VIRTUAL REALITY EXERCISE INTRADIALYSIS TO IMPROVE PHYSICAL FUNCTION: A FEASIBILITY RANDOMIZED TRIAL

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Complete List of Authors:	Segura-Ortí, Eva; Universidad Cardenal-Herrea CEU, CEU Univeristies, Physiotherapy Pérez-Domínguez, Borja; Universidad Cardenal-Herrea CEU, CEU Univeristies, Physiotherapy Ortega-Pérez de Villar, Lucía; Universidad Cardenal-Herrea CEU, CEU Univeristies, Physiotherapy Meléndez-Oliva, Erika; Universidad Cardenal-Herrea CEU, CEU Univeristies, Physiotherapy Martínez-Gramage, Javier; Universidad Cardenal-Herrea CEU, CEU Univeristies, Physiotherapy García-Maset, Rafael; Hospital de Manises, Nephrology Gil-Gómez, José; Universitat Politecnica de Valencia, Instituto Universitario de Automática e Informática Industrial

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Segura-Ortí E, Pérez-Domínguez B, Ortega-Pérez de Villar L, Meléndez-Oliva E, Martínez-Gramage J, García-Maset R, Gil-Gómez JA

1. Eva Segura-Ortí, Department of Physiotherapy, Universidad Cardenal Herrera-CEU, CEU Universities, Valencia, Spain, esegura@uchceu.es

2. Borja Pérez-Domínguez, Department of Physiotherapy, Universidad Cardenal Herrera-CEU, CEU Universities, Valencia, Spain, borjaperez91@hotmail.com

3. Lucía Ortega-Pérez de Villar, Department of Physiotherapy, Universidad Cardenal Herrera-CEU, CEU Universities, Valencia, Spain, lucia.ortega@uchceu.es

4. Erika Meléndez Oliva, Department of Physiotherapy, Universidad Cardenal Herrera-CEU, CEU Universities, Valencia, Spain, erika.melendez@uchceu.es

5. Javier Martínez Gramage, Department of Physiotherapy, Universidad Cardenal Herrera-CEU, CEU Universities, Valencia, Spain, jmg@uchceu.es

6. Rafael García Maset , Nephrology Department, Hospital de Manises, Valencia, Spain, rgarciam@hospitalmanises.es

7. José Antonio Gil Gómez, Instituto Universitario de Automática e Informática Industrial, Universitat Politècnica de València, Valencia, Spain, jgil@upv.es

Contact

Eva Segura Ortí (PhD)

Department of Physiotherapy, Universidad Cardenal Herrera-CEU, CEU Universities, Valencia, Spain

C/ Santiago Ramón y Cajal s/n, 46115 Alfara del Patriarca, Valencia (Spain)

esegura@uchceu.es

Phone number 00 34 96 1369000 Ext 64439

Fax number 00 34 96 1395972

Abstract

Objective:

The main objective of this investigation was to assess feasibility of conducting a future RCT with an intradialysis non-immersive virtual reality exercise intervention. The secondary aim was to explore the impact of either conventional or VR exercise on physical function.

Design:

Feasibility randomized trial

Participants:

18 subjects who participated in a 16 weeks intradialysis combined exercise program.

Interventions:

The program lasted 4 additional weeks of either combined exercise or virtual reality exercise.

Main outcome measures:

Physical function was measured through several reliable tests (sit to stand to sit tests 10 and 60, gait speed, one-leg heel rise tests and 6-minute walk test) at baseline, after 16 weeks of intradialysis combined exercise and by the end of 4 additional weeks of exercise. Adherence to the exercise programs was registered.

Results

There was a significant time effect, so that physical function improved in both groups. By the end of the 20 weeks, function improved as measured through the sit to stand to sit test 10 and 60, gait speed, one-leg heel rise left leg and the 6-minute walk test.

Changes that did not occur due to error in the test were seen after 20 weeks were achieved in the sit to stand to sit test 60, gait speed, one-leg heel rise test for the left leg and 6-minute walking test.

Conclusion

Virtual reality was a feasible intervention. Both interventions improved physical function. Adherence was not significantly different between groups.

Keywords: Hemodialysis; exercise; virtual reality; physical function; adherence

Introduction

Chronic kidney disease patients on hemodialysis (HD) treatment undergo a progressive and gradual deterioration regarding physical function, activity level and health-related quality of life [1,2]. Based on the actual literature, the implementation of therapeutic exercise becomes a valuable tool in order to avoid or to ameliorate this deterioration [3,4], but compliance to the exercise program is low due to several barriers and limitations, such as worries for exercise to be too difficult [5,6]. Intradialysis exercise programs achieve higher adherence rates compared to out of dialysis exercise [7], although the response rate to participate in exercise programs is low. Developing strategies to improve participation rate and compliance to exercise is an important goal.

