"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST

"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST
DOCTORAL SCHOOL
MEDICINE

Ph.D. THESIS SUMMARY

"EXTRACORPOREAL SHOCK WAVE THERAPY EFFICIENCY ON SPASTICITY, BALANCE, GAIT, AND FUNCTIONING IN PATIENTS WITH POST-STROKE SPASTICITY"

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Introduction

In accordance with the framework of the International Classification of Functioning (ICF), Disability and Health as integrated by the World Health Organization (WHO), it is of paramount importance for the field of rehabilitation to accurately detect and evaluate a condition, set goals and outcome measures, and prioritize the function of the individual.

Post-stroke spasticity (PSS) is a very frequent sequela of stroke and it commonly affects a person's ability to stand and to walk, therefore, is having enormous consequences on physical, psychological, and social level, leading to a significant decrease of involvement in activities of daily living (ADL), increased fatigue, and decrease of the Quality of Life (QoL).

The general hypothesis of this Ph.D. thesis is focused on accurately detecting and assessing the PSS, set rehabilitation goals and outcome measures while considering the functioning of the person, as well as the early initiation of rehabilitation post-stroke. Moreover, another focus point was on the delivery and efficiency assessment of a novel, non-invasive therapy (i.e.: radial extracorporeal shock wave therapy-rESWT) on various outcomes, including spasticity, pain, clonus, functional ability, balance, and gait. Another aim was to determine to what extent spasticity, poor trunk function and control, and gait pattern anomalies are related. Given the difficulties for stroke survivors in accessing healthcare services, and notably rehabilitation services during the COVID-19 pandemic, the Ph.D thesis also focused on developing and implementing a tele-rehabilitation (TR) and tele-assessment approach strategy for stroke survivors.

The purpose of the Ph.D. thesis is to also emphasize the need for a multifaceted approach towards PSS, optimizing the management and access to rehabilitation programs for individuals with lower limb spasticity, including early initiation of rehabilitation protocols, tele-rehabilitation (TR), safety profile, and global assessments through clinical outcomes and quantitative parameters.

Future research should include larger, high-quality clinical trials investigating the best approach for patients with PSS, the right time for rehabilitation initiation and the most suitable treatment option(s), long-term effectiveness, including parameters such as spasticity, pain, functioning, balance, gait, and safety profile. It is of paramount importance to perform a global assessment and integrate stabilometric and gait analysis systems in clinical practice, as well as for TR and tele-assessment strategies after patient discharge.

I. General part. Current knowledge

1. Stroke

1.1. Stroke incidence and burden

Stroke is still ranked as the second leading cause of death all over the world and the third main cause of disability-adjusted life years (DALY) (1,2). Latest data on stroke showed that from 1990 to 2019, the burden faced a substantial augmentation (70.0% increase in the incident strokes, 43.0% deaths related to stroke, 102.0% in prevalent strokes, and 143.0% DALYs), the scale of the global stroke burden (86.0% deaths and 89.0% DALYs) belonging to the lower-income and lower-middle-income countries (LMICs)(1,3). Additionally, the incidence of stroke is increasing in young and middle-aged people (i.e. age <55 years) worldwide (1). The need for prompt, high-quality, well-established rehabilitation services is a key factor for stroke management and quality of life (QoL) of stroke survivors. The goal is to develop and implement multidisciplinary rehabilitation services and consider adapting evidence-based recommendations to the local context, given this condition involves long-term care and rehabilitation practices (1,2).

1.2. Addressing the global burden of disability with rehabilitation programs

Given that stroke is the third main cause of disability all over the world, the efforts to reduce the global burden of disability are enormous and solutions need to implemented on a large-scale in order to address efficiently the functional limitations in stroke survivors (1,2). The proportion of individuals affected by disability after stroke (measured as a mRS scoring 3–5) 5 years after stroke onset ranges from 25% amid persons affected by minor strokes to approximatively 50% amid persons affected by moderate strokes and 80% amid persons affected by severe stroke (4). Therefore, the purpose of stroke rehabilitation is to improve functional outcomes and capacity, and also promote and prolong life without disability (1).

1.3. Stroke rehabilitation around the world

Over the world there are many differences regarding the approach toward stroke management and rehabilitation, in the availability of inpatient/outpatient, and community rehabilitation services, and quality of the services provided for stroke survivors according to the country they reside (1,5). Follow-up strategies should be multimodal and well-structured, and include not only the evaluation of modifiable risk factors, but also other key factors as identified by the WHO in the post-stroke checklist (1). Given the continuous evolution and

approach, rehabilitation is considered the Health Strategy for the 21st century (6). Therefore, an increasing number of therapies, interventions, and strategies are available for stroke survivors dealing with spasticity. Tele-medicine, tele-rehabilitation (TR), tele-assessment are potential emerging solutions to ease the access in the case of reduced availability of rehabilitation services (7).

1.3.1. Recommendations for improving acute stroke management and interventions for stroke rehabilitation

Acute stroke care and management require well-trained personnel who works in ambulances and emergency services to ensure early recognition of signs of stroke and quick transfer to a dedicated stroke center, quick evaluation in the emergency departments, timely initiation of acute stroke management, rapid admission to a stroke unit, multidisciplinary team management, and early initiation of the rehabilitation interventions and practices (1,8–10). A fundamental characteristic in rehabilitation, functioning is an element of major importance directing the progress of interventions in rehabilitation (11–14).

2. Post-stroke spasticity (PSS)

Stroke survivors frequently experience sensorimotor anomalies, such as impaired sensations, muscle weakness, or spasticity (15,16). Spasticity is a frequent complication related to various neurological diseases such as cerebral palsy, multiple sclerosis, traumatic brain injury, spinal cord injury, and stroke (15,17). The first definition of spasticity was outlined by Lance as a motor affliction due to a velocity dependent increase in tonic stretch reflex integrated in the upper motor neuron syndrome (UMNS) (18). Spasticity is defined as an augmentation of resistance depending not only on the muscle length, but also on the speed of movement when applied external stretching (18,19).

2.1. Spasticity pathophysiology

Spasticity appears due to an imbalance between the excitatory and inhibitory signals in the central nervous system (CNS) at supraspinal and spinal levels (20,21). At the supraspinal level, spasticity is related to a loss of inhibitory input from the subcortical nuclei, while at the spinal level, it is related to the disruption of descending pathways responsible for regulating the inhibitory modulation of α and γ motor neurons (20,21). Thus, the specific location of the injury in the affected pathways further determines the differences in the pathophysiology and clinical manifestations of spasticity.

2.2. Clinical and functional evaluation of spasticity

The assessment of spasticity follows several scales such as the Modified Ashworth Scale (MAS), Tardieu Scale (TS), Modified Tardieu Scale (MTS), or the Spinal Cord Assessment Tool for Spastic Reflexes (SCATS) (15). Other international scales are used to assess various signs and conditions related to spasticity in stroke survivors: Penn Spasm Frequency Scale and Clonus score for spasms and clonus, or Visual Analogue Scale (VAS) for evaluating pain intensity (15). Additionally, the Hypertonia Assessment Tool helps distinguishing spasticity among different types of hypertonia (i.e.: dystonia, rigidity), therefore, it is important to detect and understand the different features of these disorders.

2.3. Spasticity implications on balance, gait, ADL, and functioning

Given that spasticity impacts many aspects of balance and stance, their assessment plays an important part for stroke survivors since it can be an indicator of the suitability of

applying different therapies, interventions, orthotic prescriptions or surgeries (22).

Lower limb spasticity can often impair the gait pattern, thus resulting in early fatigue and increased falling risk due to important energy expenditure (23). The main characteristic is the integration of gait analysis systems within the clinical evaluation to ensure a comprehensive assessment of the gait abnormalities and the most suitable therapeutic approach for each patient (22). A comprehensive assessment gives a global understanding of the emerged changes in the body structure and function, and their implications on determining restrictions in ADL (1,24).

2.4. Current therapeutic approach for spasticity management

Considering the complexity of spasticity, various medications, therapies, interventions and techniques were implemented during the last decade (15,17,25). Optimal spasticity management most commonly entails a multifaceted approach strategy (25).

Physical therapy is the base in rehabilitation programs and it showed better efficacy when combined with other therapies and interventions (15). The pharmacological treatment for spasticity consists of different oral medications, including gamma aminobutyric acid agonists, central α2 receptor agonists, muscle relaxants, benzodiazepines; local injections, including botulinum toxin type A, phenol, ethanol; and intrathecal therapy, including baclofen (17,26). One of the most used pharmacologic therapies used for focal spasticity is botulinum toxin type a (BoNT-A), notably for the upper limb. The therapeutic efficiency of extracorporeal shock wave therapy (ESWT) intervention delivery is comparable to BoNT-A injection, showing non-inferiority, and long-lasting beneficial effects up to 12 weeks (17). Other various minimally invasive interventions and techniques can be used for the treatment of focal spasticity, such as neurolysis with phenol or alcohol, and cryoneurolysis (25,27).

