Measuring the Effectiveness of High-Intensity Virtual Training Programs in Stroke Survivors

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Abstract: The objective of this paper is to determine and compare the effects of two high-intensity virtual training programs, with different frequencies and standard care after stroke. First-time ischaemic stroke patients in subacute stage were randomized into three groups: 1 session/day high-intensity virtual training (VT1; n=20), 2 sessions/day high-intensity virtual training (VT2, n=20), standard care (CON, n=20). Each group performed a 5-week-long training program (1 hour/session, 5 days/week). Results were measured before and after the interventions. Our primary outcome was the modified Rankin Scale (mRS), which indicates the degree of independence in daily activities and the severity of disability at stroke survivors. Secondary outcomes were the Barthel Index (BI), the EuroQoL Visual Analogue Scale (EQ VAS), the Berg Balance Scale (BBS), the 6-minute walking test (6mWT), the Beck Depression Inventory (BDI), and posturograpic examination in four different positions (WEO, WEC, NEO, NEC). VT2 and VT1 groups improved significantly all of the results (all p<0,05). The result of the mRS, BI, BBS, 6mWT, BDI improved significantly (all p <0.05) in CON group, but there was no clinically meaningful changes in EQ VAS, WEO, WEC, NEO, and NEC (all p>0.05).Comparing the groups' measured 10 results: VT2 in 9 cases (mRS, BI, EQ VAS, BBS, 6mWT, BDI, WEC, NEO, NEC), VT1 in 5 cases (mRS, 6mWT, BDI, WEC, NEC) showed greater extent improvement than CON group, furthermore the improvements of mRS and BI were significantly higher at VT2, than at VT1 (all p<0.05). Our results show that the high-intensity virtual training programs could be good opportunities for subacute ischaemic stroke patients to improve their clinical symptoms, mobility, and quality of life. Furthermore, increasing daily frequency of the training, could also increase the beneficial effects.

This research is particularly important because the utilized therapies have the potential to yield significant economic benefits, by reducing long-term healthcare costs and improving overall patient outcomes.

Keywords: stroke; ischaemic; subacute; virtual; exercise; training; intensity

1 Introduction

Despite significant advances in primary prevention and acute treatment in recent decades, stroke and the residual symptoms resulting from the disease still affect a large number of people worldwide. Approximately 1.8 million Europeans suffered stroke in 2019, which represents a 2% increase compared to data from 2010 and approximately 70% of the cases are of ischemic origin. At 2019 the incidence of stroke was 118.7 per 100000 people in Europe, which represents a 10% decrease compared to 2010 for the whole of Europe. During this period of time, all European countries showed stability or reduction of incidence rates. However, there were large discrepancies, with several countries having incidence rates >230 per100000. The number of first strokes has increased across Europe, with the largest increases observed in Western Europe and the European Union member states. These results may be explained by the long life expectancy in these countries and the increasing incidence of age-related diseases. In 2019, the incidence of stroke in Hungary affected 146.3 out of 100000 people, which is approximately twice the data measured in Western European countries (69.8 per 100000 people). (1) In addition to the life-threatening prognosis, among people who have suffered a stroke, the need for re-hospitalization related to the disease increases (33%) and the possibility of a repeat stroke (7-13%), as well as many other residual symptoms that adversely affect health-related quality of life (2). Decision-makers have also recognized the importance of prevention in developing countries, but most of these efforts have limited effectiveness. So, the best option for people who have had a stroke is to reduce their symptoms and the chance of another stroke. The recommendations suggest moderate-intensity exercises in the exercise-based rehabilitation of patients who have suffered a subacute stroke [3-4]. However, recent trends emphasize the intensity of exercises during rehabilitation in many disease groups, such as Parkinson's disease (PD) [5-6], Multiple Sclerosis (MS) [7], spinal cord injury [8], stroke [9-11], and ischemic heart attack [12]. We can speak of high training intensity if the heart rate (HR) is greater than 60% of the maximum heart rate calculated based on the age or the rate of exertion perceived by the patient (RPE) that is between 14-17. Another indicator of high training intensity is the frequency, which in the case of high intensity can mean every consecutive day or even several times within a day [13]. We previously tested this last assumption in our previous research, which allowed us to conclude that by increasing the frequency of high-intensity exercise programs, the rehabilitation effects can be further increased among people who have suffered a stroke. However, this study was conducted in a pseudo-randomized form, which could have affected the results of the control group receiving conventional therapy [11]. There is also no agreement as to whether exercises specific to mobility limitations should be used and to what extent the technology can be incorporated during the rehabilitation of subacute stroke [3] [14-20]. Exercising in a technology-supported virtual game environment appears to accelerate the relearning of steps and balance during rehabilitation [18-21] and this effect persists for months at PD patients [24]. According to recommendations, high-intensity exercises may be suitable for lowering the resting blood pressure of patients with high blood pressure, thereby even reducing the likelihood of another ischemic event [25]. Given the high incidence of stroke and the residual symptoms that greatly affect the quality of life and mobility, it is essential to review and compare traditional therapies with new trends for more effective rehabilitation. The results of our research can be decisive in the interpretation of clinical symptoms, quality of life, and mobility in broadening the influencing factors. We expect that our research will emphasize the importance of choosing the right intensity during the rehabilitation of stroke patients and will also demonstrate the applicability of virtual environment as a therapeutic tool in a clinical setting. In addition, we can map the positive and negative effects caused by high-intensity virtual training among stroke patients. Through all of this, we can influence the outcome of rehabilitation in a positive direction, and if the intervention therapy proves to be effective, the burden of the disease on society and the health care system can also be reduced.

