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Effects of Virtual Reality versus Conventional Balance Training on Balance and Falls in People with Multiple Sclerosis: A Randomized Controlled Trial

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Running Head: Virtual Reality-Based Balance Training

Title: Effects of Virtual Reality versus Conventional Balance Training on Balance and Falls in People with Multiple Sclerosis: A Randomized Controlled Trial

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Keywords: virtual reality, exergame, balance, falls, multiple sclerosis

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Author contributions:

All authors contributed to the study design. E. Mohammadiani Nejad referred the PwMS participants after checking for the inclusion and exclusion criteria. F.Molhemi and S.Monjezi contributed to data collection. M.Mehravar and S.Hesam contributed to data analysis. All authors contributed to data interpretation. F.Molhemi, S.Monjezi and M.Mehravar drafted the manuscript. All authors revised and approved the final manuscript.

Ethics Approval:

This study received approval from the local ethics committee "Ahvaz Jundishapur University of Medical Sciences" (approval number IR.AJUMS.REC.1396.558). Informed consent was obtained from all the participants.

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Clinical Trial Registration:

This trial is registered at the Iranian Registry of Clinical Trials (Registration ID: IRCT2017110737286N1).

Conflicts of Interest:

The Authors declare that there is no conflict of interest.

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Effects of Virtual Reality versus Conventional Balance Training on Balance and Falls in People with Multiple Sclerosis: A Randomized Controlled Trial

Abstract

Objective: To assess the efficacy of Virtual Reality (VR)-based versus conventional balance training on the improvement of balance and reduction of falls in people with multiple sclerosis (PwMS).

Design: Single-blinded, randomized, controlled trial.

Setting: Musculoskeletal Rehabilitation Research Center, Ahvaz Jundishapur University of Medical Sciences.

Participants: Thirty-nine PwMS, randomized into VR (n=19) and control (n=20) groups.

Intervention: The VR group performed exergames using Kinect® while control group accomplished conventional balance exercises. Both groups received 18 training sessions for 6 weeks.

Outcome Measures: Limits of stability(LOS), Timed Up-and-Go(TUG) and 10-Meter-Walk tests with and without cognitive task and their dual-task costs(DTC), Berg Balance Scale, Multiple Sclerosis Walking Scale-12, Fall Efficacy Scale-international, Activities-specific Balance Confidence scale, and fall history were obtained pre- and post-intervention, and after a three-month follow-up.

Results: At both post-intervention and follow-up, TUG $^{\text{cognitive}}$ and DTC on the TUG were significantly lower and the 10-Meter-Walk$^{\text{cognitive}}$ was significantly higher in the VR group. At follow-up, reaction time and the number of falls demonstrated significant differences favoring

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the VR group, whereas the directional control revealed significant difference in favor of the control group($p<0.05$). The other outcomes showed no statistically significant difference neither at post-intervention nor at follow-up.

Conclusions: Both the VR-based and conventional balance exercises improved balance and mobility in PwMS, while each acted better in improving certain aspects. VR-based training was more efficacious in enhancing cognitive-motor function, and reducing falls, whereas conventional exercises led to better directional control. Further studies are needed to confirm the effectiveness of recruiting VR-based exercises in clinical settings.

Keywords: Virtual Reality, Exergame, Balance, Falls, Multiple Sclerosis

Abbreviations:

Activities-specific Balance Confidence Scale (ABC)

Berg balance scale (BBS)

Directional Control (DCL)

Dual-Task Cost (DTC)

Endpoint Excursion (EPE)

Expanded Disability Status Scale (EDSS)

Fall Efficacy Scale-International (FES-I)

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Generalized Linear Mixed-Model (GLMM)

International Classification of Functioning, Disability and Health (ICF)

KWiC (Kinecting with Clinicians)

Limits of stability (LOS)

Linear Mixed-Model (LMM)

Maximum Excursion (MXE)

Movement Velocity (MVL)

Multiple Sclerosis (MS)

Multiple Sclerosis Walking Scale-12 (MSWS-12)

People with Multiple Sclerosis (PwMS)

Reaction Time (ReT)

Suitability Evaluation Questionnaire (SEQ)

The 10-Meter-Walk (10MW)

Timed Up-and-Go (TUG)

Virtual Reality (VR)

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1. Introduction:

Balance impairment is one of the most disabling symptoms in people with multiple sclerosis (PwMS) that affects about 75% of patients during the course of the disease.[1] Impaired balance and mobility restrict the ability to perform activities of daily living which may result in a reduced quality of life.[2] These impairments are known as major risk factors for falls with more than 50% of PwMS reporting one fall or more over a 3 to 12-month period.[3–5]

A variety of approaches including motor and sensory strategies[6], strengthening exercises[7], and dual-task cognitive-balance exercises[8] have been employed to improve balance and decrease the risk of falling in PwMS. However, recent systematic reviews revealed that despite the efficacy of the conventional methods in improving balance of PwMS, these improvements are not sufficient enough to reduce the number of future falls.[2,9] Due to the chronic nature of the disease, rehabilitation of PwMS, especially when aimed at decreasing major consequences such as falling, is a long-term process.[10,11] The constant repetitive nature of conventional rehabilitation programs may decrease patient engagement in the long-term.[10,12] Therefore, patients' commitment and their motivation need to be preserved throughout the course of the program.[10] This may raise the need for more effective and enjoyable rehabilitation programs to gain durable clinical improvements.[12]

