Effect of Leap Motion-based 3D Immersive Virtual Reality Usage on Upper Extremity Function in Ischemic Stroke Patients

Efeito do uso imersivo da realidade virtual 3D baseada em movimento de salto na função de extremidade superior em pacientes com AVC isquêmico

Muhammed Nur ÖGÜN¹, Ramazan KURUL², Mustafa Fatih YAŞAR³, Sule Aydin TURKOGLU¹, Şebnem AVCl², Nebil YILDIZ¹

ABSTRACT

Immersive virtual reality (VR) is a technology that provides a more realistic environmental design and object tracking than ordinary VR. The aim of this study was to investigate the effectiveness of immersive VR on upper extremity function in patients with ischemic stroke. Sixty-five patients with ischemic stroke were included in this randomized, controlled, double-blind study. Patients were randomly divided into VR (n = 33) and control (n = 32) groups. The VR group received 60 minutes of the upper extremity immersive VR rehabilitation program and the control group received 45 minutes of conventional therapy and 15 minutes of a sham VR program. Rehabilitation consisted of 18 sessions of therapy, three days per week, for six weeks. The outcome measures were the Action Research Arm Test (ARAT), Functional Independence Measure (FIM), Fugl-Meyer Upper Extremity Scale (FMUE) and Performance Assessment of Self-Care Skills (PASS). In both the VR and control groups all parameters except the PASS improved over time. However independent t-test results showed that all of the FMUE, ARAT, FIM and PASS scores were significantly higher in the VR group compared with the control (p < 0.05). The minimal clinically important difference (MCID) scores of the FMUE and ARAT were higher than the cut-off MCID scores described in the literature in the VR group, whereas the FIM scores were below the cut-off MCID scores. All scores in the control group were below the cut-off scores. Immersive VR rehabilitation appeared to be effective in improving upper extremity function and self-care skills, but it did not improve functional independence.

Keywords: Stroke rehabilitation; upper extremity; virtual reality exposure therapy.

RESUMO

A VR imersiva é uma tecnologia que fornece design ambiental e rastreamento de objetos mais realistas do que a VR comum. O objetivo deste estudo foi investigar a eficácia da VR imersiva na função da extremidade superior em pacientes com AVC isquêmico. Sessenta e cinco pacientes com AVC isquêmico foram incluídos neste estudo randomizado, controlado e duplo-cego (clinictrials.gov. ID: NCT03135418). Os pacientes foram divididos aleatoriamente em VR (n = 33) e controle (n = 32). O grupo VR recebeu 60 minutos do programa de reabilitação imersiva da extremidade superior e o grupo controle recebeu 45 minutos de terapia convencional e 15 minutos de um programa falso de VR. A reabilitação consistiu em 18 sessões de terapia, 3 dias por semana, durante 6 semanas. As medidas de resultado foram Teste de braço de pesquisa-ação (ARAT), Medida de independência funcional (FIM), Escala de extremidades superiores de Fugl-Meyer (FMUE) e Avaliação de desempenho de habilidades de autocuidado (PASS). Nos grupos VR e controle, todos os parâmetros, exceto o PASS, melhoraram com o tempo. No entanto, os resultados dos testes t independentes mostraram que todos os escores FMUE, ARAT, FIM e PASS foram significativamente maiores no grupo VR em comparação ao controle (p <0,05). Os escores de FMUE e ARAT de diferença minimamente clinicamente importante (MCID) foram maiores que os pontos de corte de MCID descritos na literatura no grupo VR, enquanto os escores de FIM estiveram abaixo dos pontos de corte de MCID. Todas as pontuações no grupo controle estiveram abaixo das pontuações de corte. A reabilitação imersiva da VR parece ser eficaz para melhorar a função da extremidade superior e as habilidades de autocuidado, mas não melhora a independência funcional.

Palavras-chave: Reabilitação do acidente vascular cerebral; extermidade superior; terapia de exposição à realidade virtual.

¹Bolu Abant Izzet Baysal Universitesi; Nöroloji Anabilim Dalı, Bolu, Türkiye;

²Bolu Abant Izzet Baysal Universitesi; Sağlık Bilimleri Fakültesi, Fizik Tedavi ve Rehabilitasyon Yüksekokulu, Bolu, Türkiye;

³Bolu Abant Izzet Baysal Universitesi; Fizik Tedavi ve Rehabilitasyon Anabilim Dalı, Bolu, Türkiye

Muhammed Nur Ögün (D) https://orcid.org/0000-0001-5524-5767; Ramazan Kurul (D) https://orcid.org/0000-0001-8605-8286; Mustafa Fatih Yaşar (D) https://orcid.org/0000-0001-6715-8388; Sule Aydin Turkoglu (D) https://orcid.org/0000-0001-8616-832X; Şebnem Avcı (D)

https://orcid.org/0000-0003-3712-0551; Nebil Yıldız (D) https://orcid.org/0000-0002-1845-0902

Correspondence: Muhammed Nur Ögün; Abant Izzet Baysal Universitesi – Neurology; Golkoy Kampusu Golkoy Kampusu Bolu 14280, Turkey;

E-mail: dr.mogun@gmail.com

Conflict of interest: There is no conflict of interest to declare.