2 Methods

The purpose of this research is to determine and compare the effects of twice a day high-intensity virtual training program (VT2), once a day high-intensity virtual training program (VT1), and a control group receiving standard care (CON) in terms of clinical symptoms, mobility, and quality of life among people with subacute ischemic stroke.

2.1 Design of the Research and Sampling Method

Our present research is a quantitative, randomized, blind, pre-post, prospective clinical research. The data were collected in the Neurorehabilitation Unit of the Neurology Department of the Kaposi Mór Teaching Hospital in Somogy County. The study was conducted among patients who had undergone ischemic stroke and were in the subacute stage. Participants were selected from the hospital database and then screened for inclusion. Patients admitted to the emergency department with suspected stroke underwent a neurological examination, which included measurement of the NIHSS. The examination helped determine the degree of damage in terms of mobility and sensory functions. We identified a total of 121 persons who had undergone an ischemic stroke and were in the subacute stage, of whom 19 were excluded (did not meet the inclusion criteria: n=8, refused the participation n=11). Thus, a total of 102 patients were examined. After the examination, another 42 people were excluded (did not meet the inclusion criteria: n=22, refused to participate n=20). The total examined sample size remained 60 persons.

The inclusion criteria for participation in the study were as follows: having undergone a first ischemic stroke, which was diagnosed by a neurologist based on a CT or MR image; time elapsed since the stroke between 2-4 weeks; the neurological examination revealed mobility and postural limitations; mRS score was 2 or higher. The exclusion criteria are: multiple strokes in the medical history; systolic blood pressure less than 120 or greater than 160 mmHg; orthostatic hypotension; carotid artery stenosis; serious heart disease; hemophilia; traumatic brain injury; condition with seizures; untreated diabetes; abnormal electroencephalography; Mini Mental Test score < 22; abnormal blood panel; use of sedatives; irregular medication intake; severe aphasia (Western Aphasia Battery ≤ 25); severe vision or hearing loss; severe sensory dysfunction; serious orthopedic problem; other neurological condition affecting motor functions; alcoholism; drug use; smoking after stroke diagnosis; unable to walk at least 100 m with or without an aid in 6 minutes; unable to understand verbal instructions or signals on the television screen; current participation in an individual or group exercise program outside of standard physiotherapy.

The selected participants (n=60) were randomly divided in a 1:1:1 ratio into VT2 (n=20) performing two high-intensity training sessions per day, VT1 (n=20) performing one high-intensity training session per day, or the state-funded traditional receiving care into the CON (n=20) group. Randomization was performed by a person not involved in the study. Before the start of the study, all patients participated in standard physiotherapy care financed by the social insurance. The VT1 and VT2 groups suspended this care and participated only in the intervention exercise program, the CON group continued standard care. The participants agreed to participate in the research in the form of a written consent and the Institutional Research Ethics Committee approved the study protocol (permit number: IG/03133-000/2021).

Before the exercise program, the patients' cognitive functions were assessed using the Mini Mental Test (MMSE), which is suitable for identifying and determining the severity of dementia and cognitive functions' decline. The test scores based on 10 different tasks (orientation, comment, attention and calculation, recall, naming, repetition, execution of instructions, reading, writing, copying). A total of 30 points can be achieved, on the basis of which we can conclude the decline of cognitive functions: 24-30 points – Normal function; 15-23 points – Mild dementia; 10-14 points – Moderate dementia; <10 points – Severe dementia [26].

In the VT2 and VT1 groups, we used RPE to set the intensity, which was also checked based on the heart rate with the help of Polar watches. After each training session, the participants had to indicate the degree of exertion they perceived on a 20-point Borg scale. Based on this, five intensity levels can be distinguished: Very low – RPE <9; Low – RPE 9-11; Medium – RPE 12-13; High – RPE 14-17; Near maximal/maximal – RPE ≥18 [13]. The value of the RPE was also recorded for the CON group for observation purposes, but the value recorded here never affected the intensity of the traditional therapy.

2.2 Results

Primary and secondary outcomes were measured before and after the intervention. The measurements were taken by the same person each time and the grouping of the participants remained hidden. The testing method was standardized for all participants at each measurement session. Pre and post tests were conducted within 1 week of the intervention.