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In recent years, the use of Virtual Reality (VR) and exergames (video-games that require bodily movements to play; simulating an active gaming experience used as a form of exercise[13]) has received attention in neuro-rehabilitation literature. Although various studies have repeatedly demonstrated that VR exercises are motivational and enjoyable[14–16], evidence supporting the higher efficacy of VR-based training compared to conventional rehabilitation is scarce and inconsistent. A recent meta-analysis indicated that VR was at least as effective as conventional balance exercises in improving balance and reducing gait impairments in PwMS with no significant difference between the two types of training.[16] Even though other studies have shown the promising potential of VR to improve balance and gait in neurological conditions, such as Multiple Sclerosis (MS),[17] the small number of studies with matched groups in terms of training parameters (e.g., duration of exercise in each treatment session, structure, and nature of the program), and the lack of follow-up make it hard to achieve a certain conclusion.[16]

Therefore, the present study was proposed with two aims: (1) to determine if a VR-based balance training program designed according to the principals of motor learning could be more efficacious towards improving balance and mobility compared with matched conventional exercises; (2) to compare the success of these two rehabilitation programs for reducing the risk for future falls in a three-month follow-up. We hypothesized that compared to conventional training, balance improvement would be greater and last longer, and the number of future falls would decrease more when employing a VR-based balance training program.

2. *Methods*

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2.1. *Participants and Design*

This study is a prospective randomized controlled trial, with parallel groups, conducted at Musculoskeletal Rehabilitation Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, from December 2017 to November 2018. The trial was directed based on the CONSORT statement.[18] PwMS were recruited from Khuzestan MS Patients' Society based on the following inclusion criteria: confirmed diagnosis of relapsing-remitting or secondary-progressive MS according to the McDonald criteria[19,20] by a neurologist specialized in treating MS, aged 18-64 years, Expanded Disability Status Scale (EDSS) below 6, and Berg Balance Scale (BBS) lower than 53. Participants were excluded if they had exacerbation of symptoms in past 3 months, cognitive impairment determined by Mini-Mental state examination below 24, any neurologic or musculoskeletal diagnosis except MS that negatively affected their gait and balance, uncorrected visual or auditory impairments or pregnancy. All the participants signed an informed consent form prior to the participation.

This study was approved by the university ethics committee (Code: IR.AJUMS.REC.1396.558) and was registered in the Iranian Registry of Clinical Trials (Registration ID: IRCT2017110737286N1).

2.2. *Randomization*

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After the pre-intervention assessments, participants were randomized into either VR-based or conventional balance training groups. Random assignment to training arms was stratified by age and sex to ensure similar representation of these variables. A statistician who was not a member of the research team, prepared a computerized random allocation sequence with different block sizes. Sealed envelopes opened by a third-party not involved in the study, were used to achieve the allocation concealment.

2.3. Interventions

Participants in both groups received three main categories of exercise including standing, walking, and weight-shifting. In the control group, standing exercise included multidirectional stepping, and single and double-leg standing, walking exercise involved forward, backward, and side walking and weight-shifting exercise consisted of lunge, half-squat, leaning, and reaching. In the VR group, progressive balance exercises were employed using the Xbox360 with Microsoft’s Kinect® [b]. “Light Race”, “Stack’em up”, and “20,000 leaks” exergames were selected and matched to conventional exercises in each category (Table 2). When searching among available exergames, KWiC resource (Kinecting with clinicians) was also considered.[21] The KWiC takes into account specifications like stability, mobility, spatial accuracy, cognitive

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operations, augmented feedback, and scoring when selecting exergames for rehabilitation purposes[21] (Details of VR-based rehabilitation protocol are presented in supplementary File).

Each session composed of 5-minute warm-up (4-minute side-stepping plus 1-minute half-squatting) followed by 30-minute exercise (10-minute active exercise per category). Participants in both groups received 18 treatment sessions, 3 times per week for 6 consecutive weeks which were supervised by the same physical therapist, blinded to the assessment results. Progression of exercises was specifically planned according to each individual's performance (Figure 1a). VR exercises were planned to be random-block based on the motor learning principals, and internally variable[22] (Gentil's taxonomy of tasks; Figure 1b). To prevent fatigue, participants were allowed to have 5-minute rest between the main exercise categories or to have enough rest during each category upon request. When patients asked for a rest, exercises were stopped (exergames were paused) and then resumed after adequate rest so that pure exercise duration was the same for both groups.

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2.4. Outcome measures

To have a comprehensive assessment of patient's health, various outcome measures were chosen to documents changes of balance and fall risk at different levels of International Classification of Functioning, Disability and Health (ICF) including body structure and function, activity and participantion.[23,24] The description of these measures and their corresponding ICF category are presented in Table 1.

The primary outcomes included limits of stability (LOS), single- and dual-task Timed Up-and-Go (TUG), single- and dual-task 10-Meter-Walk (10MW) tests, Dual Task Costs (DTC), BBS, Multiple Sclerosis Walking Scale-12 (MSWS-12), Fall Efficacy Scale-international (FES-I), Activities-specific Balance Confidence scale (ABC). The above-mentioned outcomes are reliable, valid and responsive measures of balance in PwMS[25–30] and were evaluated at baseline, post-intervention, and after three-month follow-up. Self-reported number of falls during past three months were recorded at baseline. Also, fall history during the intervention and three-month follow-up were determined using fall diary. Falls were defined as any unexpected event that results in loss of balance and landing on the floor or ground or lower level [31]. In line with the previous studies, participants were classified as fallers if they had reported one or more falls during the 3-month period.[31,32] In addition to measurement of the primary outcomes, Suitability Evaluation Questionnaire (SEQ) was given to the VR group after the last training session to receive subjective feedback about the intervention.[17,33]

Demographic information including age, sex, height, weight, MS subtype, duration of the disease, years of education, level of disability, cognitive impairment and history of falls during past 3 months were also recorded.