Received 15 April 2019; Received in final form 30 July 2019; Accepted 07 August 2019.



Stroke is a common neurological problem and is one of the major causes of disability and death^{1,2}. In stroke patients, the mortality rate is approximately 30%, and there is an increase in the morbidity rate after stroke occurrence. In addition, stroke is one of the main factors in increases in the burden of health care expenses during adulthood³.

Upper extremity paresis is the most common deficit after stroke. Over 80% of stroke survivors experience acute upper extremity paresis and, for half of them, the paresis becomes chronic⁴. Stroke may manifest as muscle tone disorders, weakness, loss of coordination, and contractures. These impairments negatively impact the individual's daily living activities, including grasping, reaching, and handling⁵.

Virtual reality (VR) applications have been developing rapidly due to fast-moving technological advancements. Currently, these applications are used predominantly in simulations and games^{6,7}. In medicine, they are used for the training of many diagnostic and therapeutic interventions, such as laparoscopy and bronchoscopy, and they are also used for rehabilitation⁸. Interactive video games and VR have become popular as a new treatment method for stroke rehabilitation. In the clinical setting, there are certain methods involving activities that often cannot be performed or achieved by the patient. Conversely, a virtual world application allows the patient to perform these activities, with the application providing the opportunity for abundant repetitive movements and giving the patient visual feedback. Moreover, VR programs are designed to be more fun and sustainable than traditional treatment programs9.

Immersive VR consoles, which have the ability to create numerous realistic virtual environments, may lead to new rehabilitation opportunities. Those consoles provide a 360-degree interactive experience in a predesigned environment in which the individuals are completely isolated from the outside world¹⁰. As a result, these consoles provide a near real-life experience for the users. In this environment, they can see their own avatar and interact with objects. Virtual reality applications are the most advanced technology in use today and increase an individual's sense of presence in the 3D environment. This effect is achieved using headphones that provide audio, and glasses that allow for the use of the entire visual field11,12. The greatest advantage of the new generation, compared with older devices, is that it prevents the symptoms of motion sickness, such as nausea, dizziness, and headache. Compared with older models, this new technology allows for an immersive design and object tracking, meaning the device can be used for extended periods of time without the user experiencing nausea or headaches¹³.

Leap Motion is a device that can be mounted on immersive VR devices to track hand movements at the level of millimeters using infrared sensors¹⁴. This device recognizes all fingers and associated movements and can use gestures to interact with the virtual environment^{15,16}. It can also process the depth of movements through two integrated cameras,

which gives users a real-time on-screen hand simulation that is almost as accurate as real arm movements¹⁷. In most of the upper extremity rehabilitation studies using VR, a 2D screen has been used rather than 3D immersive VR. Moreover, in the studies using 3D immersive VR, Leap Motion has not been used to track finger motion¹⁸, and in the studies using Leap Motion, 2D screens were used instead of immersive VR^{19,20}.

We hypothesized that the use of 3D VR and Leap Motion together would increase the experience of immersion in the virtual environment. To the best of our knowledge, there has been no other study that combined immersive VR and Leap Motion for use in stroke rehabilitation.

In this study, we investigated the effects of using 3D immersive VR combined with motion tracking on upper extremity rehabilitation and functional independence compared with conventional methods used in ischemic stroke rehabilitation.

METHODS

Participants

A total of 65 patients who had been diagnosed with ischemic stroke and were admitted to Bolu Abant Izzet Baysal University, Physical Therapy and Rehabilitation Hospital were included in the study. Each patient's medical information was obtained by our institution's neurology clinic. Inclusion criteria were: 1) a Mini-Mental State Examination score ≥ 25²¹; 2) stroke onset between six and 24 months; 3) a Modified Ashworth Scale score < 3; and 4) an upper extremity and hand Brunnstrom score ≥ 4. Exclusion criteria were: 1) secondary neurological diseases; 2) recurrent stroke; 3) reduced or lost visual field in one or both eye(s); or 4) hemorrhagic stroke. Discontinuation criteria in the study included: 1) continuous pain after a session in the upper extremities; 2) decreased compliance; 3) a medical deterioration that could not be managed by the therapist; or 4) if a rehabilitation session was missed without the chance to catch up. The study was performed according to the Helsinki Declaration and with permission from the local ethics committee (no. 2016/233). All participants were informed about the study, and written consent was obtained. The study was registered on http://www.clinicaltrials.gov, with the unique identifier NCT03135418. This study was funded by the Bolu Abant Izzet Baysal University Scientific Research Projects Board, 2017.08.32.1165.