2.5. Emerging therapeutic approaches and strategies for spasticity management

Virtual reality (VR) is gaining rapid interest for stroke rehabilitation and it offers the possibility to stroke survivors to experience an immersive environment through haptic technology, avatars, and real-time visual feedback (23). Commonly, VR is not used as alone technology for spasticity, it is delivered alongside a CPT program and other therapies.

Given that gait recovery after stroke is a priority for recovering autonomy, the response employed the robotic systems-Robotic Assisted Gait Training (RAGT) (28).

During the pandemic of the COVID-19, tele-medicine and tele-rehabilitation were emerging strategies which proved to be beneficial (7). Through these strategies, stroke survivors had access to continuous care delivery and access to rehabilitative programs.

Self-rehabilitation is an approach that can help stroke survivors to maintain a good level of physical activity after rehabilitation training by a physical or occupational therapist and can be easily integrated within a TR and/or tele-assessment strategy (15,29,30).

A potential therapy for spasticity management is the multipotent progenitor stem cell injection, but its beneficial effects need to be further investigated. Data from different reports has indicated that there were found improvements in gross motor function and quality of life, mainly for the pediatric population (27,31,32).

2.6. Trunk training following stroke and PSS

Stroke can affect various body functions, including perception, cognitive function, speech, and motor function (33). A frequent condition affecting stroke survivors is reduced trunk function and control, including features such as coordination, proprioception, and weakness (23,33–35). The evidence suggested that trunk training integrated within rehabilitation programs showed improvements on these outcome measures.

II. PERSONAL CONTRIBUTIONS

3. Hypothesis and general objectives

Considering that spasticity affects 20% to 40% of post-stroke population, anti-spastic therapies, intervention, and medications have been used to manage the negative effects of spasticity. Among the emerging therapies, extracorporeal shock wave therapy (ESWT) is a therapeutic intervention with potential for the management of post-stroke spasticity (PSS). Consequently, a systematic review and meta-analysis of randomized controlled trials (RCTs) was carried out to investigate and evaluate the long-term efficacy of ESWT on lower limb stroke spasticity, as well as the adverse events associated.

Additionally, one of the most used pharmacologic therapies used for the treatment of focal spasticity is botulinum toxin type a (BoNT-A), notably for the upper limb. Therefore, a systematic review was conducted to assess the efficiency of ESWT compared to BoNT-A injection, and to additionally determine and assess their efficacy as combined therapies for the management of spasticity of stroke, multiple sclerosis, and cerebral palsy origin.

The impact of stroke on trunk control and sitting balance is of paramount importance since these factors can predict the functional outcome and duration of hospital stay. Thus, the aim of the RCT was to evaluate the effects of radial extracorporeal shock wave therapy (rESWT) and balance training integrated within a conventional physical therapy (CPT) program and to investigate the link between lower limb spasticity and poor trunk control. The quantitative stabilometric evaluation complemented the clinical assessment.

Through COVID-19 pandemic, tele-rehabilitation (TR) became a pillar to promote the recovery process and continuum of care, mainly for stroke survivors. The purpose of the case report was to highlight the usefulness and applicability of implementing TR strategies to complement, prolong or enhance the effects of CPT and rESWT intervention for decreasing spasticity of stroke origin. Another focus point was to carry out a case report to underline the utility of applying an early implemented rehabilitation program for a stroke survivor who received CPT and two rESWT sessions.

Considering the gait complexity and its parameters which are frequently altered in stroke survivors with lower limb spasticity, the purpose of the observational study was to objectively evaluate the efficiency of rESWT delivery and CPT program on spasticity grade and gait pattern in stroke survivors, using clinical evaluation and complementary novel gait analysis technology.

4. General research methodology

During the Ph.D. thesis I conducted multiple studies, including:

- a randomized controlled trial (RCT)
- a prospective observational study
- a systematic review and meta-analysis
- a systematic review
- two case reports
- a narrative review of literature (co-author)

The systematic reviews and meta-analysis included 338 participants from 12 studies, the RCT included 23 participants, the prospective observational study included 15 participants, and the case reports included 2 participants. Therefore, through extensive research and literature screening, the effects of extracorporeal shock wave therapy (ESWT) on various outcome measures, was assessed and investigated on a total of 378 participants of which 338 were part of the existing literature, and 40 participants took part in the clinical trials conducted in the Physical and Rehabilitation Medicine Department, Elias University Emergency Hospital, Bucharest, Romania.

Firstly, a meta-analysis and systematic review of randomized controlled trials was conducted to assess the long-lasting effectiveness of ESWT delivery on decreasing lower limb spasticity of stroke origin. Besides spasticity, other clinical and sonographic outcome measures were additionally evaluated.

Secondly, to gather more data, a systematic review assessing the efficacy of ESWT and botulinum toxin type A (BoNT-A) for spasticity treatment was carried out. It included 5 clinical trials and 168 participants (36–40).

Thirdly, two case reports including two participants were conducted on stroke survivors to underline the usefulness of early rehabilitation, TR and tele-assessment complementary to the CPT programs and rESWT to maintain or enhance the beneficial effects of these therapies in stroke survivors with lower limb spasticity (7,41).

Fourthly, a double-blind, single-center randomized controlled trial (RCT) was conducted and 23 participants at the Physical and Rehabilitation Medicine Department, Elias University Emergency Hospital, Bucharest, Romania were included in the study (23).

Finally, a prospective, single-center, observational study was carried out at the Physical and Rehabilitation Medicine Department, Elias University Emergency Hospital, Bucharest, Romania, and 15 participants were included (22). An additional review of

literature was performed as co-author, focusing on the pathophysiology of spasticity and the multifaceted approach needed for the management of this frequent sequela of stroke.

5. Effectiveness of Radial Extracorporeal Shock Wave Therapy and Visual Feedback Balance Training on Lower Limb Post-Stroke Spasticity, Trunk Performance, and Balance: A Randomized Controlled Trial

5.1. Introduction

Trunk control and sitting balance are frequently modified in stroke survivors (2,42,43). Spasticity is also common in stroke patients and it is usually associated with muscle weakness, sensorimotor anomalies, and cognitive impairments (16,34,35).

Considering the mechanism of action of radial extracorporeal shock wave therapy (rESWT) and the beneficial effects reported on spasticity degree, the aim of the trial was to assess the effects of rESWT integrated within a conventional physical therapy (CPT) program and real-time feedback balance training for stroke patients presenting lower limb spasticity. A randomized controlled trial (RCT) was conducted to further evaluate the link between lower limb spasticity and trunk deficits in stroke survivors. The stabilometric evaluation completed the clinical assessment and provided a global, objective evaluation.

5.2. Materials and methods

5.2.1. Ethical approval

The clinical trial was carried out in accordance with the Declaration of Helsinki, followed the guidelines for Consolidated Standards of Reporting Trials (CONSORT) and the CONSORT Statement (44). The study protocol was approved by the Ethics Committee of the Elias University Emergency Hospital, Bucharest, Romania and prospectively registered within the International Register ClinicalTrials.gov (NCT05196633).

5.2.2. Study design

The clinical trial is a single-center, prospective, double-blind randomized controlled trial. Patients were allocated randomly to a control group (CG) or an experimental group (EG).

5.2.3. Study participants

The final analysis and results are based on 23 patients with post-stroke lower limb spasticity.

5.2.4. Radial Extracorporeal Shock Wave Therapy (rESWT) intervention

Table 5.1. presents the type of intervention, session duration, and time points for the CG and EG. rESWT was applied on the myotendinous junction of the gastrocnemius and the soleus muscles for all the participants.

Table 5.1. Therapeutic interventions and parameters for the CG and EG (23).

	Control Group	Experimental Group
Treatment type	CP+sham rESWT+Prokin	CP+rESWT+Prokin
CP session length	1 h/day; 5 days/week; 2 weeks	1 h/day; 5 days/week; 2 weeks
rESWT session length	7 min/session; 1 session/week; 2 weeks	7 min/session; 1 session/week; 2 weeks
Visual feedback session length	20 min/day; 5 times/week; 2 weeks	20 min/day; 5 times/week; 2 weeks

5.2.5. Real-time visual feedback balance training through Prokin system

All the patients in the EG and the CG had sessions of real-time visual feedback balance training through Prokin system, in addition to the CPT protocol, rESWT intervention delivery, and sham rESWT delivery, for the CG, respectively.

5.2.6. Clinical outcomes and clinical assessment

The primary clinical outcome measures included the degree of spasticity evaluated through the Modified Ashworth Scale (MAS), knee and ankle passive range of motion (PROM) , pain intensity assessed through the Visual Analogue Scale (VAS), and Clonus score. The secondary outcome measures focused on gait and balance evaluated through Tinetti Assessment Tool (TAT), Functional Ambulation Categories (FAC), and Fugl-Meyer Assessment for Lower Extremity (FMA-LE). FMA-LE assessed lower limb sensorimotor function, and the Trunk Impairment Scale (TIS) assessed the static and dynamic sitting balance and trunk coordination in a sitting position.