2.2.1 Primary Results

The primary outcome measure used was mRS, which indicates the degree of independence in daily activities and the severity of disability. The mRS is a reliable and validated measure that is sensitive to changes over time. The method for assessing mRs is a guided interview. The assessment involves asking the patient about his/her activities of daily life, including outdoor activities. The assessment should take into account any neurological deficits (e.g., aphasia, intellectual deficits) detected during the assessment. Finally, aspects of the patient's physical, mental performance and speech should be combined when selecting the mRS score. A change of 1 unit in the mRS is considered a clinically significant change [27-29].

2.2.2 Secondary Results

The secondary results were used to detect changes at different areas of life.

To measure functional abilities, we used BI, which sensitively measures the degree of independence and the changes that occur in it during various daily activities in case of chronic, disabling diseases, especially in a rehabilitation environment. The scoring method takes into account whether the assessed person receives help during each task. The scores of the individual items are added up and the resulting total score is the result of the BI on a scale of 0-100, the higher the score, the greater the independence is [30].

The health-related quality of life was measured using the EQ VAS. A standard vertical 20 cm visual analogue scale, used in recording an individual’s rating of their overall current health-related quality of life. The scale ranges from 0 to 100, where 0 means the worst and 100 means the best state of health [31-33].

BBS was used to measure static and dynamic balances. The BBS can objectively measure the tested person's ability to balance safely during a series of predetermined tasks. It is a 14-item task series, each point of which is evaluated on a five-point scale from 0 to 4, where 0 indicates the lowest and 4 the highest level of function. The maximum score is 56, which indicates perfect functional balancing ability. A result below 45 points already means an increased risk of falling, and the lower the result, the higher the risk of falling is [34] [35].

6mWT was used to measure endurance and walking speed. During the test, the tested person walks back and forth along a pre-marked, flat, straight track 50 meters long. He/she starts the walk at the examiner's instruction, when the timer is started, the pace of the walk is determined by the examined person, the examiner does not intervene. If the examined person needs a rest during walking, he/she can stop, but the measurement of the elapsed time will not be stopped. The examined person continues to walk for 6 minutes and only stops for the examiner's instruction when the 6 minutes have elapsed. The result obtained is the distance travelled within 6 minutes, in meters. If the tested person must stop and sit down within 6 minutes, the test result, is the distance travelled up to that point [36-39].

During the postural examination, the presence and degree of postural instability was monitored using a force platform (Posture Evaluation Platform, MED-EVAL Kft). During the test, the tested person had to stand for 20 seconds in 4 different body positions with increasing difficulty: 1 – wide stance, eyes open (WEO); 2 – wide stance, eyes closed (WEC); 3 – narrow stance, eyes open (NEO); 4 – narrow stance eyes closed (NEC). The result is given by the 3-dimensional path of the center of pressure (COP) of the body, expressed in millimeters, the smaller it is, the smaller the postural instability will be [40].

The degree of depression was assessed using the BDI, which is suitable for judging the severity of depression. The questionnaire approaches specific symptoms or behavioral manifestations of depression from 13 different categories. Each category has 4 different statements, numbered as 0-3. The result is given by the sum of the number of marked statements (<7 normal mood state; 7-12 mild depression; 12-17: moderate depression; >17 severe depression) [41].

2.3 Interventions

The VT1 group participated in the sessions once a day and the VT2 group twice a day for 5 consecutive days one of a week for 5 weeks (VT1: 25 sessions in total; VT2: 50 sessions in total). In the case of the VT2 group, 5 hours elapsed between the 2 sessions within one day. Each session lasted for 60 minutes, which included a 5-minute warm-up, a 25-minute virtual training block, a 25-minute agility training, and a 5-minute cool-down. Each time, the intensity of the tasks was set between 14-17 out of 20 based on the RPE. The VT1 and VT2 groups received the same treatment in all respects, except that the VT2 group participated in the session twice a day.

During warm-up, we prepared the body for intensive exercises. For the virtual training, we used Microsoft Xbox 360 and Xbox Kinect virtual reality. With the help of the Kinect camera sensor system, it provides the participant with free spatial movement. The camera detects the shape and movement of the patient and the software records and places it in the virtual space or determines the accuracy of imitating the movements. During the intervention, we used three different VR programs: Kinect Adventure - Reflex Ridge, Kinect Adventure - Space Pop, Just Dance. During Reflex Ridge, the participant's virtual avatar stands on a platform running on rails, which, after starting, continuously moves forward, while obstacles appear from different directions. Visual stimuli provoke reflexive and voluntary avoidance movements, such as shifting body weight, stepping to the side, squatting, jumping up. The system assigns scores based on the obstacles avoided, so the patient's performance can be easily monitored, and the appropriate load can be set. Space Pop can be understood as a kind of complex target exercise which requires flawless execution of complex movements. The participant moves their avatar in different directions with forward-backward, and lateral movements, as well as up and down with specific arm movements, while touching different targets in all dimensions of the virtual space. The more targets touched, the more points scored at the end of the task. During the task, the participant performs complex spatial movement, which is based on quick reactions and direction changes with targeted movements. In the case of Just Dance, the task of the participant is to imitate as accurately as possible the constantly changing, complex rhythmic movements appearing on the screen. The task requires a quick motor response to emerging visual and acoustic stimuli and execution with appropriate accuracy.