Patients were randomly divided into two groups, VR or control, with stratified randomization according to age, sex, and stroke onset, using an online randomization website. Both patients and outcome assessors were masked, which was achieved by using sham VR therapy with the control group and the outcome assessor being blinded to the groups.

Intervention

Patients used the VR device to play task-oriented games that focused on gripping and handling of objects with arm and forearm motion and stability. The device was mounted on the patient's head to completely cover their eyes and ears. In order to prevent falls, patients were safely fastened to a chair with arm support (Figure 1). A different game was used for each function, with a total of four games: 1) a cube handling game used for grip function integrated with the Leap Motion device to make the patients feel like they were handling a real object using their own fingers without the use of any external device to track hand motion; 2) another Leap Motion-integrated game involving

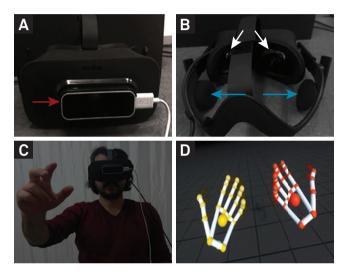


Figure 1. General features of Leap Motion and virtual reality (VR) devices: A) Leap Motion (red arrow) mounted on a VR device; B) VR device; magnifying glasses (white arrows), headphone (black arrows); C) Hand movements can be tracked without using any devices on the hands via Leap Motion; D) All hand movements and the virtual environment also can be seen on a TV screen.

decorating a tree with leaves and fruits or picking up vegetables from a bowl and putting them back, which was chosen to facilitate all hand motions combined with complex motions in a task-oriented job; 3) a kitchen experience game used for stimulating forearm supination and pronation and for combining complex arm movements; and 4) a drumming game, selected to randomly assign each separate movement of upper extremity flexion and abduction (Figure 2). The VR group received VR rehabilitation three days a week, on Monday, Wednesday, and Friday, at the same time each day, for six weeks. Each session lasted approximately 60 minutes and comprised four games that lasted 15 minutes each. The level of difficulty was the same for all of the games in all the sessions.

The control group received conventional upper extremity active exercises comprising the same tasks as used in the VR group. The control group also used the VR equipment, but only focused on visual scenes without any upper extremity interaction. Rehabilitation sessions lasted approximately 60 minutes, during which 15 minutes was scheduled for passive VR therapy.

Outcome measurements

The primary outcome measurement was assessed with the Fugl-Meyer Upper Extremity (FMUE) assessment. The Action Research Arm Test (ARAT), Functional Independence Measure (FIM), Performance Assessment of Self-Care Skills—instrumental activities of daily living (PASS-IADL), and Performance Assessment of Self-Care Skills—basic activities of daily living (PASS-BADL) were used as secondary outcome measurements. In this double-blind experiment, the participants were unaware of the intent and purpose of their group assignment, and test results and examiners were unaware of the intervention group assignment. An independent, experienced physiotherapist performed all the clinical assessments at the beginning and end of the treatment.

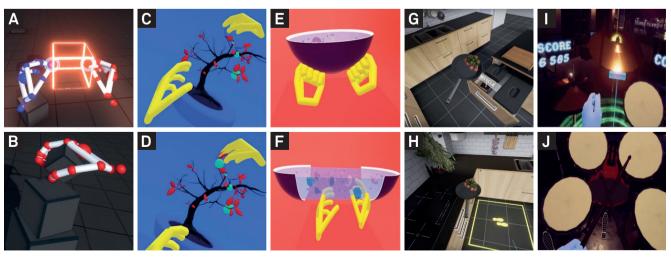


Figure 2. Types of VR programs: 1) Cube handling (A and B); 2) Decorating a tree with leaves (C and D) and picking up vegetables from a bowl (E and F); 3) Kitchen experience game (G and H); 4) Drumming For Review Only game (I and J).

The FMUE evaluates and measures recovery in poststroke hemiplegic patients. The FIM measures the level of a patient's disability and indicates how much assistance is needed for the individual to carry out daily life activities²². The purpose of the PASS is to demonstrate independence, adequacy, and safety. All the domains are rated on a four-point scale. The PASS scores can be divided into the two subsections of basic activities of daily living (BADL) and instrumental activities of daily living (IADL)²³. The ARAT assesses upper limb functions using observational methods that focus on gripping, grasping, and pinching motions of the hand²⁴.