5.2.7. Stabilometric evaluation through Prokin system

The stabilometric evaluation was carried out by a blind assessor to rESWT or sham rESWT delivery through the Prokin system (PK 252, TecnoBody, Bergamo, Italy).

5.2.8. Statistical Analysis

All the participants were assessed both clinically and through the stabilometric plaform before and after the CPT protocol and rESWT or sham rESWT intervention.

Participant characteristics were described as the mean and standard deviation (SD) for the control and the experimental group for the continuous data.

5.3. Results

Table 5.2. summarizes the characteristics of the CG and EG at the baseline evaluation.

Table 5.2. Characteristics of the participants at the baseline evaluation, clinical, and stabilometric outcomes (23).

	CG (Mean, SD)	EG (Mean, SD)	*p*-Value
Variables	*n*, 11	*n*, 12	
Age (years)	68.18 (11.51)	60.33 (11.5)	0.11 [a]
Weight (kg)	77.50 (11.53)	75.32 (17.88)	0.72 [a]
Height (cm)	174.09 (8.08)	171.16 (10.77)	0.46 [a]
Time since stroke onset (months)	24.97 (34.17)	25.02 (39.23)	0.99 [a]
Gender (M/F)	7/4	6/6	
Stroke type (Ischemic/Hemorrhagic)	8/3	9/3	0.5 [c]
Affected side of the body (Right/Left)	6/5	4/8	0.87 [c]
Clinical outcome measures			
MAS	2.54 (0.52)	2.58 (0.51)	0.86 [a]
Knee PROM (degrees)	116.90 (5.16)	116 (4.78)	0.66 [a]
Ankle PROM (degrees)	39.27 (3.16)	39.91 (4.1)	0.65 [a]
VAS	3.09 (1.13)	3 (1.12)	0.84 [a]
Clonus Score	2.36 (1.28)	2.25 (1.23)	0.82 [a]
TIS	14.63 (2.33)	14.58 (2.71)	0.85 [b]
Tinetti Assessment Tool	15.81 (4.33)	14.83 (5.62)	0.53 [b]
FAC	4.72 (0.9)	4.58 (1.37)	1.00 [b]
FMA-LE	19.27 (1.95)	19.66 (2.1)	0.60 [b]
Stabilometric outcome measures			
Dynamic	4.74 (1.04)	5.27 (3.01)	0.57 [a]
Trunk	202.54 (112.36)	193.21 (114.75)	0.84 [a]
Limits of stability	46.82 (9.17)	52.23 (20.44)	0.41 [a]
Static perimeter, mm (EO)	660.09 (289.16)	626.52 (244.94)	0.76 [a]
Static ellipse area, mm^2 (EO)	537.60 (95.62)	539.98 (276.06)	0.98 [a]
Static perimeter, mm (EC)	1079.28 (558.89)	1147.16(492.65)	0.76 [a]
Static ellipse area, mm^2 (EC)	1092.48 (661.60)	1111.07 (467.81)	0.93 [a]

5.3.1. Clinical outcome measures

Table 5.3. highlights the effect between the two groups for the primary and secondary clinical outcomes. The participants from the EG presented significant improvement compared to the CG for all the outcomes except for the knee PROM, TIS, and FAC.

Table 5.3. Comparison of the change score of clinical outcomes between the CG and EG post-treatment (23).

Clinical Outcome Measures	CG (Mean, SD) *n* = 11 Post-Treatment	Change Score	EG (Mean, SD) *n* = 12 Post-Treatment	Change Score	Diff.	*p*-Value
MAS	2.18 (0.75)	0.36	1.50 (0.52)	1.08	0.72	0.02 [a]
Knee PROM (degrees)	122.63 (5.4)	5.73	126.33 (3.96)	10.33	4.6	0.07 [a]
Ankle PROM (degrees)	44.09 (3.47)	4.82	48.33 (2.26)	8.17	3.35	0.03 [a]
VAS	2.09 (1.22)	1	1 (0.85)	2	1	0.02 [a]
Clonus score	1.90 (1.13)	0.46	0.83 (0.83)	1.42	0.96	0.01 [a]
TIS	17.54 (2.06)	2.91	18.66 (2.38)	4.08	1.17	0.2 [a]
Tinetti Assessment Tool	21.09 (3.50)	5.28	24.66 (2.83)	9.83	4.55	0.02 [b]
FAC	5.45 (0.82)	0.73	5.5 (0.79)	0.92	0.19	0.92 [b]
FMA-LE	22.36 (2.06)	3.09	24.75 (2.01)	5.09	2	0.01 [b]

The change score for the MAS was 1.08 in the EG and in the CG the change score was 0.36, (p-value < 0.02). Statistically significant improvement was noted for the ankle PROM, with a change score of 8.17 in the EG and 4.82 in the CG, (p-value < 0.03). Regarding the pain intensity evaluated on the VAS, a statistically significant difference between the two groups after the intervention was found, (p-value of 0.02).

5.3.2. Stabilometric endpoints

Table 5.4. summarizes the stabilometric endpoints assessed through the Prokin system. All the parameters showed statistically significant improvement, except for the perimeter in eyes closed (EC) condition.

Table 5.4. Comparison of change score of stabilometric outcomes between the CG and EG post-treatment (23).

Stabilometric Outcome Measures	CG (Mean, SD) *n* = 11 Post-Treatment	Change Score	EG (Mean, SD) *n* = 12 Post-Treatment	Change Score	Diff.	*p*-Value
Dynamic	4.39 (0.86)	0.35	3.10 (1.66)	2.17	1.82	0.03
Trunk	311.58 (128.28)	109.04	458.85 (166.33)	265.64	156.6	0.02
Limits of stability	51.92 (7.76)	5.1	68.37 (19.12)	16.14	11.04	0.01
Static-perimeter, mm (EO)	624.52 (201.91)	35.57	424.48 (108.40)	202.04	166.47	0.01
Static-ellipse area, mm^2 (EO)	482.81 (147.31)	54.79	328.59 (182.17)	211.39	156.60	0.03
Static-perimeter, mm (EC)	943.53 (412.42)	135.75	734.02 (332.75)	413.14	277.39	0.1
Static-ellipse area, mm^2 (EC)	1021.83 (583.39)	70.65	609.77 (128.26)	501.30	430.65	0.04

For the trunk analysis, a statistically significant improvement was found (p-value < 0.02) for the EG, reaching a change score of 156.6. Figure 5.4., Figure 5.5., Figure 5.6.

present the data processed by the means of MATLAB for one representative patient from the CG and the EG at baseline and post-intervention delivery for static stabilometric, dynamic stabilometric, and trunk stabilometric assessment.

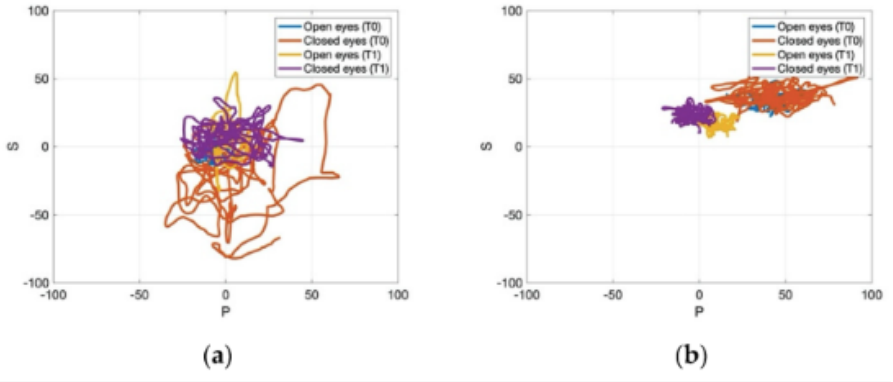

Figure 5.4. Static stabilometric assessment in the eyes open and eyes closed condition for one representative participant from the CG (a) and EG (b) pre- and post-treatment.

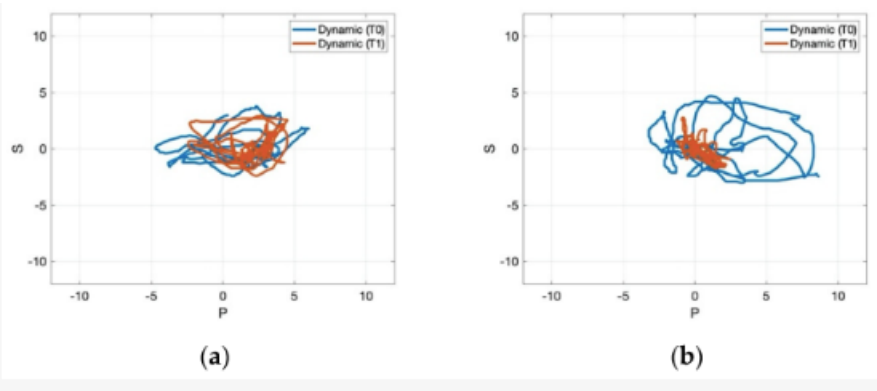

Figure 5.5. Dynamic stabilometric assessment for one representative participant in the CG (a) and EG (b) pre- and post-treatment.