During the agility training, the participants performed gait development exercises, coordination training, balance development exercises, posture correction exercises, and muscle strengthening with the help of different equipment (Dynair pillow, Bosu, fitball, pilates ball, weight ball, end-weighted stick, TRX, coordination ladder, barriers) and without equipment. This block included different surface changes and direction changes during the tasks and the manipulation of the speed of the tasks, as well as the application of height stimuli. The difficulty of the tasks was adjusted each time according to the improving performance of the participants. The training provides a strong neuromuscular stimulus thanks to the constantly changing sensory environment, such as tasks performed on soft/hard surfaces, heavy/light weight tools, slow/fast movement execution, reflex response to external stimuli/conscious response during the task. During cool-down, the participants performed light walking exercises, breathing and stretching exercises.

The CON group received standard care financed by the social security, which included a 30-minute-long group exercise program in a seated position, which aimed at the movements and strengthening of the upper limb and trunk. Furthermore, they participated in a 30-minute-long individual physical therapy session, during which they performed walking and balance exercises. In doing so, the focus was on improving the function of the lower limbs.

2.4 Statistical Analysis

Data were expressed as mean (±SD), for normally distributed data and median (+IQR) for non-normally distributed data. The normal distribution of the variables was checked using the Kolmogorov-Smirnov and Shapiro-Wilk tests. We compared the VT2, VT1, and CON groups at baseline using the one-way parametric or Kruskal Wallis analysis of variance. The degree of changes within a group was checked with a paired T-test or Wilcoxon test according to the results of the normality test. The results of the groups (VT2, VT1, CON) were interpreted according to the differences between the post-intervention and initial scores. The results showed significant differences among the groups using the one-way parametric or Kruskal Wallis analysis of variance. Tukey's post hoc test was used to identify values less than $p<0.05$ among the groups. Cohen's d was used to examine the effect size within groups (very small, 0.01; small, 0.20; medium, 0.50; large, 0.80; very large, 1.20; huge, 2.00) to determine the size of the effects over time. The data were processed using Microsoft-Excel 2010 and IBM-SPSS Statistics 26 software.

3 Results

3.1 Characteristics of the Participants

A total of 60 people were selected for our study based on the criteria and randomly allocated in a 1:1:1 ratio to VT2 (female, n=11; male, n=9), VT1 (female, n=11; male, n=9), and CON (female, n=8; male, n=12) groups. The time elapsed since the stroke was 3.1 (±0.69) weeks in the VT2 group, 2.9 (±0.75) weeks in the VT1 group, and 3.1 (±0.69) weeks in the CON group. The MMSE score for cognitive function was 27.15 (±0.99) for the VT2 group, 26.6 (±1.27) for the VT1 group, and 26.6 (±1.35) for the CON group. The physical characteristics of the participants (age, height, weight, body mass index) are summarized in Table 1, sorted by group. When examining the data, no significant differences were found among the three groups in terms of time elapsed since the stroke, MMSE score, age, height, weight, and body mass index (all $p>0.05$).

Table 1

Physical characteristics of the participants as mean (±SD) for normally (normal font) and median (+IQR) for non-normally (*italic font*) distributed data

Variable	VT2 (n=20)		VT1 (n=20)		CON (n=20)		p value
	Mean/ Median	±SD/ IQR	Mean/ Median	±SD/ IQR	Mean/ Median	±SD/ IQR	
Age (y)	65.2	5.17	65.7	6.02	65.6	6.62	0.953

Height (cm)	172.0	10.00	173.5	7.25	174.0	3.25	0.642
Weight (kg)	73.8	7.62	73.3	7.77	69.7	12.19	0.332
BMI (kg*m^2)	24.7	3.06	24.4	2.28	22.7	3.16	0.065

RPE values were collected during the 25 days of the interventions. The mean RPE score was 15.3 (±0.29) in the VT2 group and 15.0 (±0.38) in the VT1 group. There was no statistically significant difference in RPE between the two groups ($p>0.05$), but it was significantly higher in both groups than the CON group value of 9.5 (±0.41) ($p<0.05$). No significant difference was found in the initial results for any of the groups (all $p>0.5$).