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All participants were evaluated under similar conditions by a physical therapist with 6 years of experience in assessment and treatment of PwMS who was blinded to the group allocation. The order of administering the tests was randomized to avoid learning effect and fatigue. Adequate rest (2-5 minutes) was also given to participants between the tests.

2.5. *Sample size*

Sample size was estimated based on the effect size (0.9) of the TUG^{cognitive}, with alpha and power set at 0.05 and 80%, respectively. This proposed a sample size of at least 16 in each group to detect significant differences between the groups.

2.6. *Statistical analysis*

Data analysis was performed using IBM SPSS statistics 22.0 software[c]. The normal distribution was examined using Shapiro–Wilk test and Q-Q plot. Descriptive statistics were calculated for the demographic data. Student's t-test was used to compare baseline demographic and clinical characteristics between the groups. To separate two main sources of variance i.e. within-subject and between-subject variances, mixed-model analysis was recruited.[34] Linear mixed-model (LMM) was used to assess main effect of time and group on continuous quantitative variables. Negative binominal generalized linear mixed-model (GLMM), and

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logistic GLMM were used to evaluate number of falls and fall occurrence binary variable (faller/non-faller), respectively. Time, group, and their interaction were considered as fixed-effects. Also, the subject was included as random-effect in order to consider the interdependency of data during repeated measurements. The model was adjusted for age, sex, duration of disease, MS subtype, and EDSS. Pre-intervention values were included as co-variate to increase statistical power by considering interpersonal variations.[35] Since the normality of response variable is an essential assumption for LMM, when normal distribution was not confirmed, square-root, logarithmic, or inverse transformation were applied. An intention-to-treat analysis using last observation carried forward approach was conducted.[36] Effect size for change in each group was calculated using Cohen's d coefficient (mean differences/SD of the differences).[36] Magnitude of the effect sizes was classified as small (0.20–0.49), moderate (0.50–0.80), and large (>0.8). The significance level was set at 0.05.

3. *Results*

Thirty-nine PwMS participated in this study. During the intervention period three participants from control group and one participant from VR group dropped out of the study due to their work schedules (n=2) and transport problems (n=2). Finally, 35 participants completed the post-intervention assessment (see Figure 2 illustrating flow chart of study process). Compliance to the VR-based training was 98% (mean 17.58 of 18 possible sessions, min 10;

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max 18) and to the conventional training was 93% (mean 16.80 of 18 possible sessions, min 6; max 18).

No significant adverse events were reported in either group. The mean score of the SEQ for the used VR system was 57.81±5.39 from a total of 65. None of the participants reported dizziness, nausea, or discomfort.

Pre-intervention, there were no statistically significant differences in demographic and clinical characteristics between the groups (Table 3). Results of between and within-group analysis and effect sizes are presented in Table 4.

At the level of body structure and function, LOS measures showed no significant differences post-intervention. At the follow-up, ReT was significantly lower in the VR group and DCL was significantly higher in the control group. MVL, EPE, MXE showed no significant differences.

At the level of activity, at both post-intervention and follow-up, $\text{TUG}^{\text{cognitive}}$ and the DTC on TUG were significantly lower, and $\text{10MW}^{\text{cognitive}}$ was significantly higher in the VR group. BBS, TUG, 10MW, DTC of 10MW and MSWS-12 showed no significant differences.

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At the participation level, at the follow-up, number of falls was significantly lower in the VR group (Table 5). ABC, FES-I, and number of fallers (Table 6) showed no significance differences between the groups at both post-intervention and follow-up.

4. Discussion

The results of this study demonstrated that both VR-based and conventional balance training improved balance-confidence, fear of falling, perceived ability to walk, functional balance, and single-task walking speed. VR-based training was more efficacious in improving reaction time, cognitive-motor performance, and reducing number of future falls, while conventional exercises resulted in better directional control.

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LOS measures

Conventional and VR-based trainings improved different aspects of leaning function. In the follow-up assessment, there was significant difference in ReT favoring the VR group, and in DCL favoring the control group. Exercise attributes might be a possible cause for these findings. In the VR group the movement velocity was externally imposed and participants had to react as fast as possible to successfully complete the tasks, while the control group performed the exercises at a self-selected pace that enables them to have more control on their movements. This may highlight the potential of two interventions to be used as complementary treatments. Further studies with appropriate design are needed to validate this.

Cognitive-motor performance

Compared to conventional trainings, VR-based exercises were more efficacious in improving cognitive-motor performance. Moreover, retention of improvements was observed just in the VR group. Better cognitive-motor performance in the VR group could be the result of the cognitive-motor challenges provided by VR exercises[10]. Rewarding tasks combining both motor and cognitive demands, like those used in the VR-based training of the present study, could lead to activation of both motor and cognitive pathways.[10].Also, the virtual environment itself imposes a cognitive load that demands attention, planning and dual tasking.[35] For example, a meta-analysis by Stanmore et al. reported that VR improves cognitive functions in the elderly and patients with schizophrenia and Parkinson’s disease.[37] Exergames performed in virtual environment, could trigger mechanisms of motivation[10], increase the awareness of the problem that patients have (meta-cognition) and the progress that they make through providing real-time multisensory feedback[10] and facilitating motor learning process.[38] The positive feedback that patients received may have decreased avoiding real life demanding cognitive-motor tasks. Previous studies expressed that VR-based interventions can retain and transfer the treatment outcomes to everyday life[10]. Experiencing more cognitive-motor demanding situations could be the reason for retention of cognitive-motor performance improvement in the VR group.

Fall prevention

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The number of falls, at three-month follow-up compared to pre-intervention, was significantly less in the VR group compared to the control group. Actually, regarding within group analysis, VR-based exercises reduced the number of falls, while conventional training did not. This will positively influence health economics with a reduction in high medical costs and more importantly may influence morbidity and mortality from falls.[31] Despite the clinical relevance and significance, these results should be interpreted with caution owing to the relatively small sample size.