Virtual Reality (VR) programs are widely used when treating several populations such as stroke and cerebral palsy to improve mobility, balance or walking speed [8-10]. These programs consist of performing exercise while moving in a virtually reproduced setting. The leisure component in this “game-like” programs could make VR an alternative for the implementation of exercise programs on patients undergoing hemodialysis. A pilot study of one-session VR during HD showed that the game used met the requirements of usability, acceptance and security of use [11]. Only one study has implemented VR exercise in hemodialysis patients and it was implemented out of the dialysis session [12].

The main objective of the study was to assess the feasibility of conducting a definitive trial in terms of acceptability to a VR exercise intervention during HD. The secondary aim was to explore the impact of either conventional or VR exercise on physical function.

Material and methods

Design

This study was a feasibility randomized trial. Eligible participants were enrolled into a 16-week intradialytic combined exercise program (aerobic and strengthening exercise) and were randomly allocated into 4 additional weeks continuing the same program (CG), or intradialysis Virtual Reality (VRG). The whole intervention lasted up to 20 weeks, and data were collected at baseline, and weeks 16 and 20.

Participants

Participants were recruited from the hemodialysis (HD) unit at the *hospital XXX* in XXX.

Participants were assessed by the nephrologist for eligibility. Inclusion criteria were to be on HD treatment for more than 3 months and to have a stable medical condition. Exclusion criteria were: (1) myocardial infarction within the last 6 weeks, (2) cardiovascular disease that could worsen with exercise, (3) lower limb amputation beneath the knee, (4) cerebrovascular disease, (5) muscle-skeletal or respiratory complications that might worsen with exercise and (6) inability to perform the functional tests.

Written informed consent was obtained from participants. This research was approved by the Ethical Committee from *XXXX* (registration number 2015/0193) and was registered at Clinical Trials (NCT03120611).

Timeline

All Participants performed a supervised intradialysis exercise program during 16 weeks, guided and implemented by the nursing staff of the HD unit.

After 16 weeks, participants were randomized into one of two groups (blocked randomization per age and sex using www.randomization.com). An external investigator generated the random numbers and assigned participants to each group. Allocation was concealed. During 4 additional weeks, so until week 20, one group kept exercising with the same exercise program (CG) and the other one exercised using a VR software program (VRG). From week 16 until 20, both programs were implemented by a physiotherapist specialized in therapeutic exercise. The study was undertaken from January to July 2017.

Exercise Programs

All participants were offered 3 sessions per week, the day they had dialysis treatment. In both groups the warm-up consisted of free movements of hip, knee and ankle flexion and extension.

Intradialysis combined exercise program (CG)

This program included both strengthening and aerobic exercises. Participants began with a 5-minute warm-up, then performed strengthening exercises (knee extension; plantar flexion; hip flexion, extension, abduction and adduction; elbow flexion in non-fistula arm) using basic equipment such as balls, ankle braces and elastic bands. They continued with aerobic training using a cycloergometer up to a maximum of 30 minutes, and concluded with a 5-minute stretching period.

Intradialysis Virtual Reality exercise program

Participants allocated in this group started with a 5-minute warm-up, and then engaged in a VR session up to a maximum of 30 minutes, depending on the rate of perceived exertion (RPE), that should be felt between 'somewhat hard' to 'hard' (13 to 15 out of

20). Intensity progressed by increasing the number of exercise bouts (each one lasting 3 minutes), that ranged from 1 to 10. There was 1-minute rest between bouts.

The VR intervention was carried out during dialysis. An adapted version of ACT (*A la Caza del Tesoro)* was used for the VR program. ACT is a non-immersive VR system designed with a playful scheme. For participants, the system is intradialytic VR gaming, which makes the dialysis sessions more amenable. In ACT, the subject tries to catch a series of targets (avoiding obstacles) by moving their leg. Difficulty in ACT was graduated according to the characteristics of participants, and they could change the leg during the game when they felt tired.

The general hardware set-up consisted of a standard computer, a TV (which is commonly found at the hemodialysis units), and a Ms Kinect® as a motion tracking system.

At the beginning of the session, a management tool allowed therapists to define the VR intervention for the session by adding different game-break periods and configuring their duration. The level of difficulty of the exercise was also configurable initially, and therapists could activate the adaptive difficulty that enabled the system to automatically increase or decrease the level of difficulty depending on the participant's performance.