Table 2
Initial results of the groups as mean (±SD) for normally (normal font) and median (+IQR) for non-normally (*italic font*) distributed data

Variable	**VT2**		**VT1**		**CON**		**p value**
	Mean/ Median	**±SD/ IQR**	**Mean/ Median**	**±SD/ IQR**	**Mean/ Median**	**±SD/ IQR**	
mRS (point)	4.0	1.00	3.0	1.00	4.0	1.00	0.230
BI (point)	60.0	1.25	60.0	10.00	60.0	10.00	0.725
EQ VAS (mm) (mm)	60.0	10.00	70.0	16.25	60.0	10.00	0.733
BBS (point)	21.5	4.44	22.1	3.39	21.3	4.36	0.734
6MWT (m)	180.0	25.00	175.0	78.00	180.0	50.00	0.936
BDI (point)	12.6	3.30	13.0	3.16	12.5	2.14	0.829
WEO (mm)	8.0	7.38	7.9	7.29	9.1	6.37	0.830
WEC (mm)	12.8	3.19	13.6	7.90	14.6	8.31	0.919
NEO (mm)	13.7	10.82	13.0	8.06	12.7	10.06	0.975
NEC (mm)	14.8	8.76	18.47	6.15	14.7	9.10	0.440

3.2 Effects of Interventions

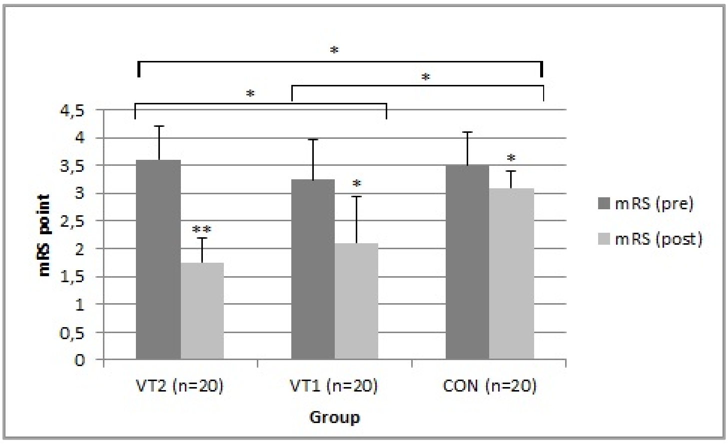

Figure 1
Comparison of mRS scores at the start and end of the exercise programs
(*: significant; **: highly significant changes)

Significant improvements in mRS were observed in all three groups. The mRS score showed a change of -1.9 (±0.67) points ($p<0.001$) in the VT2 group compared to the initial measurements. The VT1 group showed a change of -1.2 (±1.3) points ($p=0.002$). The CON group showed a significant change of -0.4 (±0.68) points ($p<0.05$). A significant difference was found among the changes in mRS scores of the groups ($H=20.26$; $p<0.001$; VT2: $d=2.76$; VT1: $d=0.91$; CON: $d=0.59$). Further examining the data using multiple comparisons, we determined which groups were significantly different. The magnitude of change observed in the VT2 group significantly exceeded the change observed in the VT1 group ($p<0.05$) and the changes observed in the VT2 and VT1 groups significantly exceeded the change observed in the CON group (all $p<0.05$).

The interventions resulted a significant improvement in the BI score of 25.8 (±7.30) points in the VT2 group ($p<0.001$) and 14.8 (±10.70) points in the VT1 group ($p<0.001$). For the CON group, a significant improvement of 10.3 (±5.50) points was detected ($p<0.001$). A significant difference among the groups was confirmed for BI ($H=27.71$; $p<0.001$; VT2: $d=-3.53$; VT1: $d=-1.38$; CON: $d=-1.87$). Multiple comparisons of the differences among the groups showed that although the magnitude of improvement in the VT1 group was greater than the change in the CON group, this difference was not significant ($p>0.05$). However, the improvement in the VT2 group was significantly greater than the change observed in the VT1 and CON groups (all $p<0.001$).

The results of the EQ VAS indicated that the VT2 group showed an improvement of 11.0 (±10.21) millimeters on the scale ($p=0.002$) while the VT1 group showed an improvement of 6.8 (±10.92) millimeters, which is significant ($p<0.05$).

The CON group showed a change of 0.8 (±5.20) millimeters, which is not significant (p>0.05). When comparing the groups with each other, a significant difference was detected among the groups (H=9.84; p<0.05; VT2: d=-1.08; VT1: d=-0.62; CON: d=-0.14), therefore, multiple comparisons were used to determine which groups showed significant differences in the results. The rate of change in the VT2 group showed no significant difference compared to the VT1 group (p>0.05), and the change in the VT1 group was not clinically significantly greater than the change in the CON group (p>0.05). When examining the results of the VT2 and CON groups, we found a significant difference in the rate of change between the two groups (p=0.002).