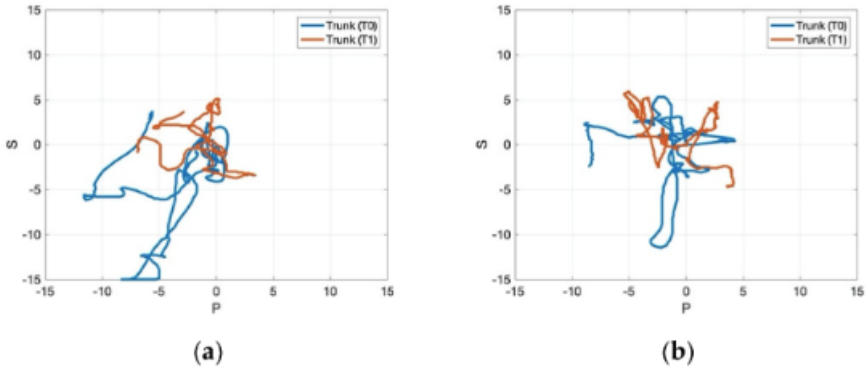

Figure 5.6. Trunk stabilometric assessment for one representative participant in the CG (a) and EG (b) pre- and post-treatment.

5.4. Discussions

The results yielded by this clinical trial concluded that besides the CPT program, additional visual feedback training through the Prokin system and rESWT delivery improved not only the clinical outcome measures, but also the stabilometric parameters in the experimental group. Since the control group received sham rESWT and the results were less pronounced compared to the experimental group, rESWT delivery was considered the key factor, notably for the clinical outcomes. A major strength of the clinical trial is the objective, quantitative evaluation of the intervention`s global effects for stroke survivors, while integrating the stabilometric assessment within the clinical evaluation.

The visual feedback balance training and rESWT delivery integrated within the CPT protocol were implemented to improve stance, balance and trunk muscle deficits, and to decrease lower limb spasticity grade. The results are consistent with the literature, and there were previous studies which focused either on core stability exercises and trunk muscle training, or used visual feedback balance training (35,45,46). Adding virtual reality to a CPT program also showed beneficial effects on improving balance and gait in neurologic patients (47,48).

5.5. Conclusions

Through the data obtained we conclude that ESWT intervention and visual feedback balance training through the Prokin system, included within the conventional physical therapy program, decreased lower limb spasticity, pain intensity, and clonus score, improved trunk control, static and dynamic balance, and ameliorated the sensorimotor functionality in stroke survivors.

6. Conventional physical therapy combined with extracorporeal shock wave leads to positive effects on spasticity in stroke survivors: A prospective observational study

6.1. Introduction

Gait is usually affected after stroke, and spatiotemporal, kinematic, and kinetic parameters are commonly modified in stroke survivors, leading to various types of walking difficulties (41,49). Lately, novel gait analysis systems are used for gait assessment. Amid all the therapies, extracorporeal shock wave therapy (ESWT) is a non-invasive therapeutic intervention used for treating various musculoskeletal disorders, inflammatory tendon diseases, and spasticity (15,15,23,50–54). The aim of this clinical trial was to objectively evaluate through a novel gait analysis system the efficacy of radial extracorporeal shock wave therapy (rESWT) delivery integrated within a conventional physical therapy (CPT) protocol on the gait pattern in stroke survivors. The technology uses spatiotemporal and kinematic parameters, and the data are correlated with the clinical assessment, thus allowing global assessment of the gait parameters.

6.2. Materials and methods

6.2.1. Study design and ethical approval

The clinical trial is a prospective, single-center, observational study conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Elias University Emergency Hospital, Bucharest, Romania. The study was prospectively registered with the ClinicalTrials.gov (registration number NCT05206240). The trial was conducted in accordance with the guidelines of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE), the STROBE Statement (55).

6.2.2. Study participants

Patients hospitalized in the Physical and Rehabilitation Medicine Department, Elias University Emergency Hospital, Bucharest, Romania were assessed for eligibility. The patients meeting the inclusion criteria were enrolled in the study.

6.2.3. CPT protocol and rESWT delivery

The duration of the CPT program was 1h/day, 5 days/week during a 10-day rehabilitation plan. Two rESWT sessions were performed for all the participants. Figure 6.1 summarizes the protocol. The site for rESWT delivery was the myotendinous junction of the hypertonic triceps surae muscle.

Figure 6.1. CPT protocol and rESWT intervention delivery summary (22)

6.2.4 Clinical outcome measures and assessment

The clinical endpoints were the spasticity grade measured through the Modified Ashworth Scale (MAS), passive range of motion (PROM), pain intensity measured through the Visual analogue Scale (VAS), Clonus score, the sensorimotor function on the Fugl-Meyer Assessment for the Lower Extremity (FMA-LE), mobility, balance, and gait assessed through Tinetti Assessment Tool (TAT), Functional Ambulation Categories (FAC), and Timed Up and Go (TUG) test.

6.2.5. Walker View instrumented treadmill gait analysis system

The instrumented treadmill system Walker View (TecnoBody®, Bergamo, Italy) was used to perform the quantitative analysis of gait parameters.

6.2.6. Spatiotemporal and kinematic parameters

The integrated software of Walker View system performs a real-time analysis of the gait parameters: spatiotemporal parameters (step cycle time, contact time, step length, stance

and swing time for foot flexion-extension and pronation-supination) and kinematic parameters (trunk flexion-extension, trunk lateral flexion, total ROM, maximum and minimum angle values in the sagittal plane of hip and knee).

6.2.7 Statistical Analysis

The statistical analyses and processing of data were computed using the Microsoft Excel (Microsoft Excel for Mac, Version 16.38, 2020, Microsoft), GraphPad Software (San Diego, CA, USA), and MATLAB (R2016a, The MathWorks, Inc, Natick, MA, USA). The p-value < 0.05 was statistically significant.

6.3. Results

Eventually, 15 participants were included in the clinical trial and the final analysis.

6.3.1. Clinical endpoints

An outline of the clinical endpoints is presented in Table 6.1.

Table 6.1. Clinical endpoints assessed pre-treatment (T0) and post-treatment (T1) (22)

Clinical endpoints	T0 Mean (SD)	T1 Mean (SD)	p	Bonferroni correction	95 % CI
MAS	2.07 (0.64)	1.15 (0.55)	<0.0001	0.00001	0.93 (0.79 ÷ -1.08)
Ankle PROM (°)	48.92 (5.25)	58 (3.58)	<0.0001	0.00001	-9.13 (-10.87 ÷ -7.40)
VAS	2.76 (1.09)	1.15 (0.89)	<0.0001	0.00001	1.60 (1.19 ÷ 2.01)
Clonus score	1.61 (1.19)	0.46 (0.77)	<0.0001	0.00001	1.13 (0.72 ÷ 1.54)
FMA-LE	20 (1.68)	22.69 (1.18)	<0.0001	0.00001	-2.53 (-3.42 ÷ 1.65)
Tinetti Assessment Tool	18.53 (3.59)	24.38 (2.75)	<0.0001	0.00001	-5.67 (-6.64 ÷ -4.69)
FAC	5.23 (0.72)	5.84 (0.37)	0.0001	0.00001	-0.67(-0.94 ÷ -0.40)
TUG (s)	28.06 (6.63)	22.93 (4.96)	<0.0001	0.00001	5.67 (4.61 ÷ 5.63)

For the spasticity grade measured on the MAS it was found a statistically significant difference ($p < 0.0001$) between the mean values of MAS scores from the baseline (T0) and post-treatment (T1). Ankle PROM scored statistically significant improvement ($p < 0.0001$), these results translating into gain in terms of degrees and being correlated to the decrease in the spasticity grade as well. Regarding the pain intensity on the VAS, statistically significant changes were found between the baseline evaluation and post-treatment comparison ($p < 0.0001$). The Clonus score showed significant improvement post-treatment, the mean value

(SD) decreasing from 1.61 (1.19) at baseline to 0.46 (0.77), ($p < 0.0001$). TAT scored significant improvement from a mean score (SD) of 18.53 (3.59) at baseline, pre-treatment to 24.38 (2.75) post-treatment delivery. The results showed improvement for endpoints such as the spasticity grade, pain intensity, clonus score, ankle PROM, lower limb function, balance, and gait post-treatment, compared to the baseline evaluation, pre-treatment.

6.3.2. Kinematic parameters

The kinematic and spatiotemporal parameters are summarized in Table 6.2. All the parameters have shown statistically significant change post-treatment compared to baseline except for the trunk lateral flexion ($p= 0.9$). Hip flexion-extension ROM and knee flexion-extension ROM were also assessed, and both of them scored improved results in terms of degrees. For the foot flexion-extension, a statistically significant change was found, with a mean value (SD) 10.46 (4.73) pre-treatment to 11.92 (3.93) post-treatment, ($p= 0.02$).

