



## The Effect of Functional Electrical Stimulation on Gait in Patients After Stroke: Review of Scientific

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### Abstract

The article provides a systematic review of the results of the researches on the effectiveness of the application of functional electrical stimulation (FES) for low extremities during the rehabilitation of patients after stroke. It is considered the effect of using FES on the improvements of walking speed, kinematics and gait symmetry, the ability to overcome obstacles, as well as improvements in the range of ankle movement and foot clearance while walking. In addition, it is discussed the positive impact of FES on muscle tone, on reducing the energy consumption and the risk of falls during walking, increased confidence and comfort of patients when walking with FES. This analysis also considers the speed of patients' adaptation and their tolerance for FES devices, provides a comparative characteristic of functional electrical stimulation with using other ankle orthoses (AFO).

**Keywords:** Stroke; Rehabilitation; FES: Functional Electrical Stimulation; Gait Disorder; Gait Restoration; Motor Recovery

### Section 1: Introduction

#### Clinical and functional changes in gait in patients after a stroke

Stroke is an acute illness that encompasses a wide range of clinical conditions, including thrombosis, hemorrhage, and embolism. Mortality from stroke ranges from 12 - 29%, second place after mortality from heart disease and malignant tumors. A stroke has serious consequences, is often accompanied by disability, and only 20% of patients who have suffered from this ailment return to work. Disability after stroke ranks first among other diseases and amounts to 3.2 per 10,000 population [1].

The purpose of this review is to summarize the data published in the scientific literature on the use of functional electrical stimu-

lation in the medical rehabilitation of neurological patients, as well as to analyze the experience accumulated in the world medical systems on this problem.

In order to accomplish this task, we performed a systematic search for information in such data sources as PubMed, Cochrane, Web of Science, ScienceDirect, Embase, Pedro. The search was carried out using keywords and combinations of the following words: "stroke", "rehabilitation", "FES", "functional electrical stimulation", "gait disorder", "gait restoration", "post-stroke rehabilitation", "motor recovery".

One of the main problems of patients after a stroke, contributing to an increase in the level of disability, are different gait disorders, including not only a decrease in walking speed, but also in a change

in the kinematics of gait, its asymmetry, the appearance of compensatory movements, gait instability and rapidly onset of patient fatigue.

The above negative factors can certainly damage the patient's freedom of movement, reduce the safety of his walking, and also lead to an increase in the number of falls, which occur with high probability among stroke patients. In their turn, falls contribute to the trauma of patients and, ultimately, lead to a significant decrease in their quality of life [1,2].

In addition, there are several very common problems that complicate the rehabilitation of patients, one of the most problematic of them is the so-called "foot drop", which is formed as a result of paresis of the muscles involved in lifting the foot (dorsiflexors).

The main factor in the development of a dragging a foot is ankle extensor weakness (dorsiflexion), which is associated with the inability to contract the tibialis anterior muscle, extensor longus of the big toe, and extensor digitorum. Weakness of the muscles involved in ankle and foot extension leads to numerous gait disorders, including a decrease in walking speed and gait asymmetry [3].

The next negative factor is all kinds of disorders of the walking pattern, such as: "dragging" the foot and toes or the use of compensatory strategies, adaptive passive stiffness (plantarflexion), peripheral circular movement of the limb (circumduction) [4]. Since obstacle avoidance requires modulating stride length and changing the trajectory of limb transfer when crossing an obstacle, overcoming obstacles becomes problematic in patients with a foot drop, especially when the paretic leg overcomes an obstacle with significantly less clearance (the degree of elevation of the foot when walking) than a healthy leg. It has been shown that for these patients significantly increase the risk of falling compared with healthy patients [5,6].

Also, gait speed factor is of high clinical significance. As a rule, a patient staying at home has a walking speed of less than 0.4 m/s, and a person moving at a speed in the range from 0.4 to 0.8 m/s has a limited ability to move around the place of residence. The walking speed for a working patient is 0.8 m/s and higher [7].

It is important to note that a factor contributing to the development of gait asymmetry in a patient after a stroke is spasticity of the ankle muscles [8]. During walking, dynamic spasticity of the

sole flexors (plantar flexion) increases the spatial asymmetry of stride, and ankle stiffness is a predictor of falls [9]. All of the above disorders of active muscle contraction, as well as asymmetric gait kinematics and compensatory strategies, lead to a decrease in the quality and efficiency of gait, as well as to an increase in the risk of falling.