Before their first session, each participant received instructions in the common usage of the system, and carried out a test session.

Once the program ended, participants concluded the session with another 5 minutes of gentle stretching.

Outcomes

Clinical and anthropometric characteristics were collected.

Physical function was assessed with a battery of functional tests, that were recorded at baseline, at week 16 and at week 20. These tests were performed prior to every dialysis session by trained physiotherapists who were blinded to the subjects' allocation. A previous study had developed detailed scripts for all functional tests in order to standardize the procedure [13].

Prior to the first weekly-dialysis session normal gait speed in 4 meters was measured [14]. Three tests were assessed previously to the second dialysis weekly session, The Sit-to stand tests 10 and 60 (STS-10, STS-60) are tests that assess the capacity to stand up from a chair. The STS-10 is calculated as the total time needed to complete 10 repetitions of standing up and sitting down again, and the STS-60 registers the repetitions performed in 60 seconds. The One-Leg Heel-Rise (OLHR) is a test that assesses the muscular strength of the triceps surae by counting the number of lifts the participant could do with one leg, paced by a metronome up to a maximum of 25 repetitions. Reliability of all tests is high for this cohort (ICC = 0.88 - 0.97) [15].

The 6-Minute Walk Test (6MWT) was assessed prior to the third dialysis weekly session due to the high cardiovascular demands. It registers the maximal number of meters the participant is able to walk in a 30-meter distance corridor, and it is reliable (ICC 0.94) [15].

Adherence to the different exercise programs

Adherence was defined by the number of sessions the participant performed divided by the total number of sessions offered, multiplied by 100.

Statistical Analysis

Since this was a feasibility study, a sample size calculation was not required. Nevertheless, the calculation was done based on number required for future definitive

RCT. The sample size calculation was based on detecting changes in physical function, as measured by the STS-60. Considering an alpha error of 0.05 and a statistical power of 80%, a minimum of 10 participants was required to detect an effect size of 0.45, taking into account the mean difference and standard deviation of the result by using previous published data of an exercise intervention in HD patients [13] (GPower, ANOVA: Repeated measures, within-between interaction). Future definitive studies should increase the sample size accordingly to the effect size calculated, and also due to the high attrition rate found in previous studies on exercise for HD patients.

The statistical analysis was performed according to intention-to-treat. Baseline differences between groups were tested through chi-square and U Mann Whitney tests to ensure successful randomization.

Two-way mixed ANOVA tests were used to test the study effects on the functional variables and adherence between groups, with time of the measure serving as the within-group factor (three levels) and intervention type as the between-group factor. If a main time effect was found for the ANOVA, a post-hoc analysis was performed (three comparisons, from baseline to 16 weeks, baseline to 20 weeks and 16 to 20 weeks of exercise). The data are presented as mean (SD). Results followed an *intention to treat* analysis. Statistical analyses were performed using the SPSS 23.0 for Windows (SPSS Inc, Chicago, IL). Statistical significance was set at $p<0.05$.

Results

Thirty-six HD patients that previously undertook a combined intradialysis program were offered to participate in the study. Eighteen participants were randomly allocated into VRG or CG. There was one dropout by the end of the study (Figure 1).

Baseline clinical characteristics and demographics are summarized in Table 1.

Effects of the intervention in the physical functioning test

There were no differences between groups at the beginning of the study in any of the functional measurements (Table 2).

Primary outcomes

Table 2 reports values achieved per each group at baseline, after 16 weeks of combined exercise and after 4 additional weeks of either combined exercise or virtual rehabilitation.

With regard to the STS – 60, the group per time interaction was non-significant (p=0.399). There were no significant differences between groups for any of the functional outcomes, so that the physical function improvement was equivalent for both the combined and the VR exercise groups.

Regarding adherence, for the first 16 weeks of exercise the CG attended 56.6 (19.6) % of the sessions offered, and the VRG was 60.3 (19.3) (Mann-Whitney U test, difference non-significant p=0.757). The last 4 weeks of the exercise program the adherence rate was 70.1 (32.5) vs 81.2 (16.7) %. The ANOVA analysis showed that there was no group per time interaction, so that the VR group did not achieve significant higher adherence compared to the CG. A significant time effect was found (F= 8.514, p = .010, η_p^2= 0.347), so that both groups increased adherence during the last 4 weeks of the exercise program.

Secondary outcomes

Changes from baseline to 16 weeks, baseline to 20 weeks and 16 to 20 weeks of exercise are shown in Table 2.