Statistical methods

All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA). The chi-square test was used to compare the distribution of sex, and affected side, between the VR and control groups. The Shapiro-Wilk test was used to test for normal distribution of continuous variables, with normal distribution observed for the FMUE, ARAT, PASS and FIM scores, and age in both groups. A paired sample t-test was used for analyzing changes in pre- and post-test results in each group, and an independent t-test was used to analyze the mean values of test results in both groups. A p-value of less than 0.05 was considered statistically significant. To achieve $\alpha < 0.05$ and $\beta = 80\%$, according to the FMUE, 28 participants were

required in each group²⁵. Minimal clinically important difference (MCID) scores were obtained, based on previous studies, with MCID scores defined as 22 units for the FIM²², 5.7 units for the ARAT²⁶, and 5.25 units for the FMUE²⁷. To the best of our knowledge, there is no MCID score for the PASS described in the literature.

RESULTS

The 65 patients who met the inclusion criteria and were included in the study were randomly divided into either the VR group (n = 33) or the control group (n = 32). During the study, 10 patients from the VR group and nine patients from the control group discontinued their sessions. All of the dropouts in our study resulted from compliance issues. (Figure 3).

There were no significant differences between the two groups in terms of baseline characteristics (p > 0.05) (Table 1).

Paired sample t-test results showed that the FMUE, ARAT, FIM, and PASS scores increased significantly compared with the baseline in the VR group (p < 0.001). There was a significant increase in the FMUE (p < 0.001), ARAT (p < 0.001), and FIM (p = 0.002) scores in the control group; however, the differences in the PASS-BADL (p = 0.509) and PASS-IADL (p = 0.542) scores were not significant (Table 2).

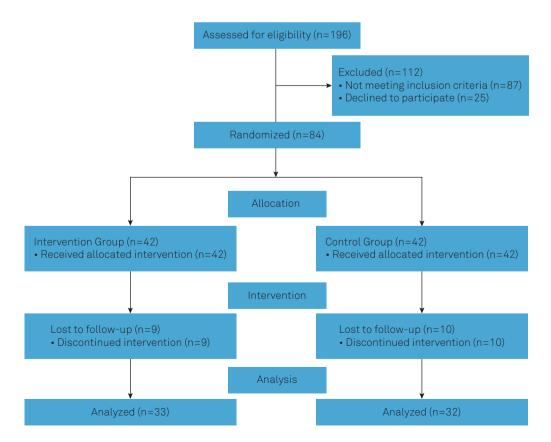


Figure 3. Flow chart of study.

Table 1. Baseline characteristics.

	Virtual reality	Control	p-value	
Variable	Group (n = 33)	Group (n = 32)		
Mean age ± SD	61.48 ± 10.92	59.75 ± 8.07	0.440	
Mean stroke onset ± SD	14.72 ± 7.38	15.37 ± 9.77	0.750	
MMSE score ± SD	28.69 ± 1.94	28.59 ± 1.84	0.690	
Sex distribution				
Male (%)	28 (84.8)	23 (71.9)	0.694	
Female (%)	5 (15.2	9 (28.1)		
Affected side				
Right (%)	18 (54.5)	19 (59.4)	0.667	
Left (%)	15 (45.5)	13 (40.6)		
Education				
Elementary (%)	7 (21.2)	5 (15.6)		
Junior High (%)	8 (24.2)	7 (21.9)	0.797	
High School (%)	7 (21.2)	11 (34.4)	0./9/	
University (%)	9 (27.3)	8 (25)		
Masters (%)	2 (3.2)	1 (3.1)		

SD: standard deviation; %: percentage; p < 0.05; MMSE: Mini-Mental State Examination

When the differences between the post-test and pre-test values of all outcome measures (FMUE, FIM, ARAT, PASS-BADL, and PASS-IADL) of the patients in both groups were compared, a significant difference was found in favor of the VR group (p < 0.001) (Table 3).

The mean difference between the post-test and pre-test scores of the FMUE was found to be 6.90 in the VR group and 1.48 units in the control group (MCID for FMUE: 5.25). For the ARAT, it was found to be 8.33 units in the VR group and 1.25 unit in the control group (MCID for ARAT, 5.7). The mean difference between the post-test and pre-test scores of the FIM was found to be 4.78 points in the VR group and 0.71 in the control group. However, this value was below the acceptable MCID limit of 22 units (Table 3).

DISCUSSION

In this randomized, controlled, double-blinded study, we found that six weeks of upper extremity training using immersive VR improved the functional activities of the upper extremity, functional independence, and self-care skills in stroke victims.

Table 2. Paired Sample t test results.