The number of fallers, at three-month follow-up compared to pre-intervention, decreased in both groups; the odds of being labeled as a faller became 11.18 times less for the VR, and 4.29 times less for the control group. Despite the statistical insignificance of between-group difference, the chance of experiencing falls in the control group was more than the VR group (Table 6) which may clinically be important. Whereas surveying the causative relationship between the obtained performance measures and fall risk was not in the scope of the present study, other studies mentioned the significant advantage of VR-based training in reducing the fall rate among older adults and people with Parkinson's disease.[35] According to Mirelman et al, the cognitive-motor nature of VR-based exercises performing in an environment requiring attention, concentration, motor planning, and problem-solving, could implicitly enhance fall-prevention strategies and improve functional performance during daily challenging and attention demanding situations, which reduces falling in real-life.[35]

Suitability of the VR exercises

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SEQ scores of the VR group demonstrated that participants expressed having immense fun and success in using the system and felt that it was useful, motivating, and positively affected their rehabilitation. Interestingly, most participants expressed desire to continue treatment with the used program.

4.1. Study Limitations

Although post-intervention and follow-up fall data were collected prospectively using fall diaries, the pre-intervention falls were recorded retrospectively which may have been subjected to recall bias.[39] To reduce this bias, family members of subjects were interviewed to confirm their estimation. Also, concerning the nature of VR-based training, blinding of participants was not possible which could be considered as another limitation. It is recommended that future studies use subjective scales such as Borg rating of perceived exertion to ensure matching exercise intensity between the groups, recruit more participants, and consider longer follow-up with prospectively collected baseline fall data to increase generalizability of findings. VR-based exercises in the present study were applied in a research setting under the supervision of a physiotherapist. Practicality of VR-based rehabilitation will be prominent if future studies confirm that home-based VR exercises could gain the same results as their supervised versions.

5. Conclusions

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Both the VR-based and conventional balance exercises improved balance and mobility in PwMS, while each acted better in improving certain aspects. VR-based balance training was more efficacious in enhancing cognitive-motor function, and reducing falls, whereas conventional exercises led to better directional control. Further studied are needed to confirm the effectiveness of recruiting VR-based exercises in clinical settings.

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Suppliers:

a. Long platform; Smart EquiTest CRS® NeuroCom® International, Clackamas, Oregon, USA
b. Microsoft's Kinect; Microsoft Inc, Redmond, Washington
c. IBM SPSS statistics software (Version 22.0 for Windows); IBM Corp.

Legends of figures and tables:

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Figure 1: Progression of exercises. A) Each exergame had 3 mode of difficulty (Simple, moderate and difficult). B) Designed VR training representation into Gentile's taxonomy. Exercises applied using light Race and Stack'em up had internal variability. Exercises applied using 20,000 Leaks had no internal variability.

Figure 2. CONSORT flow diagram

Table 1. Outcome measures for balance and falls assessment

Table 2. Types of conventional exercises and their corresponding exergames in each training category

Table 3. Demographic and clinical characteristics of virtual reality and control groups (n=39)

Table 4. Intention-to-treat analysis of within-group and between-group changes (n=39)

Table 5. Within-group and between-group changes in number of falls (n=39)

Table 6. Within-group and between-group changes in number of fallers (n=39)

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Table 2. Types of conventional exercises and their corresponding exergames in each training category

Category	Conventional Exercise	Corresponding Exergame
Standing	• Multidirectional stepping • Single and double leg standing	• Light Race • Stack’em up
Walking	• Walking in different directions	• Stack’em up • 20,000 Leaks
Weight shifting	• Lunge, half-squat, leaning, and reaching	• 20,000 Leaks • Stack’em up

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Table 3. Demographic and clinical characteristics of virtual reality and control groups (n=39)

	VR (n = 19)	**Control (n = 20)**	***P*-value**
Demographic data			
Age (y)	36.8 (8.4)	41.6 (8.4)	0.08
Gender (n)			
Male	7	8	-
Female	12	12	-
Height (cm)	164.7 (8.8)	167.6 (10.7)	0.37
BMI (kg/m^2)	26.2 (4.9)	25.3 (3.9)	0.54
Education (y)	13.9 (2.7)	12.9 (3.7)	0.66
Clinical data			
Type of MS (n)			
RRMS	14	16	-
SPMS	5	4	-
Duration of disease (y)	7.7 (3.6)	11.2 (6.8)	0.06
Participants with history of falls in past 3 months (n, %)	15 (78.9)	12 (60)	0.30
Falls (n)	177	63	0.09
MMSE[a] (score)	28.7 (1.4)	28.0 (1.3)	0.09
EDSS[b] (score)	4.8 (0.9)	4.7 (1.1)	0.84

Values are means ± SD unless otherwise stated.
VR: Virtual Reality; BMI: Body mass index; MS: Multiple Sclerosis; RRMS: Relapsing Remitting MS; SPMS: Secondary Progressive MS; MMSE: Mini-Mental State Examination; EDSS: Expanded Disability Status Scale.