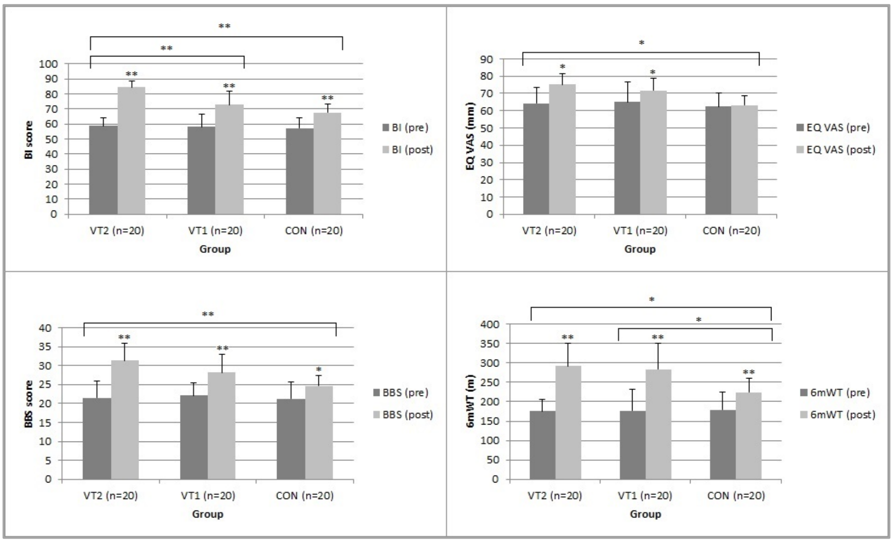

Figure 2
Comparison of BI, EQ VAS, BBS scores, and 6mWT at the start and end of the exercise programs
(*: significant; **: highly significant changes)

The BBS score in the VT2 group showed a significant improvement of 9.8 (±6.01) points after the intervention (p<0.001), compared to 6.1 (±5.78) points in the VT1 group, which also showed significant value (p<0.001). The change of 3.4 (±3.76) points in the CON group was also significant (p<0.05). Positive changes in BBS showed a difference among the groups (H=10.71; p=0.005; VT2: d=-1.63; VT1: d=-1.06; CON: d=-0.90). The results of multiple comparisons showed that there was no statistically significant difference in scores between the VT2 and VT1 groups and between the VT1 and CON groups (all p>0.05). However, a significant difference in the change in BBS score was found between the VT2 and CON groups (p=0.001).

Looking at the results of the 6mWT, we see that, members of the VT2 group walked an average distance of 116.4 (±65.95) meters more than the initial measurements (p<0.001). For the VT1 group, participants improved by 106.1 (±86.52) meters compared to their previous results (p<0.001). For the CON group, the value of this change was 45.05 (±42.31) meters, also a significant improvement (p<0.001). Changes detected in the 6mWT showed a significant difference (F=6.54; p<0.003; VT2: d=-1.76; VT1: d=-1.23; CON: d=-1.06) among the groups. The results of multiple comparisons showed that there was no significant difference between the changes measured in the VT2 and VT1 groups (p>0.05), but both groups (VT2, VT1) showed significantly greater improvement in 6mWT scores compared to the CON group (all p<0.05).

Table 3
Changes in posturographic test scores in four different body positions, expressed as the difference between post-intervention and initial scores

Variable	**VT2 (n=20)**		**VT1 (n=20)**		**CON (n=20)**		**All (n=60)**	
	Mean	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**
WEO (mm)	-4.2	5.63	-3.5	4.58	-1.0	5.04	-2.9	5.20
WEC (mm)	-8.7	3.60	-6.8	4.91	-1.6	6.03	-5.7	5.71
NEO (mm)	-7.9	7.26	-7.1	6.80	-1.8	7.68	-5.6	7.63
NEC (mm)	-9.9	7.96	-9.8	5.70	-0.1	7.48	-6.6	8.40

The VT2 and VT1 groups showed significant reductions in COP pathway in all four test positions (all p<0.05). In contrast, at the CON group, none of the four test positions showed significant improvements in any of the results by the end of the exercise program (all p>0.05). When examining the differences among the groups in terms of posturographic test scores, no significant difference was found among the changes in WEO (F=2.15; p>0.05; VT2: d=0.75; VT1: d=0.76; CON: d=0.20) among the three groups. In case of WEC (H=14.12; p<0.001; VT2: d=2.41; VT1: d=1.38; CON: d=0.27), NEO (F=4.17; p<0.05; VT2: d=1.09; VT1: d=1.05; CON: d=0.24) and NEC (F=12.65; p<0.001; VT2: d=1.24; VT1: d=1.73; CON: d=0.01), we detected significant differences among the three groups. Examining the data further, it can be seen that the changes in WEC and NEC were greater in the VT2 and VT1 groups than in the CON group (all p<0.05), but no difference was observed in the VT2 and VT1 groups (p>0.05). The change in NEO did not show any difference between the VT2 and VT1 groups and the VT1 and CON groups (all p>0.05), but a significant difference was observed in the changes in the VT2 and CON groups (p<0.05). The results also showed that the VT2 group achieved an average improvement of 62.9% in the four postures, the VT1 group 53.9% and the CON group 9.0% in the COP pathway by the end of the exercise program, with no significant difference between the VT2 and VT1 groups in the four postures (p>0.05), but significantly greater improvement in both groups than at the CON group (p<0.001).