Evaluation toools	Groups	Pre-test - X ± SD	Post-test - X ± SD	t	dF	p-value
Lvataation toooto						•
FMUE	VR (n = 33)	39.63 ± 8.84	46.54 ± 7.91	9.935	32	< 0.001
	Control $(n = 32)$	38.56 ± 8.80	40.06 ± 8.33	5.729	31	< 0.001
ARAT	VR (n = 33)	32.81 ± 7.17	41.15 ± 7.82	10.761	32	< 0.001
	Control (n = 32)	30.84 ± 6.32	32.09 ± 5.94	4.846	31	< 0.001
FIM	VR (n = 33)	84.81 ± 5.96	89.60 ± 8.20	4.722	32	< 0.001
	Control $(n = 32)$	84.25 ± 6.37	84.96 ± 6.42	3.474	31	0.002
PASS-BADL	VR (n = 33)	1.46 ± 0.27	1.84 ± 0.24	6.208	32	< 0.001
	Control (n = 32)	1.53 ± 0.25	1.56 ± 0.17	0.668	31	0.509
PASS-IADL	VR (n = 33)	1.58 ± 0.16	1.98 ± 0.18	10.493	32	< 0.001
	Control $(n = 32)$	1.57 ± 0.17	1.61 ± 0.32	0.616	31	0.542

PASS-BADL: Performance Assessment of Self-Care Skills – basic activities of daily living; ARAT: Action Research Arm Test; FIM: Functional Independence Measure; PASS-IADL: Performance Assessment of Self Care Skills – instrumental activities of daily living; FMUE: Fugl-Meyer Upper Extremity Assessment; t: paired sample t-test; SD: standard deviation; dF: degree of freedom; p < 0.05.

Table 3. Independent t-test result of mean differences between groups.

Variable	Virtual reality (n = 33)	(n = 33) Control $(n = 32)$		J.F	
	X±SD	X ± SD	· · ·	dF	p-value
FIM	4.78 ± 5.82	0.71 ± 1.17	3.876	63	< 0.001
ARAT	8.33 ± 4.44	1.25 ± 1.45	8.569	63	< 0.001
FMUE	6.90 ± 3.99	1.50 ± 1.48	7.193	63	< 0.001
PASS-BADL	0.38 ± 0.35	0.03 ± 0.29	4.295	63	< 0.001
PASS-IADL	0.39 ± 0.21	0.03 ± 0.33	5.083	63	< 0.001

PASS-BADL: Performance Assessment of Self-Care Skills – basic activities of daily living; ARAT: Action Research Arm Test; FIM: Functional Independence Measure; PASS-IADL: Performance Assessment of Self Care Skills – instrumental activities of daily living; FMUE: Fugl-Meyer Upper Extremity Assessment; t: independent sample t-test; SD: standard deviation; dF: degree of freedom; p < 0.05.

Despite similar applications being used in stroke rehabilitation, our study was the first to combine immersive VR with real-time hand and arm motion tracking without any wearable sensors, which eliminates the sensory integration on these devices²⁸. Gloves and other wearable sensors may potentially increase the proprioception of the related extremity. Because proprioception training and approximation are already part of conventional rehabilitation, it may not be determined whether any improvement is caused by the wearable sensors or the VR rehabilitation. Therefore, we eliminated sensory integration by using Leap Motion. In non-immersive VR applications, individuals see their avatars reflected on the screen²⁹. However, immersive VR provides accurate real-time motion feedback that can be used to correct motion that deviates from normal. Using VR in this study, we aimed to create an environment that resembles the real one. The VR increases the measurable parameters of motor learning, which have been described as 1) repetitive and varied practice; 2) progression of task difficulty; 3) problem solving and error correction; 4) motivation; and 5) the frequency and quality of feedback. In addition, VR provides task-specific exercises, adequate exercise intensity, and repetition³⁰. Therefore, we intended to enhance motor learning with the use of a virtual environment. To achieve this and to improve upper limb functions, the game sessions for the VR group included exercises matching the test functions (a kitchen with interactive kitchenware, a room with a desk full of different sized objects for handling and reaching functions, and five drums of different sizes and heights) where participants had to use their upper extremities and hands in activities.

Stroke rehabilitation programs are individualized for each patient. However, when it comes to applying those individualized programs, therapists are often limited by something related to the patient environment, like the need for a musical instrument or a workstation that is similar to the patient's work environment³¹. An individualized program refers to the fact that it is necessary to design therapy according to the functional needs of each individual, and it is easy to design and implement these things in VR rehabilitation. Thus, the question that needs to be asked here is, "Are immersive VR programs as effective as conventional therapy?" According to Laver's review, VR does not cause significant improvement in upper extremity function²⁸. And, while studies that used VR training for more than 15 hours reported better results, these results were obtained without subgrouping the VR used into non-immersive and immersive categories^{32,33}.