[a] Score range: 0-30

[b] Score range: 0-10

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Table 1: Outcome measures for balance and falls assessment

Outcome Measure	ICF Category	Details
Limits of stability (LOS)	Body Structure / Function	LOS was assessed using a static long platform.[a] In the LOS, reaction time (ReT), movement velocity (MVL), endpoint excursion (EPE), maximum excursion (MXE), and directional control (DCL), all averaged for leaning in 8 different directions, were calculated.
Berg Balance Scale (BBS)	Activity	Performance of the participants in 14 balance related tasks was scored by assessor on a scale of 0 (cannot perform) to 4 (normal performance).
Timed Up-and-Go (TUG)	Activity	TUG assesses dynamic balance and mobility. Time to rise from a chair, walk 3 meters, turn, walk back, and sit down, as fast as possible was recorded. To evaluate dual-task performance, TUG was repeated with concurrent backward counting by 7 from a randomized number between 100 and 200 ($TUG^{cognitive}$).
10-Meter-Walk (10MW)	Activity	10MW assess walking speed. Participants walked 10 meters at their self-selected comfortable speed and the time to complete the middle 6 meters was recorded. To measure dual-task performance, 10MW was repeated with concurrent backward counting by 7 from a randomized number between 100 and 200 ($10MW^{cognitive}$).
Dual-Task Cost (DTC)	Activity	DTC defines as the percentage of the change in outcome measure (e.g. the duration of the TUG and the speed of the 10MW) after adding concurrent cognitive task. Values closer to zero correspond to lower cognitive-motor interference. DTC = 100*(single task - dual task)/ single task
Multiple Sclerosis Walking Scale-12 (MSWS-12)	Activity	In the MSWS-12, participants rate their perceived ability of walking during 12 different conditions in a scale of 1 (no limitation) to 5 (very limited).
Fall Efficacy Scale-International (FES-I)	Activity Participation	In the FES-I, participants rate the level of concern relating to falls during 16 activities of daily living (including social activities that may contribute to quality of life) from 1 (not at all concerned) to 4 (very concerned).
Activities-specific Balance Confidence Scale (ABC)	Activity Participation	ABC, is a 16-items patient-reported measure of balance confidence. For each item, participants rate their balance confidence between 0% (no confidence) to 100% (complete confidence).
Falls	Participation	Participants were asked to prospectively record details of falls (including date and time, location, activities in which fall occurred, levels of fatigue and hurry, and any possible injuries) in a standardized paper fall diary during the intervention and over a 3-month period after the intervention.

ICF: International Classification of Functioning, Disability and Health.
In the TUG, $TUG^{cognitive}$, 10MW, and $10MW^{cognitive}$ average performance in two trials was used for statistical analysis.
Persian versions of the MSWS-12, FES-I, and ABC were used.

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Table 4. Intention-to-treat analysis of within-group and between-group changes (n=39)

Variable	**Pre-intervention Mean (SD)**	**Post-intervention Mean (SD)**	**Follow up Mean (SD)**	***P*-value for change[*]; Effect size**		***P*-value for difference[†]**	
				Pre to post intervention	**Pre-intervention to follow up**	**Post intervention**	**Follow up**
ReT (s)							
VR	1.0 (0.3)	0.9 (0.2)	0.8 (0.2)	0.58; -0.74	**0.006;** -0.86	0.25	**0.01**
Control	0.9 (0.2)	0.9 (0.3)	0.9 (0.3)	0.94; -0.03	0.67; 0.05		
MVL (deg/s)							
VR	2.7 (1.7)	3.6 (1.7)	3.6 (1.5)	**0.003;** 1.18	**0.001;** 0.97	0.50	0.11
Control	2.8 (1.3)	3.2 (1.3)	2.9 (0.9)	0.08; 0.46	0.27; 0.07		
EPE (%)							
VR	47.8 (11.2)	58.3 (10.2)	58.9 (10.7)	**0.001;** 1.06	**0.001;** 1.05	0.46	0.12
Control	47.7 (11.9)	53.8 (16.6)	51.9 (12.9)	**0.03;** 0.63	0.13; 0.48		
MXE (%)							
VR	61.5 (10.9)	69.6 (9.8)	68.8 (10.5)	**<0.001;** 1.19	**0.01;** 0.76	0.36	0.17
Control	61.5 (14.4)	66.1 (16.7)	64 (14.5)	**0.01;** 0.70	0.40; 0.35		
DCL (%)							
VR	68.7 (8.3)	71.6 (7.9)	69.9 (8.6)	0.09; 0.37	0.20; 0.23	0.56	**0.04**
Control	62.9 (12.9)	67.7 (10.6)	69.3 (13.2)	0.08; 0.58	**0.03;** 0.70		
BBS (points)							
VR	46.6 (3.9)	52.4 (2.1)	52 (2.7)	**<0.001;** 1.87	**<0.001;** 1.73	0.32	0.10
Control	45.5 (7.2)	49.9 (5.5)	49 (5.7)	**<0.001;** 0.93	**0.01;** 0.91		
TUG (s)							
VR	10.6 (3.04)	8.5 (2.5)	8.7 (2.03)	**<0.001;** -1.58	**0.001;** -1.20	0.42	0.60
Control	12.1 (7.5)	10.9 (5.7)	10.7 (4.5)	**0.031**; -0.38	0.276; -0.29		
TUG$^{\text{cognitive}}$ (s)							
VR	12.7 (4.7)	9.6 (2.6)	9.2 (2.2)	**<0.001;** -1.23	**<0.001;** -1.08	**0.01**	**0.01**
Control	15.03 (9.4)	13.8 (9.8)	12.7 (5.3)	**0.03**; -0.53	0.06; -0.38		
DTC on TUG							
VR	-18.6 (18.9)	-7.4 (9.4)	-5.8 (9.2)	**0.02**; 0.62	**0.007**; 0.71	**0.01**	**0.01**
Control	-26.2 (20.2)	-24.2 (28.3)	-21.4 (19.6)	0.40; 0.28	0.3; 0.18		
10MW (m/s)							
VR	0.9 (0.2)	1.1 (0.2)	1.1 (0.2)	**<0.001;** 1.07	**0.005;** 0.75	0.28	0.87
Control	0.9 (0.3)	0.9 (0.3)	0.9 (0.3)	**0.03**; 0.50	**0.04**; 0.47		
10MW$^{\text{cognitive}}$ (m/s)							
VR	0.7 (0.27)	0.9 (0.3)	0.9 (0.2)	**<0.001;** 1.1	**0.001;** 0.9	**0.006**	**0.03**
Control	0.8 (0.32)	0.8 (0.33)	0.8 (0.3)	0.21; 0.29	0.16; 0.29		
DTC on 10mw							
VR	22.8 (22.1)	13.4 (14.2)	10.5 (10.7)	**0.026**; -0.56	**0.005**; -0.73	0.05	0.06
Control	11.9 (23.4)	18.9 (20.9)	15.7 (17.8)	0.23; 0.28	0.42; 0.18		
MSWS-12 (points)							
VR	43.6 (10.4)	31.4 (10.9)	36.7 (11.8)	**<0.001;** -1.37	**0.001;** -0.94	0.79	0.70
Control	41.3 (10.8)	30.5 (11.2)	35.5 (12.3)	**<0.001;** -1.40	**0.003;** -0.75		
FES-I (points)							
VR	42.3 (10.9)	31.3 (8.5)	32.1 (10.4)	**<0.001;** -1.52	**<0.001;** -1.25	0.05	0.06
Control	40.9 (8.4)	35 (9.9)	35.7 (9.5)	**0.001;** -0.89	**<0.001;** -1.13		
ABC (points)							
VR	52.6 (21.9)	74 (15.6)	69.1 (20.1)	**<0.001;** 1.58	**<0.001;** 1.06	0.23	0.24
Control	46.1 (19.8)	63.9 (17.2)	59.1 (17.8)	**<0.001;** 1.19	**<0.001;** 1.02		