The change in the BDI score for the VT2 group was -2.9 (±1.98) points ($p<0.001$). The change at the VT1 group was -3.2 (±2.28) points, which was also significant ($p<0.001$), as was the change at the CON group of -1.4 (±2.19) points ($p<0.05$). Statistically significant differences among the groups were detected by the statistical analysis ($H=6.67$; $p<0.05$; VT2: $d=1.44$; VT1: $d=1.40$; CON: $d=0.64$). Using multiple comparisons, the results showed that there was no significant difference between the results of the VT2 and VT1 groups ($p>0.05$) and that the improvement in both groups significantly exceeded the change in the CON group (all $p<0.05$).

4 Discussion

In the present study, we determined and compared the effects of once a daily high-intensity virtual training program (VT1), twice a daily high-intensity virtual training program (VT2), and conventional care (CON) on clinical symptoms, mobility, quality of life at people with subacute ischaemic stroke. As the date of stroke was approximately three weeks before the interventions, the stroke survivors had a pronounced difficulty in walking, but they successfully completed all occasions, and no adverse events occurred during the measurements and interventions. The preponderance of the evidence supported our hypotheses, suggesting that all three therapies are effective in treating patients with subacute ischaemic stroke. Twice a daily virtual training achieved better results compared to once a daily training and lower intensity conventional care, and both high intensity training had better effects on clinical and motor symptoms than conventional therapy. We included stroke survivors in the sub-acute stage (2-4 weeks since stroke) instead of people with a chronic stroke, who showed greater developmental potential with movement therapy. The 3.5-point mRS at baseline and the 58-point BI indicated that participants had a moderate degree of disability affecting their activities of daily life. However, their gait difficulty was severe, as the distance of 177 m measured at baseline during 6mWT was shorter than that of age-matched PD (232 m), SM (240 m), older adults with mobility difficulties (334 m) and healthy older adults (529 m) [14, 15, 39]. Despite the subacute status and severity of disability, intensive and frequent exercise proved to be an effective therapeutic option for patients.

Improvements in mRS of -1.9 points (VT2) and -1.2 points (VT1) exceeded the 1 unit change required for a clinically significant change. As expected, these changes in mRS scores showed a significant difference between the two and one training sessions per day groups and in both cases exceeded the results obtained with low-intensity conventional therapy. Few studies have examined the effect of high-intensity exercise on mRS at people with subacute ischaemic stroke. In our previous study, similar results were obtained with patients participated in high-intensity exercise programs (-1.8 and -1.4 points change), but in this case no significant difference was found between the different frequency groups [11]. Looking at the results of other studies, the improvements we observed were much greater. For example, in one study, exergaming combined with conventional therapy was compared with a group receiving conventional therapy alone improved mRS by 0.58 and 0.23 points, respectively, at people with subacute stroke [43]. High-intensity exercise 24 hours after the stroke (n=86) improved mRS scores for three months follow-up to a greater extent than either conventional care (n=80) or very early mobilization within 24 hours of stroke (n=82) [44]. These data suggest that high-intensity exercise, particularly when supplemented with exergaming elements, is effective in increasing the degree of independence during activities of daily life among people with subacute ischaemic stroke, but that these improvements may be particularly significant when the frequency of interventions is increased and participants receive therapy twice a day.