A common complaint of stroke patients is rapid tiredness and fatigue, which is associated with low safety and an increased risk of falling. It was found that the energy consumption for walking is directly proportional to the walking speed [10], and the higher the patient's energy consumption for walking, the faster he gets tired [11].

## Section 2: Historical foundations of functional electrical stimulation in rehabilitation

Functional electrical stimulation (FES) refers to a technology used in the physical rehabilitation of stroke patients. FES of the tibialis anterior muscle, leading to dorsiflexion of the ankle joint, can help prevent foot drop during the leg swing phase.

According to the Russian Clinical Guidelines for the Management of Patients with Ischemic Stroke and Transient Ischemic Attacks (2017), "the impact of physical rehabilitation technologies on the outcome and the degree of functional recovery was assessed as the level of evidence - 1A" [12].

According to the clinical guidelines "Diagnosis and rehabilitation of impaired walking and balance in central hemiparesis syndrome in the recovery period of stroke" (2017), FES is recommended for patients with model B1 and B2 [13].

Note that patient model B is a patient with moderate or severe hemiparesis. The patient of subgroup B1 is able to stand and walk independently (walking with support on a cane is allowed). According to the scale for assessing gait function and risk of falling (Dynamic Gait Index - DGI), a patient of this subgroup corresponds to Group II (low risk of falling) when walking with a cane and Group I (high risk of falling) when walking without support, according to the Berg balance scale, - Group II (walking with support). In addition, the patient of subgroup B1 has 2 - 3 points, according to the Ashworth scale, and from 39 to 52 points, according to the section of motor activity on the functional independence scale (Functional Independence Measure - FIM).

Patient of subgroup B2 is able to stand and walk independently using a cane or walker. According to the scale of assessment of walking function and risk of falling (DGI), a patient of this subgroup corresponds to group I (high risk of falling) when walking with a cane, according to the Berg balance scale, to group II (walking with support). According to the Ashworth scale, the patient of subgroup B2 has 2-3 points, according to the section of motor activity on the scale of functional independence (FIM) - from 26 to 39 points.

One of the widely used rehabilitation methods is FES of the anterior tibial and peroneal muscles of the paretic limb when walking during the leg swing phase. The practice of using FES for restoring movements after a stroke has convincing evidence, which is primarily due to the use of a single paradigm, which consists in stimulating the extensor muscles of the ankle joint in walking mode.

This direction of rehabilitation, which emerged in the early 60s, was a significant step in world medicine. The essence of this method lies in the fact that FES is used as a way to restore the movement of not only an individual organ, but also a complex locomotor act. The FES method was first used to restore walking in 1961 by V. Lieberman, who patented it in 1965 as a method of stimulating human neuromuscular formations [18,19]. V. Lieberman used FES of the peroneal nerve while walking. Then, based on the research of V. Lieberman, Moe J.H., Post H.W. developed a device to aid walking in patients with tibialis anterior muscle weakness [20]. Over the next 40 years, in the course of research on FES, the principles of the safety of neuromuscular stimulation were developed, contributing to the increase in strength in the affected muscles and an increase in the range of active movements in the ankle joint of the paretic limb.

In Russia, one of the founders of the FES method for walking is Anatoly Samoilovich Vitenzon, who investigated the biomechanics of human walking as a single integral motor act, consisting of the movement of the muscles of the lower leg, foot, hip, pelvis, spine, upper limbs, leading to a displacement of the general center of mass of the human body in the sagittal, frontal and horizontal planes. In his method of artificial movement correction A.S. Vitenzon uses electrical muscle stimulation exactly during the phases of excitation and muscle contraction. FES does not change the program of muscle contractions during a locomotor act, but only strengthens those elements of it that were weakened as a result of a deficiency in muscle function. According to A. S. Vitenzon, the goal of FES is,

firstly, to restore, or at least improve, the biomechanics of walking and the functional state of muscles, and secondly, to make a certain correction to the work of locomotive centers. The program and intensity of FES electrostimulation should be comfortable for the patient and set with minimal parameters that sufficient to obtain a corrective effect and maintain walking close to the physiological motor stereotype [21,22].