Table 6.2. Quantitative gait analysis. Spatiotemporal and kinematic parameters pre-treatment (T0) and post-treatment (T1) (22)

Gait analysis	T0 Mean (SD)	T1 Mean (SD)	p	Bonf. Corr.	95 % CI
Spatiotemporal parameters					
Step length (m)	0.08 (5.24)	0.12 (7.25)	0.02	0.001	-3.47 (-6.48 ÷ 0.46)
Step cycle time (cycles/s)	0.38 (0.16)	0.48 (0.20)	0.02	0.001	-0.09 (-0.17 ÷ -0.01)
Contact time of the affected side (s)	2.43 (1.55)	2.57 (1.53)	0.50	0.038	-0.20 (-0.83 ÷ -0.43)
Foot stance flexion-extension (°)	-2.18 (2.94)	-1.14 (3.63)	0.05	0.003	-1.39 (-2.80 ÷ -0.02)
Foot stance pronation-supination (°)	1.9 (2.32)	3.23 (3.38)	0.04	0.003	-1.67 (-3.26 ÷ -0.08)
Foot swing flexion-extension (°)	-12.86 (5.05)	-13.06 (3.23)	0.05	0.003	3 (-0.03 ÷ 6.03)
Foot swing pronation-supination (°)	-0.18 (3.15)	1.10 (3.92)	0.10	0.007	0.88 (-2.20 ÷ -0.44)
Kinematic parameters					
Trunk flexion-extension (°)	2.65 (0.88)	3.18 (0.89)	0.03	0.002	-0.68 (-1.30 ÷ -0.05)
Trunk lateral flexion (°)	5.63 (2.26)	5.36 (2.14)	0.9	0.069	0.03 (-0.69 ÷ 0.75)
Hip flexion-extension (°)	15.12 (5.19)	18.85(6.54)	0.01	0.0007	-3.90 (-6.92 ÷ -0.88)
Knee flexion-extension (°)	16.14 (8.51)	23.47 (9.04)	0.02	0.001	-2.08 (-3.84 ÷ -0.32)
Foot flexion-extension (°)	10.46 (4.73)	11.92 (3.93)	0.02	0.001	-2.08 (-6.64 ÷ -4.69)
Foot pronation-supination (°)	0.84 (2.21)	1.76 (2.61)	0.03	0.002	-0.78 (-1.53 ÷ -0.04)

6.3.3. Spatiotemporal parameters

With regard to the spatiotemporal parameters, significant changes for the step length, step cycle time, foot stance flexion-extension/pronation-supination, and foot swing flexion-extension were noted. The only parameters which did not score any significant change were the contact time on the affected side and foot swing pronation-supination. The mean value (SD) of step length (m) scored statistically significant change from the baseline, ($p= 0.02$), increasing from 0.08 (5.24) pre-treatment to 0.12 (7.25) post-treatment. The mean value (SD) for foot stance flexion-extension was -2.18 (2.94) pre-treatment and -1.14 (3.63) post-treatment, ($p= 0.05$). The mean (SD) for foot stance pronation-supination was 1.9 (2.32) pre-treatment and 3.23 (3.38) post-treatment, ($p = 0.04$). With regard to the swing foot flexion-extension, the mean values (SD) pre-treatment were -12.86 (5.05) compared to 13.06 (3.23) post-treatment, ($p= 0.05$). The mean values (SD) for foot swing pronation-supination, pre-treatment were -0.18 (3.15) and post-treatment they were 1.10 (3.92), ($p= 0.10$).

6.4. Discussions

The aim of this observational study was to assess in an objective manner the effects of rESWT integrated within a CPT protocol on the gait pattern, spatiotemporal and kinematic parameters through a novel gait analysis system and correlate the results with the clinical outcomes. The results from showed a significant reduction ($p < 0.0001$) of the spasticity degree on the MAS and, consequently augmented PROM, ($p < 0.0001$). These results are in concordance with the results from other studies, indicating that after rESWT it was noted a decrease of the spasticity grade, with a consequent augmentation of the ROM, and increase of the plantar surface area and peak pressure at the pedobarometric assessments (56,57). The quantitative gait analysis provides comparative assessments during the rehabilitation program and TR strategies, and offers the possibility to objectively track patient's progress.

6.5. Conclusions

The results should be further confirmed by larger trials which should also evaluate the use of gait analysis systems in current clinical practice, and their implementation in TR programs. More data would allow a better insight into adapted protocols for the development and implementation of tailored CPT programs for the treatment of stroke survivors.

7. Long-Term Efficacy of Extracorporeal Shock Wave Therapy on Lower Limb Post-Stroke Spasticity: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

7.3. Introduction

It is estimated that spasticity affects 20% to 40% of stroke survivors (58). Lately, extracorporeal shock wave therapy (ESWT) has been described as a potential therapeutic intervention in the management of post-stroke spasticity (PSS), showing short and long-term beneficial effects (22,23,51,53,59–61). The aim of this systematic review and meta-analysis was to evaluate the long-term effects of ESWT on decreasing lower limb PSS in adult population. The primary outcome measure was spasticity grade and secondary outcomes included passive range of motion (PROM), pain intensity, gait assessment, electrophysiological parameters, and adverse events.

7.4. Materials and methods

Seven randomized controlled trials (RCTs) were included and a beneficial effect on spasticity was found when analyzing the data (60,62–67).

7.4.1. Outcome measures

The primary outcome measure was spasticity grade. Secondary outcome measures included PROM, pain intensity, gait assessment, electrophysiological parameters, and adverse events related to the ESWT delivery.

7.4.2. Quality assessment

The risk of bias assessment was carried out for all the studies included.

7.5. Results

A forest plot was performed to evaluate spasticity through MAS on the long-term while comparing the control group (CG) and experimental group (EG) after ESWT. The meta-analysis yielded positive effects in the EG, in favor of ESWT: standardized mean difference (SMD) = 0.32; 95% confidence interval (95% CI): (0.01-0.65), p =0.06. (Figure 7.1.).

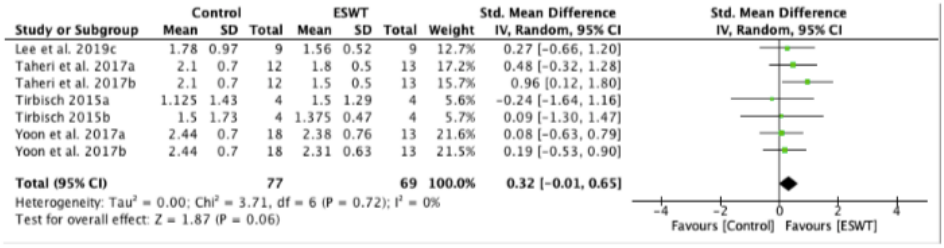

Figure 7.1. Forest plot of the standardized mean difference (SMD) and 95% confidence interval (95% CI) for spasticity assessment through the Modified Ashworth Scale (MAS) comparing the long-term effects in control group (CG) and the experimental group (EG) after extracorporeal shock wave therapy (ESWT) intervention delivery (15).

On the short and long-term the effects of ESWT on pain intensity (Figure 7.2.) were significantly greater after ESWT delivery and had long-lasting effects at twelve weeks follow-up.

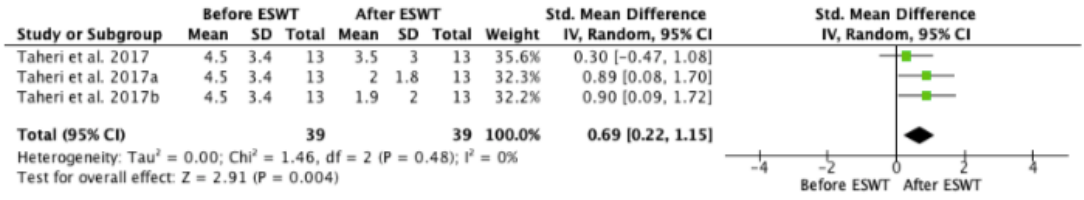

Figure 7.2. Forest plot of the standardized mean difference (SMD) and 95% confidence interval (95% CI) evaluating the short and long-term effects on pain intensity assessed through the Visual Analogue Scale (VAS) before and after extracorporeal shock wave therapy (ESWT) (15).

A statistically significant effect was found in the EG for the PROM, favoring ESWT delivery, and the effects lasted 12 weeks after the treatment delivery (Figure 7.3.). The standardized mean difference (SMD) = 0.69; 95% confidence interval (95% CI): [0.20–1.19]; $p = 0.006$.

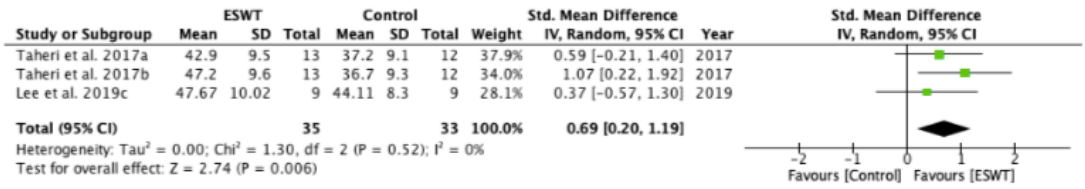

Figure 7.3. Forest plot of the standardized mean difference (SMD) and 95% confidence

interval (95% CI) evaluating the long-term effects on passive range of motion (PROM) before and after extracorporeal shock wave therapy (ESWT) (15).