Cortical lesions disrupt cortical and cortico-subcortical connections, resulting in a decrease in signal processing capacity. It has been shown that the process of relearning skills and compensating for affected functions may improve with multisensory stimulation³¹. The recovery of motor skills depends on neurological recovery, adaptation, and learning new strategies and motor programs. Virtual reality systems

apply relevant concepts for driving neuroplasticity (repetition, intensity, and task-oriented training of the paretic extremity) and lead to benefits in motor function improvement after stroke. This is possible due to cortical reorganization and rewiring in the injured brain (brain plasticity)³⁴. The use of VR has shown practice-dependent enhancement of the affected arm through the facilitation of cortical reorganization. This process may be enhanced by the provision of multisensorial (visual, auditory, tactile) feedback available in some VR systems (e.g., Wii, Kinect, PlayStation)³⁵. It has been reported that the movements performed in the virtual environment stimulate plasticity³². Similarly, it has also been shown with neuroimaging methods that virtual motion can activate motion-related representation sites in the brain^{33,36}.

We found that both VR and conventional rehabilitation provide significant improvement in both upper extremity function and functional independence. However, selfcare performance did not improve in the control group. A group-wise comparison showed that the VR group had significantly more improvement on all the tests for functionality, independence, and self-care. When the patients' upper extremity function, level of independence, and daily life activity scores were analyzed and compared with the MCID scores, we found that the FMUE and ARAT scores improved enough to be considered clinically important, but the FIM scores did not show a clinically important difference. Since there was no MCID cut-off value described in the literature in terms of the PASS scores, the change in the PASS scores may be interpreted as significant. Our findings were similar to the existing studies in the literature that have used non-immersive VR applications^{37,38}.

In our study, we observed that the patients needed time to adapt to the VR system, and at least one session was required for individuals to orient to the device and the user interface. During the games, where shoulder movement was required, the 10-minute session times were exhausting, and the quality of movement diminished after 10 minutes for some of the patients. However, we did not allow any breaks because they were not in our initial study design. We advise that at least one break should be given, especially for upper extremity repeated motions, depending on the patient's endurance. During the rest period the patient can rest on their chair without taking off the VR device.

The main limitation of the current study was the high dropout rates and single-center design. Further multicenter and large sample size studies are needed to compare the results of the present study. We had a 23% dropout rate in the VR group and 22.5% in control group in this study. Similar studies investigating stroke rehabilitation experienced dropouts due to medical reasons related or unrelated to rehabilitation and compliance issues. Our dropout rates were higher than previous VR studies investigating stroke rehabilitation and expected dropout rates. All of the dropouts in our study resulted from compliance issues. Although we used the

Mini-Mental State Examination score to assess the patients' self-efficacy and compliance issues, high rates of dropout due to compliance issues indicate that a more detailed assessment tool is needed for VR rehabilitation^{39,40}. Another limitation of this study was that the long-term effects of immersive VR-based rehabilitation were not investigated, and further

studies are needed to determine the long-term effects of immersive VR-based rehabilitation.

In conclusion, the results of the present study suggest that using immersive VR applications in rehabilitation has a positive impact on upper extremity function and daily life activities, but does not improve independence, for stroke patients.

References

- Donnan GA, Baron JC, Ma H, Davis SM. Penumbral selection of patients for trials of acute stroke therapy. Lancet Neurol. 2009 Mar;8(3):261-9. https://doi.org/10.1016/S1474-4422(09)70041-9
- Sims NR, Muyderman H. Mitochondria, oxidative metabolism and cell death in stroke. Biochim Biophys Acta. 2010 Jan;1802(1):80-91. https://doi.org/10.1016/j.bbadis.2009.09.003
- Levine DA, Morgenstern LB, Langa KM, Piette JD, Rogers MA, Karve SJ. Recent trends in cost-related medication nonadherence among stroke survivors in the United States. Ann Neurol. 2013 Feb;73(2):180-8. https://doi.org/10.1002/ana.23823
- Cramer SC, Nelles G, Benson RR, Kaplan JD, Parker RA, Kwong KK, et al. A functional MRI study of subjects recovered from hemiparetic stroke. Stroke. 1997 Dec;28(12):2518-27. https://doi.org/10.1161/01.STR.28.12.2518
- Hatem SM, Saussez G, Della Faille M, Prist V, Zhang X, Dispa D, et al. Rehabilitation of motor function after stroke: a multiple systematic review focused on techniques to stimulate upper extremity recovery. Front Hum Neurosci. 2016 Sep;10:442. https://doi.org/10.3389/fnhum.2016.00442
- Burdea Grigore C, Coiffet P. Virtual reality technology. London: Wiley-Interscience; 1994.
- Gallagher AG, Ritter EM, Champion H, Higgins G, Fried MP, Moses G, et al. Virtual reality simulation for the operating room: proficiency-based training as a paradigm shift in surgical skills training. Ann Surg. 2005 Feb; 241(2):364-72. https://doi.org/10.1097/01.sla.0000151982.85062.80
- Grantcharov TP, Kristiansen VB, Bendix J, Bardram L, Rosenberg J, Funch-Jensen P. Randomized clinical trial of virtual reality simulation for laparoscopic skills training. Br J Surg. 2004 Feb;91(2):146-50. https://doi.org/10.1002/bjs.4407
- Laver K, George S, Thomas S, Deutsch JE, Crotty M.
 Cochrane review: virtual reality for stroke rehabilitation.
 Eur J Phys Rehabil Med. 2012 Sep;48(3):523-30.
 https://doi.org/10.1161/STROKEAHA.117.020275
- Niehorster DC, Li L, Lappe M. The accuracy and precision of position and orientation tracking in the HTC vive virtual reality system for scientific research. I-Perception. 2017;8(3):2041669517708205. https://doi.org/10.1177/2041669517708205
- 11. Munafo J, Diedrick M, Stoffregen TA. The virtual reality head-mounted display Oculus Rift induces motion sickness and is sexist in its effects. Exp Brain Res.. 2017;235(3):889-901. https://doi.https://doi.org/10.1007/s00221-016-4846-7
- Dolgunsöz E, Yildirim G, Yildirim S. The effect of virtual reality on EFL writing performance. J Lang Ling Stud. 2018;14(1):278-92.
- Desai PR, Desai PN, Ajmera KD, Mehta K. A review paper on oculus rift-a virtual reality headset. arXiv preprint arXiv:14081173. 2014. https://doi.org/10.14445/22315381/JJETT-V13P237
- Weichert F, Bachmann D, Rudak B, Fisseler D. Analysis of the accuracy and robustness of the leap motion controller. Sensors (Basel). 2013 May;13(5):6380-93. https://doi.org/10.3390/s130506380