In numerous Soviet studies, E.V. Lakhno, R.V. Chagovets, G.F. Kolesnikov, N.N. Yakovlev, V.Yu. Davidenko notes that electrical stimulation affects not only the stimulated muscles, but also the entire body, and primarily the central nervous system, neurohumoral mechanisms of regulation of functions. Especially in these studies, it is emphasized that electric current impulses affect not only muscle, but also nerve structures: receptors, nerve fibers. Thus, a variety of reflex changes in the whole organism are caused [23].

In their studies of E.V. Lakhno and R.V. Chagovets was the first to formulate ideas about the advisability of using electrical stimulation for reflex control of the functional state of the human body. Apparently, this circumstance led to the fact that G.F. Kolesnikov proposes to conduct electrical stimulation of the locomotor system in three modes - subthreshold, threshold and suprathreshold. Moreover, he proposes to consider a subthreshold one as such, in which contractions of the stimulated muscle are not caused, but only a sensation of electric current passing through the body tissues arises. In other words, such a regime serves exclusively for influencing numerous receptors and reflex influence on processes, both in the muscle itself and throughout the body.

Table 1 shows the indications and contraindications for the use of functional electrical stimulation.

### Section 3: Modern FES technologies and their distinctive features

Certainly, a number of improvements have been made in modern FES systems. Thus, the devices have become more compact and wireless, the need for external sensors has disappeared, the shape of the electrical pulse has become more similar to the physiological electrical activity of the human body, the reliability of the equipment has significantly increased, and it has become possible to create individual programs of gait settings for each individual patient, taking into account the nosology, the level of activity of the patient, tolerance to stimulation, skin condition, pain threshold and indi-

Damage to the upper motor neuron (direct indication for the use of FES)	Damage to the peripheral motor neuron (the use of FES may be ineffective)	Relative contraindications to the use of FES
Stroke	Intervertebral disc injury or lumbosacral spine surgery	Implanted pacemaker or defibrillator
Transverse myelitis	Dangling foot due to total knee replacement or hip replacement	Uncontrolled epileptic seizures
Multiple sclerosis	Sciatica	Pregnancy
Traumatic brain injury	Spinal stenosis at the level of the lower spine	Alcoholism
Postoperative brain injury	Polio	Mental disorders
Cerebral palsy	Guillain-Barré Syndrome	Malignant tumor in the affected leg
Incomplete spinal cord injury (Th-12 and higher)	Muscle injury or disease	Open wounds or symptomatic active thrombosis in the affected leg
Hereditary (familial) paraplegia	Charcot-Marie-Tooth amyotrophy	Failure to take at least 10 consecutive steps (including with assistive devices)
Hereditary spastic paraparesis	Neuropathy of various origins (including diabetic)	
Toxic encephalopathy	Charcot/Lou Gehrig's disease/amyotrophic lateral sclerosis (ALS)	
Parkinson's disease		

**Table 1:** Indications and contraindications for the use of functional electrical stimulation.

vidual sensations from stimulation. Modern FES technologies use wireless sensors under the foot and tilt sensors, which make such devices more practical and user-friendly.

Currently, there are quite a few models of FES medical devices on the market designed for patients with various neurological diseases. The devices are quite versatile in their principle of action and are suitable for all pathologies of lesions of the central nervous system (multiple sclerosis, stroke, cerebral palsy, spinal injuries, etc.). Some of the well-known stimulators include devices with the brand names Walkaide, MyGait, Odstock, Bioness, STIMuSTEP, ActiGait and FESIA WALK. All of these devices are Risk Class 2a Medical Devices (Medium Risk Medical Devices) and are internationally approved by the US Food and Drug Administration (FDA) and CE (European Union Standard) for electrostimulation and neuromuscular stimulation for central and peripheral paresis [24-26].

All available FES systems can be divided into two groups depending on the level of invasiveness: implantable and with non-invasive electrodes. The STIMuSTEP and ActiGait systems are implanted requiring neurosurgeon intervention. With other stimulants, electrodes are applied to the skin for transdermal electrical stimulation.

Most modern neurostimulation systems are “open-loop” systems that are very popular today due to their simple application. Unfortunately, in the “open-loop” systems there is no biological feedback from the muscle and nerve, that is, when using them, the problem with the emerging muscle fatigue remains unresolved.

Future closed-loop devices will be able to provide feedback from muscle and nerve through the use of technology using electromyography and electroneurography [24,25,27].