Concerning the adverse effects related to ESWT delivery, one study described mild pain during the first two ESWT sessions (64), and in two other studies, no pain or discomfort were reported and no other adverse events were otherwise reported (62,63).

7.6. Discussions

Besides the spasticity grade, there were other several endpoints assessed in the included studies: PROM, pain intensity, gait, and sensorimotor function. The meta-analysis yielded a statistically significant effect of ESWT on reducing the lower limb spasticity on the short and the long-term, these results being consistent with findings from a previous systematic review and meta-analysis (51). The EG showed statistically significant improvement of the PROM on the long-term. ESWT led to a statistically significant decrease both on the short and long-term for pain intensity. No significant improvements were found for the Hmax/Mmax ratio after ESWT, and the results were consistent with the literature (60,63,68,69). Only mild local reactions or no reactions at all were reported.

7.7. Conclusion

Data from the systematic review and meta-analysis showed that ESWT decreased the degree of lower limb spasticity and increased the range of motion in stroke survivors whereas being effective up to 12 weeks, showing long-term efficacy. Besides these beneficial effects, ESWT additionally reduced pain intensity and maintained a satisfactory safety profile. However, these results need to be further confirmed by larger randomized clinical trials.

8. A systematic review on extracorporeal shock wave therapy and botulinum toxin for spasticity treatment: a comparison on efficacy

8.1. Introduction

Spasticity is a complex condition requiring continuous efforts for developing and implementing more adapted treatments and interventions. The aim of this systematic review was to assess and compare the efficacy of extracorporeal shock wave therapy (ESWT) with botulinum toxin type A (BoNT-A) as alone or combined therapies, on reducing spasticity both in the pediatric and adult population. Nowadays, the ultimate approaches are used as part of the multimodal approach strategy (15,25).

8.2. Materials and methods

8.2.1. Search strategy and eligibility criteria

A search strategy of the electronic databases PubMed/Medline, Physiotherapy Evidence Database (PEDro), Scopus, Ovid Medline(r), and Google scholar was conducted.

8.2.2. Data extraction and quality assessment

The process of study selection was based initially on title and abstract and finally, full-text articles were examined. Risk of bias was assessed through PEDro scale.

8.2.3. Outcome measures

Different outcome measures were considered as markers of efficacy for ESWT and BoNT-A, including spasticity degree, pain intensity, passive range of motion or gait pattern.

8.2.4. Evidence synthesis

The total number of participants from the five studies included 168 participants, 97 men and 71 women.

8.3.Results

The primary outcome measure was spasticity grade. One study compared BoNT-A plus fESWT with BoNT-A plus electrical stimulation (ES), with a better efficacy of BoNT-A and fESWT applied together on decreasing spasticity (39). ESWT is a non-inferior alternative to BoNT-A for upper limb spasticity in stroke survivors and led to a more

significant improvement in wrist and elbow PROM and consequently, on the UE-FMA score when compared to BoNT-A injection (37). The secondary endpoints corresponded to the active and passive range of motion, pain intensity, spasm frequency, motor recovery, ultrasonographic parameters, treatment response rate, and between-group comparisons. With regard to the adverse events, one study did not report any information (38), while the other trials did not report any adverse events (36,37,39,40). Regarding the pain intensity and frequency of spasms, at follow-up, it was found a continuous decrease for BoNT-A followed by fESWT when compared to the patients receiving BoNT-A followed by ES (39). Regarding the sonographic parameters, at one month after toxin injection follow-up, there were no significant differences in the Heckmatt Scale scores between the group receiving only the BoNT-A injection and the group receiving both BoNT-A and fESWT. A significant decrease was found in the hardness percentage measurement in the group receiving both BoNT-A and fESWT (40).

8.4. Discussions

Evidence from all the studies included in the systematic review indicated that BoNT-A, fESWT, and rESWT applied alone or together, have led to a substantial improvement on the spasticity degree, range of motion, pain intensity, spasm frequency, motor recovery, and ultrasonographic parameters regardless of the age of the participants, condition onset, or underlying neurological conditions (36–40). Adding ESWT to BoNT-A injection, the effect on decreasing pain is prolonged (37,39). To optimize the benefits of other therapies on PSS, including BoNT-A, ESWT should be considered as alternative (70).

8.5.Conclusion

ESWT combined with BoNT-A yielded positive effects on decreasing spasticity, pain intensity and spasm frequency in stroke survivors, multiple sclerosis, and cerebral palsy patients, whereas a satisfying safety profile was maintained. ESWT increased the range of motion and improved motor recovery either with CPT or combined with BoNT-A injection. However, these results need to be further confirmed by larger, high-quality research studies.

9. Tele-Rehabilitation Strategies for a Patient With Post-stroke Spasticity: A Powerful Tool Amid the COVID-19 Pandemic: a case report

9.1. Introduction

A timely management after stroke leads a good risk stratification and more effective rehabilitative programs (1). Nonetheless, due to the COVID-19 pandemic, rehabilitation and long-term follow-up became difficult to continue (71,72). As a solution, tele-assessment and tele-rehabilitation (TR) became reasonable alternatives to implement.

9.2. Materials and methods

The patient gave his informed consent to take part in this case report, which was conducted in accordance with the Declaration of Helsinki. He was part of the rehabilitative program during hospital stay (CPT and rESWT applied on the myotendinous junction of the triceps surae muscle) and after discharge he continued his rehabilitative program remotely, through TR. All the assessments were performed pre-treatment (T0), at the end of the CPT program and rESWT (T1), as well as at 20 weeks (T2).

9.3. Results

9.3.1. Clinical assessments

Several clinical outcome measures were considered for the assessments. The spasticity grade decreased by one point for the MAS score, and the effect lasted at the 20 weeks follow- up. Knee and ankle passive range of motion (PROM) showed a small decrease at T2 compared to the T1 evaluation. The pain intensity sand Clonus score showed a decrease at T1 and T2 evaluations. The patient also benefited from significantly improved mobility, functionality, balance, gait and safely walking speed on the long-term. The Tinetti Assessment Tool (TAT) score, Functional and Ambulation Categories (FAC), Fugl-Meyer Assessment for Lower Extremity (FMA-LE), and Timed Up and Go Test (TUG) showed significant improvement. Table 9.1. summarizes the results.

Table 9.1. Clinical outcomes assessed at T0, T1, T2 (7)

Clinical outcome measures	T0	T1	T2
MAS	2	1	1
Knee PROM (degrees)	119	125	123
Ankle PROM (degrees)	44	48	47
VAS	3	1	1
Clonus score	4	2	2
Tinetti Assessment Tool	14	23	23
FAC	5	6	6
FMA-LE	22	25	25
TUG (seconds)	31.01	25.04	19.08

9.3.2. Stabilometric evaluations

The stabilometric evaluation and gait analysis were performed through ProKin 252 (TecnoBody®, Bergamo, Italy) and Walker View system (TecnoBody®, Bergamo, Italy). The results of the stabilometric parameters were consistent with the clinical outcomes. Dynamic balance, trunk analysis, and limits of stability were significantly improved at T1 and continued to improve at T2 (Table 9.2.). The gait analysis showed that the right foot pitch and foot roll improved at T1 and T2.

Table 9.2. Stabilometric parameters at T0, T1, T2 (7)

ProKin (Stabilometric outcome measures)	T0	T1	T2
Dynamic	7.59	4.85	3.75
Trunk	359.72	677.07	670.98
Limits of stability	28.92	39.51	38.01
Static-perimeter, mm (EO)	540.58	369.59	320.41
Static-ellipse area, mm^2 (EO)	501.61	311.42	300.01
Static-perimeter, mm (EC)	830.99	570.89	579.98
Static-ellipse area, mm^2 (EC)	1071.46	665.6	601.89

The assessment and the results were transmitted via Internet to the assessor's tablet, who correlated the stabilometric and gait parameters with the clinical assessment, as showed in Figure 9.1. and Figure 9.2.

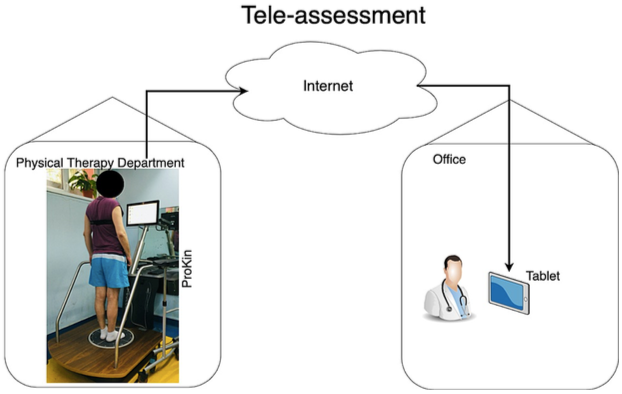

Figure 9.1. Tele-assessment of stabilometric parameters through ProKin system (7).