- Valentini PP, Pezzuti E. Accuracy in fingertip tracking using leap motion controller for interactive virtual applications. Int J Interac Desig Manufact. 2017;11(3):641-50. https://doi.org/10.1007/s12008-016-0339-y
- Lupu RG, Botezatu N, Ungureanu F, Ignat D, Moldoveanu A. Virtual reality based stroke recovery for upper limbs using leap motion.
 In: 20th International Conference on System Theory, Control and Computing; 2016 [cited 2016 Oct 15]. Available from: https://ieeexplore.ieee.org/document/7790681
- 17. Holmes D, Charles D, Morrow P, McClean S, McDonough S, editors. Usability and performance of Leap Motion and Oculus Rift for upper arm virtual reality stroke rehabilitation. Proceedings of the 11th International Conference on Disability, Virtual Reality & Associated Technologies; 2014 [[cited 2014 Sept 02]. Avaliable from: http://centaur.reading.ac.uk/66645/8/ICDVRAT2016_Full_ Proceedings_11th%20_Conf.pdf
- 18. Huang Q, Wu W, Chen X, Wu B, Wu L, Huang X, et al. Evaluating the effect and mechanism of upper limb motor function recovery induced by immersive virtual-reality-based rehabilitation for subacute stroke subjects: study protocol for a randomized controlled trial. Trials. 2019 Feb;20(1):104. https://doi.org/10.1186/s13063-019-3177-y
- Iosa M, Morone G, Fusco A, Castagnoli M, Fusco FR, Pratesi L, et al. Leap motion controlled videogame-based therapy for rehabilitation of elderly patients with subacute stroke: a feasibility pilot study. Top Stroke Rehabil. 2015 Aug;22(4):306-16. https://doi.org/10.1179/1074935714Z.0000000036
- Wang Zr, Wang P, Xing L, Mei Lp, Zhao J, Zhang T. Leap Motion-based virtual reality training for improving motor functional recovery of upper limbs and neural reorganization in subacute stroke patients. Neural Regen Res. 2017 Nov;12(11):1823-1831. https://doi.org/10.4103/1673-5374.219043
- Bour A, Rasquin S, Boreas A, Limburg M, Verhey F. How predictive is the MMSE for cognitive performance after stroke? J Neurol. 2010 Apr;257(4):630-7. https://doi.org/10.1007/s00415-009-5387-9
- Beninato M, Gill-Body KM, Salles S, Stark PC, Black-Schaffer RM, Stein J. Determination of the minimal clinically important difference in the FIM instrument in patients with stroke. Arch Phys Med Rehabil. 2006 Jan;87(1):32-9. https://doi.org/10.1016/j.apmr.2005.08.130
- McCue M, Rogers JC, Goldstein G. Relationships between neuropsychological and functional assessment in elderly neuropsychiatric patients. Rehabil Psychol. 1990;35(2):91-9. https://doi.org/10.1037/h0079052
- 24. Platz T, Pinkowski C, van Wijck F, Kim IH, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. Clin Rehabil. 2005 Jun;19(4):404-11. https://doi.org/10.1191/0269215505cr832oa
- Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. Neurorehabil Neural Repair. 2008 Mar-Apr;22(2):111-21. https://doi.org/10.1177/1545968307305457