There are models in which, instead of a sensor under the foot, a tilt sensor is used, which measures the orientation of the leg in 3D space, causing the stimulator to turn on during the leg swing phase and turn off during the leg stance phase in the person’s gait cycle. The tilt sensor is located in the control unit, which is attached to the cuff located on the lower leg (in the projection of the tibia). When the lower leg is tilted back at the end of the stance phase, the tilt sensor acts as a trigger to activate stimulation, then deactivate the stimulation when the leg tilts forward at the start of the stance phase during heel-to-floor contact. The optimal stimulation time usually lasts the entire phase of the leg swing, however, the exact time of the beginning and end of stimulation is adapted according to the individual needs of each patient [28].

A number of studies have confirmed the validity and reliability of tilt sensors, as well as the fact that devices with an accelerometer provide reliable data for monitoring and measuring the results of the functioning of the lower extremities during rehabilitation procedures for stroke [28].

**Section 4: Influence of FES on walking speed. Comparative characteristics of the efficiency of FES and ankle orthosis**

Reviewing modern studies on the effect of modern FES devices on the restoration of gait function in patients after stroke, we first of all considered main issues of interest to rehabilitation specialists in the field of gait restoration, such as: increasing gait speed, range of motion of the ankle joint, foot clearance, improving kinematics and gait symmetry, a decrease in muscle spasticity, a decrease in energy consumption for walking, a decrease in the frequency of falls, the ability to overcome obstacles and increase confidence when walking, an effect on neuroplasticity, comfort of use, tolerance and speed of adaptation to FES, as well as comparative performance characteristics with an ankle orthosis (AFO).

Table 2 shows a comparative analysis of the influence of the ankle orthosis (AFO) and the device of functional stimulation (FES) on the parameters of walking.

Numerous studies of the effectiveness of rehabilitation of patients after stroke indicate both an improvement in walking characteristics and a significant increase in walking speed during the stimulation period compared to the non-stimulation period. Thus, in the studies of C. Barrett and P. Taylor (2008), the effect of stimulation was registered already in the first week of treatment, and

Impact on the patient’s musculoskeletal system	Ankle foot orthoses	FES
Improving gait stability and balance	Yes	Yes
Improving mobility of movement	Yes	Yes
Improving muscle strength and endurance	No	Yes
Reduction/delay in the development of muscle atrophy	Yes	Yes
Improving blood circulation in the lower limb	No	Yes
Decrease in increased muscle tone	No	Yes
Maintain/increase range of motion in the ankle	No	Yes
Maintaining/increasing bone density	No	Yes
Retraining motor function and developing a new walking stereotype	No	Yes
Impact and restoration of the neuromuscular system as a whole	No	Yes

**Table 2:** Comparative analysis of the influence of the ankle orthosis and functional stimulation device on gait parameters.

by the 18<sup>th</sup> week, a significant training effect was obtained, and an increase in walking speed was recorded [29].

A number of studies indicate a statistically significant improvement in walking speed during a 10 min walking test, both with the use of the FES apparatus separately and in combination with traditional rehabilitation [30-32].

The results of another study showed a statistically significant increase in walking speed and improvement in step sequence after 6 months of FES application (p < 0.001) [33].

It was found that the inclusion in the rehabilitation program of a training gait performed with a neurostimulator in the phase of early rehabilitation after a stroke contributes to a significant improvement in walking speed in the group of patients who used a functional electrostimulation device (WalkAide) in comparison with the control group that underwent standard rehabilitation without using this electrostimulation device [34].

In addition, Taylor PN., *et al.* (2013) [35] found that when using FES, the walking speed of patients after a stroke was on average



45% higher, including a 24% training effect, and the performance of the functional walking test (Functional Ambulation Categories) improved by 52%. This test is a 6-point scale that assesses a patient's ability to move by determining whether the patient needs support from another person while walking, regardless of whether the patient is using a personal assistive device or not.

According to the results of the study, the functional test of walking in 22 patients (20%) improved already during the first use of FES, and during the next 16.5 months this indicator increased to 38% [35]. Similar results were obtained by Van Swigchem R., *et al.* (2012): as early as one day after the start of gait training using FES, an increase in gait speed was recorded during testing of gait speed when overcoming obstacles [36].

