffness after stroke. J *Neurol Neurosurg Psychiatry.* 2000 Jul;69(1):34-9. doi: 10.1136/jnnp.69.1.34.
42. 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 Jan 20;11:616097. doi: 10.3389/fneur.2020.616097.