VR: Virtual reality; SD:Standard deviation; ReT: reaction time; MVL: movement velocity; EPE: end point excursions; MXE: maximum excursions; DCL: directional control; BBS: berg balance scale; TUG: timed up and go; DTC: dual-task cost; 10MW: 10 meters walk; MSWS-12: multiple sclerosis walking scale 12; FES-I: fall efficacy scale-international; ABC: activities-specific balance confidence scale

[*] *P*-value from univariable analysis

[†] *P*-value from multivariable analysis (mixed-model)

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Table 5. Within-group and between-group changes in number of falls (n=39)

Time / Group	Three months before the intervention Mean (SD) Median (min,max)	Post intervention Mean (SD) Median (min,max)	Follow-up Mean (SD) Median (min,max)	***P*-value for change[*] ; Effect size**		***P*-value for difference[†]**	
				Post intervention	**Follow-up**	**Post intervention**	**Follow-up**
VR	6.2 (6.9) 5 (0, 30)	2.2 (4.1) 0 (0, 15)	1.9 (3.8) 0 (0, 15)	**0.004;** -0.99	**0.002;** -1.17	0.21	**0.04**
Control	3.2 (4.1) 1 (0, 14)	1.9 (3.2) 1 (0, 14)	1.9 (3.5) 0 (0, 14)	**0.01;** -0.51	0.06; -0.43		

VR: virtual reality; SD: standard deviation; min: minimum; max: maximum.

[*] *P*-value from univariable analysis

[†] *P*-value from multivariable analysis (mixed-model)

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CONSORT
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CONSORT 2010 Flow Diagram