With regard to the STS-60, the ANOVA indicated a significant time effect (F= 5.542, p = .017, η_p^2= 0.442). The within – group analysis reported significant improvements from baseline to 16 and 20 weeks respectively.

A significant time effect was also found for the STS – 10 (F= 12.234, p = .001, η_p^2= 0.636) and gait speed (F= 26.461, p < .001, η_p^2 = 0.638). The within – group analysis reported significant improvements for all comparisons, baseline to 16 and 20 weeks, and 16 to 20 weeks of exercise (Table 2). The 6MWT (improvement from baseline to 20 weeks and from 16 to 20 weeks) and for the OLHR left leg test (improvement only from 16 to 20 weeks) also showed a significant time effect.

Discussion

The benefits of exercise interventions for physical functioning of subjects undertaking HD are well known [3,4], but to our knowledge this is the first study that implements VR exercise during HD. In this study both groups improved their physical function. In future studies, it will be important to include a control group and to power the sample to test the impact VR exercise programs on physical function or other health related outcomes.

This study shows that adherence to VR was similar to combined exercise. There is a limitation of the present feasibility study, since the groups were not virgin to exercise during dialysis which means that adherence to both interventions in the 16 to 20-week period does not reflect true clinical practice. A significant time effect was found, so that both groups increased adherence after 16 weeks of exercise. This might be due to an increase in motivation after both groups performed the battery of physical function tests at this point. Since low adherence to exercise programs for HD patients seems to be associated with the lack of achievement of important changes [4,16,17] looking for strategies to increase adherence to exercise is very important. Future studies should check if adding testing at the middle of exercise interventions could be used to increase adherence rates.

Data on Table 2 show that the high adherence rate achieved from 16 to 20 weeks of exercise was determinant to achieve changes that were not due to error in the gait speed, OLHR left leg and 6MWT. Since neither group nor group per time interaction was significant for any of the variables, it seems that adherence to exercise instead of modality of exercise is a determinant factor to achieve an improvement in this cohort.

It was found that the STS-60 improved significantly over time from baseline to 16 and 20 weeks, above the minimal detectable change, 90% confidence interval (MDC_{90}) for the STS-60 (4 repetitions) [15]. The MDC_{90} is defined as the amount of change in a measurement necessary to conclude that the difference is not attributable to error. Ten out of 17 participants showed an important change by the end of the program, two more than by the end of 16 exercise weeks, distributed equally in both groups. One previous study showed a significant mean increase of more than 5 repetitions on the STS-60 after 3 months of cycling out of the dialysis treatment [18], and another study of combined exercise during dialysis also found a significant improvement [19].

STS – 10 results improved from baseline to 20 weeks that was close to achieve a MDC_{90} of 8.4 seconds [15], and 3 VR plus 4 CG participants achieved this change. These results are in agreement with previous studies that reported improvements in the STS-10 that ranged from 2.5 to 5.75 seconds [20-24]. The fact that the STS-10 showed a significant change from baseline to 16 weeks of exercise confirms that the STS-10 is a sensitive test. We also tested the STS-5 and results showed an improvement over time only after 20 weeks of exercise with values that were far to achieve the MDC_{90} previously calculated of 5.8 seconds [13]. A previous study showed a significant improvement in the STS-5 after a cycling program out of the dialysis treatment, but it did not reach the MDC_{90} [18]. Another study on intradialysis resistance training did not find a significant effect [25]. We conclude that STS-10 has higher responsiveness to change than STS-5, and so we would recommend to use 10 repetitions instead of 5 as a functional test that measures the ability to stand up from a chair.

Gait speed increased between baseline and 20 weeks above the MDC_{90} calculated for this population (0.26 m/s) [13], so that 11 out of 17 participants from both groups increased gait speed above this value. A previous study found an increase in normal gait speed of 0.12 m/s after a home based program with high adherence rates [26]. Another study that implemented a combined exercise program in CKD patients stages 3 to 4 also found an increase of 0.28m/s in gait speed after a 12-week intervention [27]. In our study we found no differences between groups. Previous research concluded that substituting a standard rehabilitation regimen with VR based rehabilitation elicits greater benefits in walking speed in stroke [8], healthy population [28], cerebral palsy [10] and multiple sclerosis [9]. Interventions that result in gait speed improvement are important since gait speed is essential for active life style participation [28].