- Van der Lee JH, De Groot V, Beckerman H, Wagenaar RC, Lankhorst GJ, Bouter LM. The intra- and interrater reliability of the action research arm test: a practical test of upper extremity function in patients with stroke. Arch Phys Med Rehabil. 2001 Jan;82(1):14-9. https://doi.org/10.1053/apmr.2001.18668
- Wagner JM, Rhodes JA, Patten C. Reproducibility and minimal detectable change of three-dimensional kinematic analysis of reaching tasks in people with hemiparesis after stroke. Phys Ther. 2008 May;88(5):652-63. https://doi.org/10.2522/ptj.20070255
- Laver K, George S, Thomas S, Deutsch J, Crotty M. Virtual reality for stroke rehabilitation. Cochrane Database Syst Rev. 2011 Sep 7;(9):CD008349. https://doi.org/10.1002/14651858.CD008349.pub2
- Holper L, Muehlemann T, Scholkmann F, Eng K, Kiper D, Wolf M. Testing the potential of a virtual reality neurorehabilitation system during performance of observation, imagery and imitation of motor actions recorded by wireless functional near-infrared spectroscopy (fNIRS). J Neuroeng Rehabil. 2010 Dec;7(1):57. https://doi.org/10.1186/1743-0003-7-57
- Levin MF, Weiss PL, Keshner EA. Emergence of virtual reality as a tool for upper limb rehabilitation: incorporation of motor control and motor learning principles. Phys Ther. 2015 Mar;95(3):415-25. https://doi.org/10.2522/ptj.20130579
- Dobkin BH. Training and exercise to drive poststroke recovery. Nat Clin Pract Neurol. 2008 Feb;4(2):76-85. https://doi.org/10.1038/ncpneuro0709
- You SH, Jang SH, Kim YH, Hallett M, Ahn SH, Kwon YH, et al. Virtual reality-induced cortical reorganization and associated locomotor recovery in chronic stroke: an experimenterblind randomized study. Stroke. 2005 Jun;36(6):1166-71. https://doi.org/10.1161/01.STR.0000162715.43417.91
- 33. Jang SH, You SH, Hallett M, Cho YW, Park CM, Cho SH, et al. Cortical reorganization and associated functional motor recovery after virtual reality in patients with chronic stroke: an experimenter-blind

- preliminary study. Arch Phys Med Rehabil. 2005 Nov;86(11):2218-23. https://doi.org/10.1016/j.apmr.2005.04.015
- Johansson BB. Current trends in stroke rehabilitation. A review with focus on brain plasticity. Acta Neurol Scand. 2011 Mar;123(3):147-59. https://doi.org/10.1111/j.1600-0404.2010.01417.x
- Saposnik G, Levin M. Virtual reality in stroke rehabilitation: a meta-analysis and implications for clinicians. Stroke. 2011 May;42(5):1380-6. https://doi.org/10.1161/STROKEAHA.110.605451
- 36. Tunik E, Saleh S, Adamovich SV. Visuomotor discordance during visually-guided hand movement in virtual reality modulates sensorimotor cortical activity in healthy and hemiparetic subjects. IEEE Trans Neural Syst Rehabil Eng. 2013 Mar;21(2):198-207. https://doi.org/10.1109/TNSRE.2013.2238250
- Connelly L, Jia Y, Toro ML, Stoykov ME, Kenyon RV, Kamper DG. A pneumatic glove and immersive virtual reality environment for hand rehabilitative training after stroke.
 IEEE Trans Neural SystRehabil Eng. 2010 Apr;18(5):551-9. https://doi.org/10.1109/TNSRE.2010.2047588
- Saposnik G, Teasell R, Mamdani M, Hall J, McIlroy W, Cheung D, et al. Effectiveness of virtual reality using Wii gaming technology in stroke rehabilitation: a pilot randomized clinical trial and proof of principle. Stroke. 2010 Jul;41(7):1477-84. https://doi.org/10.1161/STROKEAHA.110.584979
- 39. Zheng CJ, Liao WJ, Xia WG. Effect of combined low-frequency repetitive transcranial magnetic stimulation and virtual reality training on upper limb function in subacute stroke: a double-blind randomized controlled trail [Medical Sciences]. J Huazhong Univ Sci Technolog Med Sci. 2015 Apr;35(2):248-54. https://doi.org/10.1007/s11596-015-1419-0
- Kong KH, Loh YJ, Thia E, Chai A, Ng CY, Soh YM, et al. Efficacy of a virtual reality commercial gaming device in upper limb recovery after stroke: a randomized, controlled study. Top Stroke Rehabil. 2016 Oct;23(5):333-40. https://doi.org/10.1080/10749357.2016.1139796