In a study by F Bethoux (2014), when comparing walking parameters and quality of life among 495 patients after stroke with a drooping foot using the WalkAide functional electrostimulation device and a traditional ankle orthosis in 30 US rehabilitation research centers (242 people in the group using neuroorthoses and 253 people in the group with ankle brace) showed a significant improvement in physical activity [37].

The studied criteria for the effectiveness of rehabilitation in the framework of this study were walking speed and the total score on the SIS (Stroke Impact Scale) scale. The results of the analysis of the primary efficacy criteria (walking speed and total SIS score) and primary safety criteria (frequency of serious adverse events associated with the use of the device) showed that neuroorthoses was not inferior to ankle braces in any criterion.

There were no statistically significant differences between the groups with regard to walking speed and total SIS score. Both groups showed a statistically significant increase in walking speed and an improvement in the SIS total score at 6 months after the start of the study. There were two reported serious adverse events associated with the use of the ankle brace, and the absence of those in the neuroorthoses group.

Patients in the neuroorthoses group, in contrast to the group of patients using ankle orthoses (AFO), also showed a statistically significant improvement in functional improvement in gait performance change.

## Section 5: Influence of FES on the range of motion in the ankle joint and foot clearance

The study of the range of motion in the ankle joint and the foot clearance (distance between the support and the foot) during walking, the ability to overcome obstacles as a significant factor determining the prognosis of patients' recovery after stroke has been the subject of several studies. Moreover, in the framework of many of these studies carried out in Europe, as well as in clinical practice, non-invasive portable FES devices were used [38-41].

In a study by Van Swigchem R., *et al.* (2011) showed that both implanted and superficial percutaneous FES devices allow the patient to achieve adequate foot lift. The authors of this study argue that FES in relation to the peroneal muscle group effectively activates the extensors of the ankle joint (dorsiflexion), bringing this joint outward (eversion), as well as the extensors of the fingers of the lower extremity. This kind of intervention can lead to a significant improvement in the walking pattern and an increase in its speed compared to walking without using FES [42,43].

In a study by Gervasoni E., *et al.* (2017), the use of non-invasive FES in neurological patients had a positive effect on movement in the ankle joint, as well as on an increase in foot clearance during the leg transfer phase in the gait cycle [31].

Activation of the foot extensors (dorsiflexion) by FES correlates with an increase in gait speed in stroke patients. At least 11 European studies have demonstrated the effectiveness of FES to improve dorsiflexion and increase walking speed in patients with a foot drop. Studies proving an increase in walking speed with the use of FES encompass four similar randomized controlled trials [30,32,34,41] and one cohort study [44].

Van Swigchem R., *et al.* (2010, 2011) argue that FES of the peroneal muscle group activates dorsiflexion and eversion of the ankle joint, the extensor muscles of the fingers of the lower extremities and contributes to a significant improvement in the gait pattern compared to unaided gait.

The authors found that in FES, the angles of flexion of the joints of the paretic side are similar to those of the joints of the healthy side. At the same time, when using ankle orthoses, the nature of movements in the joints of the paretic and healthy limbs was sig-

nificantly different (a time shift was noted at the beginning of the leg transfer phase). These results indicate that when using FES, the nature of joint movement becomes more symmetrical, and the ranges of motion in the ankle and knee joints and in the hip are practically normalized [42,43].

According to a study by Street T., *et al.* FES had the most significant therapeutic and orthopedic effect on a group of patients suffering from minor walking disorders. According to the author, in order to obtain greater clarity regarding the effectiveness of the therapeutic effect of FES, additional studies will be required on the use of neuroorthoses not only as an assistive orthopedic device, but also as a device for restorative treatment of motor function [44].

### Section 6: Influence of FES on kinematics and gait symmetry

In a meta-analysis by S. Prenton., *et al.* (2016) presented statistically significant evidence of the effectiveness of the use of modern devices of functional electrical stimulation for hanging feet, which provide effective extension of the ankle joint (dorsiflexion) and have a positive functional effect on walking in patients after stroke.

When using these devices, the ankle joint is activated, the gait pattern improves and the level of its safety increases, which is confirmed by an increase in speed, improved kinematics and gait symmetry, a decrease in the severity of spasticity, compensatory movements and abnormal patterns, a decrease in fatigue and the number of falls, an increase in patient confidence [45].