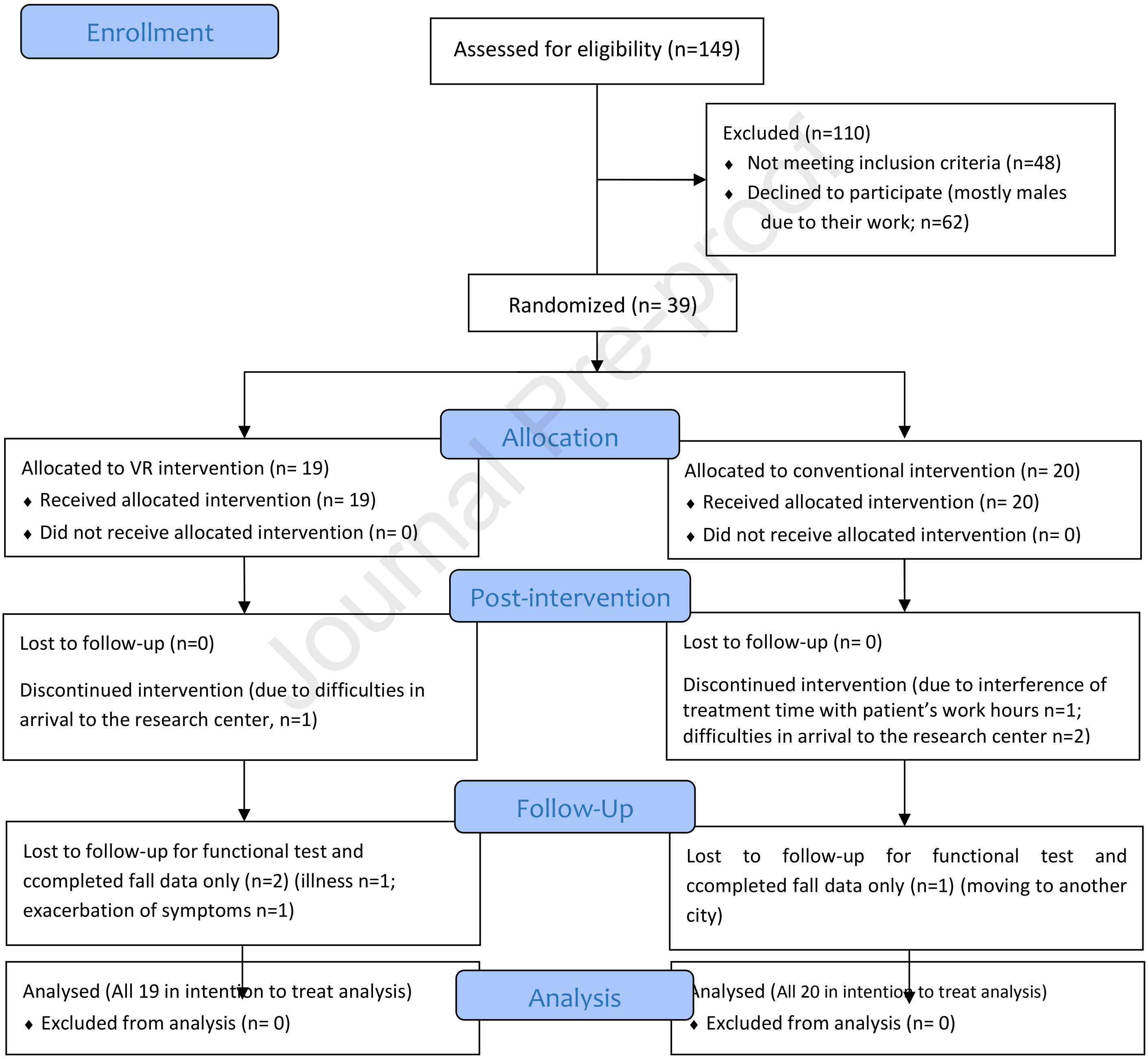

Figure 1: CONSORT flow diagram

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Table 6. Within-group and between-group changes in number of fallers (n=39)

Time / Group	Three months before the intervention (n, %)	Post intervention (n, %)	Follow-up (n, %)	*P*-value; OR (95% CI) for change[*]		*P*-value; OR (95% CI) for difference[†]	
				Post intervention	**Follow-up**	**Post intervention**	**Follow-up**
VR	15 (78.9)	10 (52.6)	8 (42.1)	**0.03**; 5.94 (0.98, 35.84)	**0.002**; 11.18 (1.79, 69.98)	0.17; 10.11 (0.35, 293.55)	0.37; 3.79 (0.20, 73.57)
Control	12 (60.0)	11 (55.0)	8 (40.0)	0.56; 1.44 (0.26, 7.97)	**0.04**; 4.29 (0.73, 25.17)		

VR: Virtual Reality; OR: odds ratio; CI: Confidence Interval

[*] *P*-value from univariable analysis

[†] *P*-value from multivariable analysis (mixed-model)

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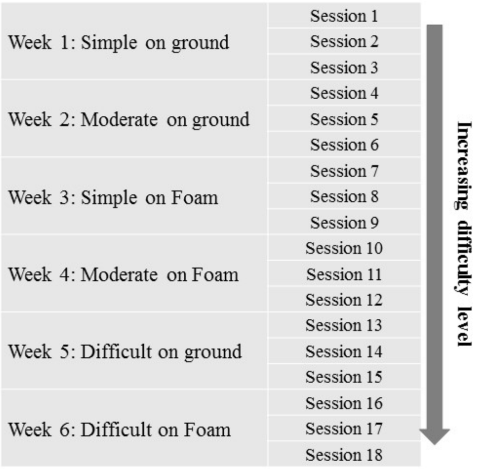
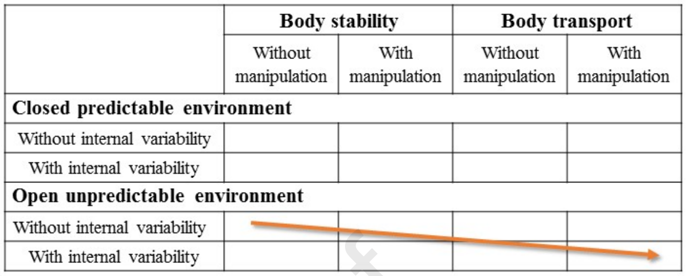


Week 1: Simple on ground	Session 1
	Session 2
	Session 3
Week 2: Moderate on ground	Session 4
	Session 5
	Session 6
Week 3: Simple on Foam	Session 7
	Session 8
	Session 9
Week 4: Moderate on Foam	Session 10
	Session 11
	Session 12
Week 5: Difficult on ground	Session 13
	Session 14
	Session 15
Week 6: Difficult on Foam	Session 16
	Session 17
	Session 18

A



	Body stability		Body transport	
	Without manipulation	With manipulation	Without manipulation	With manipulation
Closed predictable environment				
Without internal variability				
With internal variability				
Open unpredictable environment				
Without internal variability				
With internal variability				