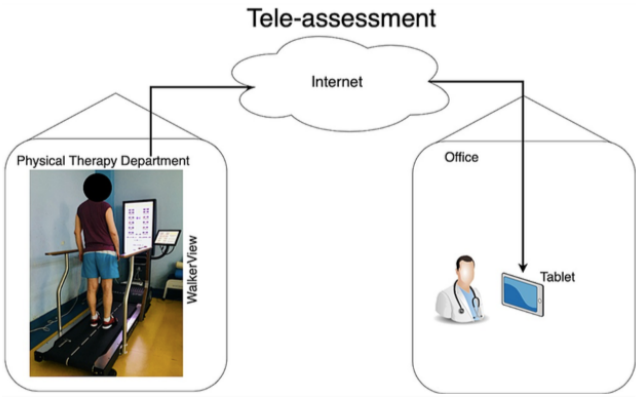

Figure 9.2. Tele-assessment through Walker View gait analysis system (7).

Through TR the results obtained during the hospital stay were maintained and even improved. At discharge, the patient had already gained improved functional independence with greater functional mobility, and consequently decreased spasticity grade, decreased clonus rate and pain intensity. He also achieved a better walking speed, with less expenditure and more safety during ambulation. There were no adverse events during or after the CPT program, and no falls were registered during the evaluations, tests, or hospital stay.

9.4. Discussions

The purpose of this case report was to emphasize the usefulness of an adapted tele-assessment and TR approach for a stroke survivor who took part into the CPT program and received rESWT during hospital stay. TR proved to be cost-effective and gave easy access to a rehabilitation program for persons who cannot otherwise receive proper, continuous rehabilitative care, thus increasing patient satisfaction (73). Future research should focus on the efficiency and cost-effectiveness of tele-rehabilitation in post-stroke survivors, as well as on early implementation within the healthcare plan.

9.5. Conclusions

This case report underlines TR and tele-assessment as valuable tools in enhancing and maintaining the effectiveness of rESWT within a CPT program in stroke survivors affected by spasticity. At discharge and follow-up, the patient presented decreased lower limb spasticity, improved trunk control, static and dynamic balance, decreased pain intensity and clonus score, and enhanced sensorimotor performance, functionality, and gait. Through TR, the effects obtained at discharge lasted 20 weeks, proving that TR programs are key features for the continuum of care, maintaining results, and even prolonging them.

10. Early Individualized Approach for a Patient with Spasticity of Stroke Origin: a case report

10.1. Introduction

The aim of this case report is to present an early tailored rehabilitative strategy for a stroke survivor with upper and lower limb spasticity. Besides the clinical outcomes, a gait analysis provided by a novel system was added, and results were correlated for a global assessment. Additional outcome measures were the pain intensity, passive range of motion (PROM), mobility, ambulation capacity, and adverse events. The case presents a 75-year-old female, stroke survivor affected by spasticity who started an early neurorehabilitation program including conventional physical therapy (CPT) and two radial extracorporeal shock wave therapy (rESWT) sessions.

10.2. Materials and methods

This case report was conducted in accordance with the Declaration of Helsinki and the patient signed the written consent to take part in the study. Additionally to the clinical evaluation, stance and gait parameters were assessed through the Walker View system (TecnoBody®, Bergamo, Italy) which provided a quantitative analysis through real-time visual feedback. Therefore, data obtained through the gait analysis system provided an objective analysis to be integrated within the clinical assessment, leading to a global, comprehensive evaluation approach. The clinical assessment and quantitative analysis were conducted at three different time points which corresponded to: T0 (baseline assessment), T1 (assessment at the end of the rehabilitation program), and T2 (8 weeks follow-up). Also, rESWT was applied on the myotendinous junction of the triceps surae muscle

10.3. Results

The spasticity grade was reduced by one point on the MAS and at 8 weeks follow up it had the same level. For the PROM, the degree gain was significant at T1 and T2 assessment compared to T0. Regarding the pain intensity on the VAS, the score decreased by one point at T1 and maintained the same level at T2 evaluation. The patient also had better scores for several parameters, experiencing improved mobility, balance, and gait on the clinical level on the short and the long-term. For the gait parameters as provided through the gait analysis system, the gait pattern improved at T1 and prolonged the same level at 8 weeks follow-up assessment. The step length and contact time improved significantly at T1 compared T0

evaluation. The stance phase, the foot flexion-extension, and foot eversion-inversion improved at T1 and maintained the level at T2. The eversion-inversion of the swing phase also showed improvement at T1 and T2 evaluations compared to T0. A highlight of the clinical outcomes and gait parameters through Walker View is presented in Table 10.1.

Table 10.1. Clinical outcomes and gait parameters through Walker View analysis at T0, T1, T2 (41)

Clinical outcome measures and Walker View analysis	T0	T1	T2
MAS	3	2	2
Ankle PROM (degrees)	38	48	45
VAS	2	1	1
Tinetti Assessment Tool	12	20	20
FAC	4	5	5
Trunk flexion-extension (degrees)	8.4	10.5	10.2
Trunk lateral flexion (degrees)	4.2	6.6	6.5
Left hip flexion-extension (degrees)	6.4	12.8	12
Left knee flexion-extension (degrees)	28.5	35.5	34
Left foot pitch (degrees)	52	55	60
Left foot roll (degrees)	8	12	17

The foot pitch and foot roll showed improvements at T1 and T2 compared to T0. Post-processing data were carried out through MATLAB (R2016a, The MathWorks, Inc, Natick, MA, USA), and the results are presented in Figure 10.1. and Figure 10.2.

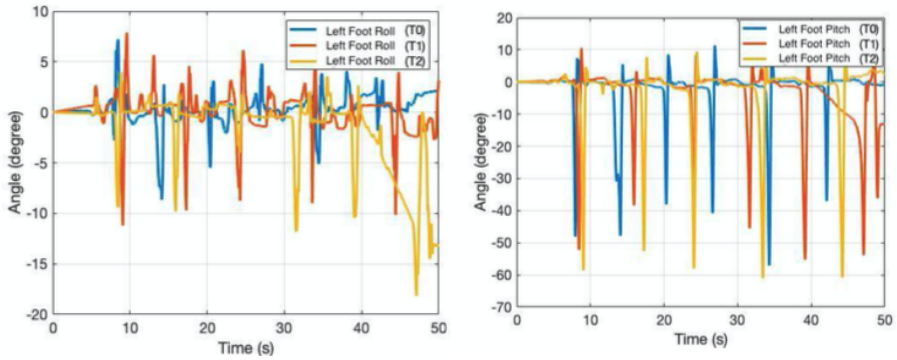

Figure 10.1. and **Figure 10.2**. Left foot roll and left foot pitch assessed through the gait analysis system (data processed in MATLAB) (41).

The stroke survivor achieved a good level of functional mobility, reduced spasticity grade and pain intensity, and improved balance and gait, thus proving the efficiency of implementing early phase neurorehabilitation strategy. These satisfying levels of the clinical outcomes and gait parameters maintained at discharge and at the 8 weeks follow-up, showing long-term effectiveness of early implementation of individualized rehabilitative program

through CPT and two rESWT sessions. There were not reported any adverse events during or afterwards the rESWT delivery, nor during the neurorehabilitation program.

10.4. Discussions

The MAS grade decreased, whereas the ankle PROM consequently increased. TAT and FAC significantly improved and these results correlated with the gait parameters resulted from the gait analysis provided by the Walker View system. Stance, swing phase, and the gait pattern showed to be ameliorated as showed by the quantitative gait analysis through Walker View system which provided the assessor with objective parameters to correlate with the clinical examination. Considering the prospect of early rehabilitation from the subacute phase of stroke, the strategy yielded good results in stroke patients. Spasticity grade, pain intensity, functional capacity, mobility, and gait were clinically assessed and correlated with data from a technological robotized assessment, thus leading to a tailored assessment and rehabilitation program, and progress tracking through objective data. Another important feature is the significant functional improvement since accessing posture and gait both clinically and through a gait analysis system offering real-time feedback. Even though the botulinum toxin type A (BoNT-A) injection is commonly used for limb spasticity, the rehabilitation program focused on promoting early recovery through non-invasive interventions.

10.5. Conclusions

The interventions proved long-term efficacy and a good safety profile. The patient presented a decreased degree of spasticity and pain intensity, whereas stance, balance and gait improved considerably at discharge and at 8 weeks follow-up. Through quantitative evaluation, the case underlined the long-lasting efficiency of early implementation of the classical CPT program and non-invasive intervention, rESWT. This type of quantitative, predictive analysis helps implement more adapted rehabilitative programs and interventions on a larger scale. However, these results have to be further confirmed through larger clinical trials and future research should focus on timely implementation of the rehabilitative, patient oriented neurorehabilitation techniques and tools for objective evaluation.