Disorders of joint kinematics and gait asymmetry that develop in patients after a stroke represent a significant problem for the rehabilitation and recovery of patients. Activation of the extensor muscles of the foot by FES correlates with improvements in kinematics, symmetry, and gait pattern in patients. Many studies have studied the effect of FES on gait kinematics and symmetry.

Several studies and case reports have shown that FES of the foot extensor muscles improves gait kinematics, symmetry, and gait pattern. So, Wilkinson IA., *et al.* (2014) reported that only in patients of the FES group there was an intragroup statistically significant improvement according to the visual analysis of Rivermead gait already at the 8th week of rehabilitation with the preservation of improvements at the 20<sup>th</sup> week [30]. Dujovic S., *et al.* (2017) report that the use of FES in comparison with traditional rehabilitation programs is more effective in improving the mobility of the lower limbs, restoring balance and daily life [32].

Another 2017 randomized controlled trial using wireless peroneal nerve stimulation triggered by an accelerometer (WAFES) showed that ankle kinematics (ankle speed and maximum angle) improved over 10 weeks of gait training. Its extension in passive mode) and kinematics of the knee joint (flexion of the knee joint at high speed) [41].

Kinematic analysis of gait before and after the application of FES showed an increase in the speed of movement and the maximum angle of extension of the ankle joint (dorsiflexion in passive mode) and the angle of flexion of the knee joint [30,31,46].

Another study demonstrated improved hip and knee flexion angles and improved symmetry of the hip and knee movement while walking [42]. These improvements in flexion angles, accompanied by improved repulsion at the end of the support phase, combined to show that gait symmetry was restored to nearly normal [42]. These results show that FES improves not only dorsiflexion of the ankle joint and symmetry of limb transfer, but also the entire structure of the stride pattern [42]. Another study found that the use of FES resulted in improved Rivermead Visual Gait Analysis, an instrument that assesses the degree of asymmetry of the trunk, pelvis, hip, knee, and ankle [30]. The improvements shown in all of these studies support the fact that the use of FES can positively influence the kinematics and gait symmetry of the patient after stroke.

A study by Kyeongjin L (2020) was conducted to investigate the effects of electromyogram-induced FES (EMG-triggered FES) balance training on improving static balance, dynamic balance, and ankle muscle activation in stroke patients. Forty-nine participants (> 6 months post-stroke) were randomly assigned to treatment (n = 25) and control groups (n = 24). The experimental group underwent EMG-triggered FES balance training for 40 minutes per day, 5 days per week, for a 6-week period in addition to general rehabilitation. The control group underwent balance training without EMG-induced FES along with conventional therapy. Measurements included static balance ability, dynamic balance ability, and leg muscle activation. Static and dynamic balance abilities were significantly improved after the intervention in both groups ( $p < 0.05$ ), although the experimental group showed significantly greater improvement than the control group ( $p < 0.05$ ). Activation of the leg muscles on the affected side resulted in significant improvements in the treatment group ( $p < 0.05$ ) compared to baseline, but not in

the control group. Balance training with FES triggered by EMG is an acceptable and effective intervention for improving static balance, dynamic balance and activation of the ankle muscles in stroke patients [47].

## Conclusion

Thus, short- and long-term use of devices using FES technology is a potentially effective rehab strategy for improving the biomechanical and neurophysiological parameters of walking in stroke patients. Functional electrical stimulation, according to the results of numerous studies, is an effective and safe method for improving walking and restoring mobility.

It is extremely important that FES is performed correctly while walking exactly at that moment of the two-step-cycle, when the tibialis anterior muscle must be contracted, in order to enhance muscle contraction and significantly improve the patient's gait pattern.

One of the advantages of the FES technology when walking is the possibility of its use both within the framework of complex rehabilitation, and also after a standard course of rehabilitation at home rehabilitation. In all over the world FES devices are used by the patients in everyday life in the usual comfortable home conditions.

FES, promoting an increase in the range of motion of patients, is one of the most effective areas of rehabilitation treatment based on the principles of motor retraining. In the results of various studies, it was proven an increase in the efficiency of using FES by most frequent users, in adequate doses according to the clinician's instructions and in the most appropriate context of therapy during the rehabilitation period.

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## Contribution of Authors

The authors made an equal contribution to the research and preparation of the article, and read and approved the final version before publication.

## Conflict of Interest

The authors of this article have confirmed that they have no conflicts of interest to disclose.

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