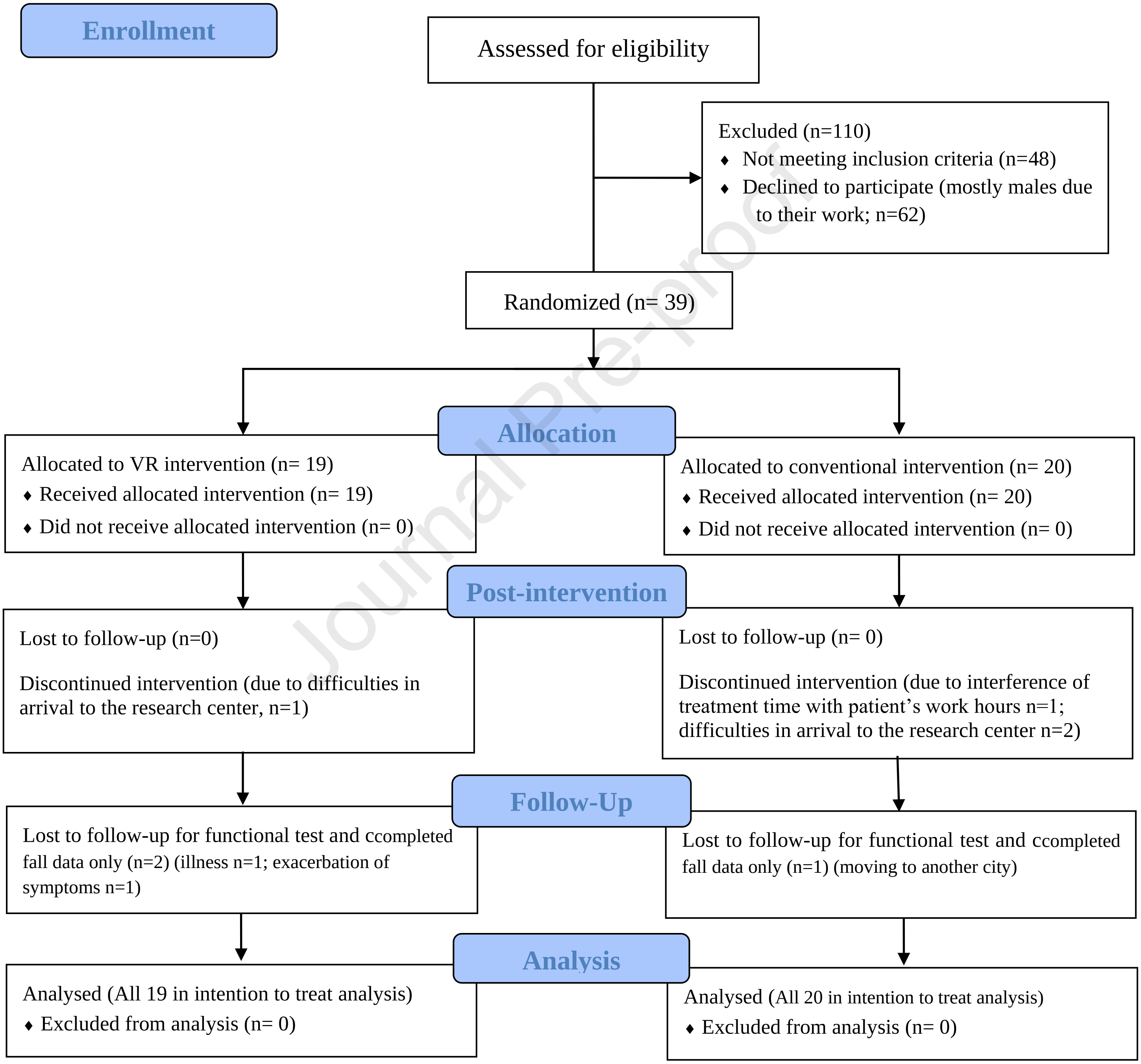
B

Journal Pre-proof

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



Assessed for eligibility

Excluded (n=110)
- Not meeting inclusion criteria (n=48)
- Declined to participate (mostly males due to their work; n=62)

Randomized (n= 39)

Allocated to VR intervention (n= 19)
- Received allocated intervention (n= 19)
- Did not receive allocated intervention (n= 0)

Allocated to conventional intervention (n= 20)
- Received allocated intervention (n= 20)
- Did not receive allocated intervention (n= 0)

Lost to follow-up (n=0)

Discontinued intervention (due to difficulties in arrival to the research center, n=1)

Lost to follow-up (n= 0)

Discontinued intervention (due to interference of treatment time with patient's work hours n=1; difficulties in arrival to the research center n=2)

Lost to follow-up for functional test and ccompleted fall data only (n=2) (illness n=1; exacerbation of symptoms n=1)

Lost to follow-up for functional test and ccompleted fall data only (n=1) (moving to another city)

Analysed (All 19 in intention to treat analysis)
- Excluded from analysis (n= 0)

Analysed (All 20 in intention to treat analysis)
- Excluded from analysis (n= 0)

Figure 2.

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Details of the Virtual reality-based exercises:

Virtual reality (VR) is an open environment in which objects around the individual are in motion; or the support surface could be unstable during exercise. In open environments, individuals need to anticipate the speed and the direction of moving objects, and predict time and pattern of postural adjustments[1].

Participants were instructed to stand in front of a screen, where the device sensor scans their body position in real time and displays it as a virtual avatar. This avatar simulates the person’s movements instantaneously on the screen. In the next step, participants got familiarized with the system and the information was given about the purpose of each exercise and how it should be performed. Three exergames, each in three difficulty levels, were considered to be performed on both ground and foam surfaces. At each session, following 5 minutes of warm-up (including 4 minutes of side stepping and 1 minute of half squatting, both with real-time VR feedback), the participants performed each category of the exercises for 10 minutes. In the first exergame, participants were asked to turn off randomly turned on virtual lights; by stepping forward, backward, to the right, or the left. In the second exercise, the participants needed to collect boxes released from the top and put them in certain places using a virtual stick. In the third exercise, the participants stocked in a virtual empty aquarium, asked to prevent the leakage inside from random breaking parts on the aquarium walls and floor, by shifting weight, reaching and stepping.

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According to motor learning principals, the rapid shifting from blocked practice to random or random-blocked practice is necessary when progressing treatment programs [1,2]. Random-block practices allow individuals to correct their errors before jumping to the next level, resulting in faster learning compared to the random exercises; and higher retention compared to blocked exercises [1–3]. Hence, all exercises in this study considered to be random-blocked.

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