11.Conclusions and personal contributions

The Ph.D. thesis focused on presenting key features regarding a global assessment of the effects of radial extracorporeal shock wave therapy (rESWT) and conventional physical therapy (CPT) on stroke survivors presenting lower limb spasticity, highlighting areas that require special attention. Specifically, the absence of well-established protocols and guidelines for the management of lower limb spasticity regarding the number of ESWT delivery sessions, number of pulses, intensity, application area, safety profile, the need of ultrasonographic guidance or lack of it, objective outcome measures or electrophysiological parameters to be considered.

Nonetheless, given the complexity of mechanisms behind spasticity and gait pattern, therapies and medications that lack long-term effectiveness or present a multitude of adverse events, the management of this condition and its negative effects, remains a demanding task. Therefore, developing new, non-invasive therapies and applying the right protocols focused on the symptoms, causes, and functioning, becomes crucial. Early implementation of neurorehabilitation programs can help achieve the outcome measures not only in terms of decreasing limb spasticity and pain intensity, but also on improving the gait pattern, functional outcomes and social reinsertion of stroke survivors. Furthermore, the carried studies sought to highlight the usefulness of the rehabilitation interventions following lower limb spasticity of stroke origin and gait pattern disablement.

Based on extensive research and literature screening, there were also formulated some recommendations regarding the non-invasive spasticity management: implementing tailored conventional rehabilitation program and radial extracorporeal shock wave therapy for stroke survivors affected by lower limb spasticity in order to optimize outcome measures and increase quality of life (QoL); continuity of care and easy-access to rehabilitation services through tele-rehabilitation (TR) strategies.

11.1. General conclusions

Data analyzed through the systematic review and meta-analysis showed the following:

1. Extracorporeal shock wave therapy decreased lower limb spasticity grade and increased the range of motion in post-stroke patients whereas maintaining its effectiveness up to twelve weeks, proving long-lasting efficacy. It additionally reduced the pain intensity, maintained a good safety profile and did not present any significant short-term and long-term adverse events.

The systematic review conducted showed the following:

4. Non-inferiority for this non-invasive type of therapy compared to the gold standard for focal spasticity- botulinum toxin type A.

5. Extracorporeal shock wave therapy combined with botulinum toxin type A injection led to positive effects on decreasing spasticity, pain intensity and spasm frequency in stroke, multiple sclerosis, and cerebral palsy patients.

Data obtained by conducting a double-blind randomized controlled trial indicated the following:

8. Compared to the control group, the experimental group showed significantly decreased lower limb spasticity grade, pain intensity, and clonus score, improved trunk control, static and dynamic balance, and enhanced sensorimotor function.

12. The findings indicated there is a link between spasticity, trunk deficits, poor balance, and gait pattern and the way they influence each other.

The case of the stroke survivors who received early neurorehabilitation techniques/tele-rehabilitation and radial extracorporeal shock wave therapy highlighted the following:

13. Neurorehabilitation strategies implemented from the subacute phase of stroke improved the spasticity grade, pain intensity, stance, balance and gait, and yielded long-lasting efficacy whereas maintaining a good safety profile. Tele-rehabilitation and tele-assessment strategies indicated good results for maintaining and prolonging the beneficial effects.

Data obtained from the observational study indicated that following:

19. Two delivery sessions of rESWT integrated within the conventional rehabilitation program led to beneficial effects by decreasing the spasticity grade, pain intensity, and clonus score, improved balance, gait pattern, and sensorimotor and functional outcome in stroke survivors affected by lower limb spasticity.

20. The main feature of the study is the integration a gait analysis system in clinical practice and correlating the findings with the clinical assessment.

11.2. Personal contributions

The personal contributions consist of:

1. Give an insight into the best practices and therapies for stroke survivors by taking into account not only the usage of non-invasive therapeutic interventions, but also the long-lasting beneficial effects (Chapter II.7, Chapter II.8).
2. The way of assessing these beneficial effects may help changing the paradigm by integrating a quantitative analysis of the gait pattern in the clinical practice as a major component of the clinical evaluation (Chapter II.5, Chapter II.6).
3. Synthesizing the need for the best practices in rehabilitation, continuum of care and easy access to rehabilitative techniques through tele-rehabilitation and tele-assessment, along with quantitative analysis (Chapter II.5, Chapter II.6, Chapter II.9).
4. Highlighting novel non-invasive therapeutic interventions for the management of lower limb spasticity, innovative training and assessment tools through a multidimensional approach and strategy: namely radial extracorporeal shock wave therapy delivery, real-time visual feedback balance training, tele-assessment and tele-rehabilitation, individualized rehabilitation program from the subacute stage of stroke, and the perspective of global evaluation and easy track of progress landmarks (Chapter II.7, Chapter II.9, Chapter II.10.).
5. A **software interface** started to be developed in collaboration with a team from Automatic Control and Industrial Informatics Department, Faculty of Automatic Control and Computers, National University of Science and Technology Politehnica of Bucharest (Chapter II.9, page 107 lower paragraph, page 108 upper paragraph). The software platform retrieves and displays the graphical data in accordance to the patient's movements and range of motion, transferring data in real-time to the evaluating physician or assessor, thus helping implementing and conducting tele-rehabilitation and tele-assessment strategies. Additionally, for more advanced stages, the platform could be developed to target other conditions.
6. A **software application** started to be developed. The software application is designed to easily detect any movement correctly so that the patient can receive personalized haptic and visual guidance whenever uses the application to perform the prescribed set of physical exercises through the tele-rehabilitation program. The software application can be used in translating the satisfying results from implementing tele-rehabilitation and tele-assessment approaches at patient discharge, as part of the **home-based rehabilitation program**. Tele-rehabilitation and tele-evaluation are research directions of great interest, notably to maintain a

good physical status for patients after discharge, increase their interest and satisfaction, lower the readmission rate by having easy access to rehabilitation services with quick feedback, and ease the social and economic burden.

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Scientific publications list

Articles published in Journals with high Impact Factor (I.F), ISI, PubMed, PubMedCentral, Scope indexed.

[1] Mihai EE, Mihai IV, Berteanu M. Effectiveness of Radial Extracorporeal Shock Wave Therapy and Visual Feedback Balance Training on Lower Limb Post-Stroke Spasticity, Trunk Performance, and Balance: A Randomized Controlled Trial. *Journal of Clinical Medicine*, 11(1), 147, 2021, IF 3.9, http://dx.doi.org/10.3390/jcm11010147 (Chapter II.5, pages 31-51)

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[8] Moita Gonçalves E, Costa J, **Mihai EE**, Gonzales L, Andrade I, Verraest X, Pereira P, Pítrez J, Filipe J, Berteanu M, Juan Garcia FJ, Rodrigues M**.** Spasticity in Practice: From Pathophysiology to Rehabilitation *(under review)*

E-Posters

[9] Mihai EE, Gheorghe L, Berteanu M. Effects Of The Conventional Rehabilitation Program And Extracorporeal Shock Wave Therapy In Patients With Post-Stroke Spasticity. *The 44th Annual National Congress of Physical Medicine and Rehabilitation, online 2021 (e-poster)*

[10] Mihai EE, Popescu MN, Berteanu M**.** Innovative Treatment And Evaluation Through An Individualized Program In Post-Stroke Spasticity Patient. *The 44th Annual National Congress of Physical Medicine and Rehabilitation, online 2021 (e-poster)*

[11] Mihai EE, Popescu MN, Berteanu M. Synergic Use Of Botulinum Toxin Injection And Radial Extracorporeal Shock Wave Therapy. Effects On Spasticity And Gait Pattern In Stroke Patients. *The World Stroke Congress, Toronto, Canada, 2023 (e-poster)*

[12] Mihai EE, Berteanu M. Efficacy of Extracorporeal Shock Wave Therapy and Assessment Strategy Through a Novel Gait Analysis System for Post-stroke Spasticity. *The 10th edition of the Congress of the Carol Davila University of Medicine and Pharmacy, hybrid, Bucharest, Romania 2022 (e-poster)*

[13] Mihai EE, Berteanu M. The Efficiency of Radial Extracorporeal Shock Wave Therapy Delivery on Spasticity Post-stroke and Evaluation Strategy Through a Gait Analysis System. *The 45th Annual National Congress of Physical Medicine and Rehabilitation, Bucharest, Romania 2022 (e-poster)*

Oral presentations

[14] Mihai EE, Berteanu M. Effects Of Extracorporeal Shock Wave Therapy On Post-Stroke Spasticity And Assessment Strategy Through A Gait Analysis System. *The 15th Mediterranean Congress of Physical and Rehabilitation Medicine, Rome, Italy* 2023

[15] Mihai EE, Gheorghe L, Mîniceanu A, Anghel AM, Berteanu M. Prolonging the Effects of Conventional Rehabilitation and Radial Extracorporeal Shock Wave Delivery through Tele-rehabilitation Strategies For Stroke Survivors. *The 24th European Congress of Physical and Rehabilitation Medicine – ESPRM, Ljubljana, Slovenia, 2024*

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