The vast majority of secondary outcomes showed clinically significant changes in the hierarchical ordering we expected among the groups as a function of intervention intensity and frequency. BI was used to measure the degree of independence of participants in activities of daily life, which showed an improvement of approximately 4.5 points for those receiving high-intensity training once daily compared to those receiving conventional care, but this difference was not significant. The really significant change was seen at those who completed two high intensity sessions a day, they achieved 15.5 points greater change compared to the control group and 11 points greater change compared to those who completed one session a day. These results strongly suggest increasing the frequency and intensity of exercises over lower intensity conventional physiotherapy. Previous research has shown that high-intensity exercise programs can improve clinical and musculoskeletal symptoms and endurance at stroke survivors, but no evidence has been found that high-intensity exercise programs are more effective than lower-intensity programs in improving quality of life [11] [45]. The results of the EQ VAS showed that only patients who participated in high-intensity exercise programs achieved significant improvements. Providing evidence that high exercise intensity may lead to greater improvements in quality of life among subacute stroke survivors. Changes measured by the BBS used to test static and dynamic equilibrium also showed the pattern we expected among the groups. The rate of improvement for the conventional care group was 3.4 points. With an increase in intensity at the same frequency, the VT1 group achieved more than one and a half times of this value (6.1 points), and with increase in frequency and intensity, the VT2 group showed an improvement rate almost three times that of the control group (9.8 points). However, the difference between the results of the VT1 and CON groups was not significant, as in a previous study comparing high and moderate intensity trainings [46]. However, increasing the frequency of high-intensity training resulted in significantly better results for BBS compared to conventional therapy, suggesting that increasing the frequency may be more effective in improving the static and dynamic balances of the affected patients, especially when combined with virtual training elements [23, 47, 48]. The changes measured at the results for stamina and walking speed (6mWT) are particularly impressive, as the twice a day high-intensity group was able to walk 116.4 m more distance within 6 minutes at the end of the intervention than at the beginning. This is more than 10 m longer than the improvement measured in the once a day high-intensity group (106.1 m) and more than two and a half times of the 45.1 m change measured at the lower frequency and intensity control group. These changes are significantly greater than the maximum change of 37 m described in a systematic review of four studies also investigating high intensity training at one session per day (38) or the 64 m change observed in a study investigating high-intensity training 3 times per week for 3 months [36]. These data suggest that high frequency and high intensity training alone can achieve good results in improving gait speed and endurance, but adding virtual training elements can further increase the effectiveness. The results measured in the posturographic examination show that increasing the frequency and intensity is more effective in treating postural instability. In the four body positions studied, on average, those receiving conventional care shortened the COP pathway by 1.1 mm. In contrast, participants in the high-intensity group who completed one session per day shortened the COP pathway by 6.8 mm and participants who completed two sessions of intensive training per day shortened the COP pathway by an average of 7.7 mm, seven times the results of the control group. Although a significant difference was only found between the control group and the intervention groups and there was no significant difference between the two virtual training groups in either outcome, the results were slightly greater in the VT2 group than in the VT1 group at all four test postures. Perhaps if treatments had continued, this difference could have shown a more significant differentiation in the longer term. In a previous study of posturographic testing, only the unusually high frequencies and high intensity therapies were able to achieve significant difference in COP pathway reduction compared to conventional physiotherapy [11]. Furthermore, at the four body positions tested, the VT2 group showed a significant difference compared to the control group in 3 out of the four cases, while VT1 only showed a significant difference in 2 cases. Thus, increasing the intensity may be specifically suited to improve postural instability, and it is likely that by increasing the frequency, these effects may be further enhanced in the longer term. We can draw parallels between the change in the EQ VAS scores for patient-perceived subjective health and the change in the mRS, BI, BBS, 6mWT, and posturographic examination scores, as the scores improved similarly among the groups. This means that participants perceived an improvement in their health status, which is likely caused by the reduction of the severity of disability, a more efficient performance of daily activities, an improved quality of life, improved static and dynamic balance, thus reducing the likelihood of falling, improved stamina and walking ability, and greater stability of standing. These changes and the group exercises reduced depression in all three groups, with greater reductions in the virtual training groups, where there were greater improvements in other outcomes, and more time spent socializing during group sessions.

Conclusions

No significant differences were found among the groups, in the participants' physical characteristics, cognitive functions and time elapsed, since the stroke and initial outcomes, so the three study groups were considered to be similar at baseline.

Time elapsed since the stroke corresponds to subacute stage in all three groups. The exercise intensity of the intervention groups was set between 14 and 17 according to the high intensity criterion based on RPE, which was successfully achieved in both the VT2 and VT1 groups based on the RPE values collected during the 25 days of intervention and there was no difference in intensity between the two groups and it exceeded the low intensity of the CON group.

The overwhelming majority of evidence supports that all three treatments are effective in improving the clinical symptoms, mobility and quality of life of people with subacute stroke. All outcomes measured in the VT2 and VT1 groups showed significant improvements by the end of the exercise programs. There was no clinically meaningful changes in EQ VAS and posturographic tests (WEO, WEC, NEO, and NEC), however, the result of the mRS, BI, BBS, 6mWT, BDI improved significantly in CON group.

Comparing the two high-intensity exercise programs with the control group receiving conventional therapy, we can see that the VT2 group achieved significantly greater improvements in mRS, BI, EQ VAS, BBS, 6mWT, BDI, and three out of four posturography postures (WEC, NEC, NEO), and the VT1 group achieved significantly greater improvement in mRS, 6mWT, BDI, and two out of four posturography postures (WEC, NEC) than the CON group. Since the VT2 group achieved significantly greater improvements than the CON group in 9 out of the 10 outcomes measured and the VT1 group in 5 out of the 10 outcomes measured, it can be concluded that the high intensity programs have more beneficial effects than the exercise program of the control group.

Among the high-intensity exercise groups, the VT2 group that performed two sessions per day showed significantly greater improvements in mRS and BI than the VT1 group, that performed one session per day. No significant differences were found between the two groups in other outcomes. In addition, the VT2 group made greater improvement than the CON group in 10 out of the 11 measured outcomes, while the VT1 group made greater improvement than the CON group in only 6 out of the 11 measured outcomes. These results suggest that increasing frequency may further increase the rehabilitation effectiveness of high intensity exercise programs.

This study underscores the potential health economic benefits of more frequent high-intensity exercise programs, as they could lead to better rehabilitation outcomes, potentially reducing long-term healthcare costs and the burden on healthcare systems. Recent studies showed that evidence-based, technology-driven therapies are gaining wide acceptance across our society [49]. This gives hope to a better, more inclusive, more efficient and more sustainable future care system [50].

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