The 6MWT results showed a significant improvement between baseline and 20 weeks that achieved the MDC_{90} (66.3m), and was seen in 10 out of 18 participants (6 VRG and 4 CG). The increase in walked distance is above the results published in exercise during dialysis [29-31] and home-based programs [32,33]. The high motivation of the sample could help to gain better results than previous studies. We infer they are highly motivated since they kept exercising 4 more weeks, while other counterparts were not willing to participate.

The MDC_{90} for the left triceps surae strength was set at 5.2 repetitions [15]. We observed mean increases in repetitions above the MDC_{90} from 16 to 20 weeks. This test was performed only by 11 participants, and in both legs 3 of them presented a ceiling effect (25 repetitions in all measurements) and 5 of them reached the MDC_{90} (4 VRG and 1 CG). Future studies could consider not to stop the test at 25 repetitions, but to achieve as many repetitions as possible, and to measure only the left leg since results from both legs for each subject were very similar and MDC for left side is higher.

Equipment to implement VR exercise include a TV, a camera and a computer. Since most of HD units have TV, the cost is around 500 euros, and each equipment could be used by 3 participants per HD shift. We have developed a game, but as a clinical routine more games should be developed so that the participant can make his own choices and keep the fun.

Study limitations

The sample is small and may not be representative since their motivation to exercise was high. Subjects were part of a group of 36 subjects that had implemented previously 16 weeks of combined exercise intradialysis [34], and it is unknown how much of confounding variable this is in the improvements observed since it could still be a result of the 16 weeks program. The VR intervention was short and was not compared to a control intervention. While the first 16 weeks were monitored by nursing staff of the unit, the last 4 weeks were monitored by a physical therapist, what could explain the increased adherence rate for both groups.

Conclusions

Intradialysis VR is a feasible intervention and it improves physical function in HD patients. The results of the present study support the idea that adherence to exercise is more important than exercise modality to achieve significant changes in physical function of CKD patients undergoing HD.

Perspectives

Exercise in subjects undertaking hemodialysis is recognized as medicine since it improves function and health-related quality of life [35]. Nevertheless, exercise during hemodialysis is not commonly implemented as a clinical routine and adherence to exercise is poor. Our data suggest that non immersive virtual reality exercise is as effective as conventional exercise to improve physical function. The results of the present study are preliminary because the program lasted only 4 weeks and the sample was a highly motivated group that had already performed 16 weeks of exercise intradialysis. However, we believe that the study provides evidence of the positive effects of virtual reality intradialysis.

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Table 1. Baseline clinical characteristics and demographics

Variable	Combined Exercise Group (n=9)	Virtual Reality Exercise Group (n=9)
Age (years)		
Mean (SD)	61.8 (13.0)	68.3 (15.6)
Median (min-max)	59 (46-81)	70 (39-90)
Time on HD (months)		
Median (min-max)	22 (19-78)	35 (10-86)
Sex n (%)		
Male	5(55.6)	6 (67)
Female	4 (44.4)	3 (33)
Weight, (kg)		
Mean (SD)	68.4 (12.2)	76.3 (16.4)
Median (min-max)	67.2 (53.6-84.5)	71.2 (57.8-108.2)
Height, (cm)		
Mean (SD)	165.4 (9.6)	163.4 (11.4)
Median (min-max)	164.5 (149-178)	162.0 (149-188)
Body Mass Index (kg/m^2)		
Mean (SD)	25.4 (3.8)	28.6 (5.5)
Median (min-max)	26.7 (19.2-30.6)	30.0 (23.0-40.4)
Albumin (mg/dL)		
Mean (SD)	3.9 (0.3)	3.9 (0.3)
Median (min-max)	3.8 (3.6-4.3)	3.9 (3.5-4.5)
Creatinine (mg/dL)		
Mean (SD)	7.5 (1.8)	7.2 (1.6)
Median (min-max)	8.2 (5.0-9.9)	7.5 (5.3-9.5)
Hemoglobin (g/dL)		
Mean (SD)	11.9 (1.2)	11.4 (0.9)
Median (min-max)	12.1 (0.9)	11.9 (0.6)
Diagnosis CKD		
Diabetes Mellitus	2	1
Glomerulonephritis	0	1
Lupus	1	0
Polycystosis	1	0
Others	5	7
Diabetes		
No	6	3
Type I	1	2
Type II	2	4
Smoking habit		
No	5	6
Yes	4	3
Charlson’s Commorbidity		
Mean (SD)	5.1 (2.8)	6.0 (1.7)
Median (min-max)	4 (2-10)	6 (2-8)

(CKD) Chronic Kidney Disease; (min) Minimum; (max) Maximum; (SD) Standard Deviation

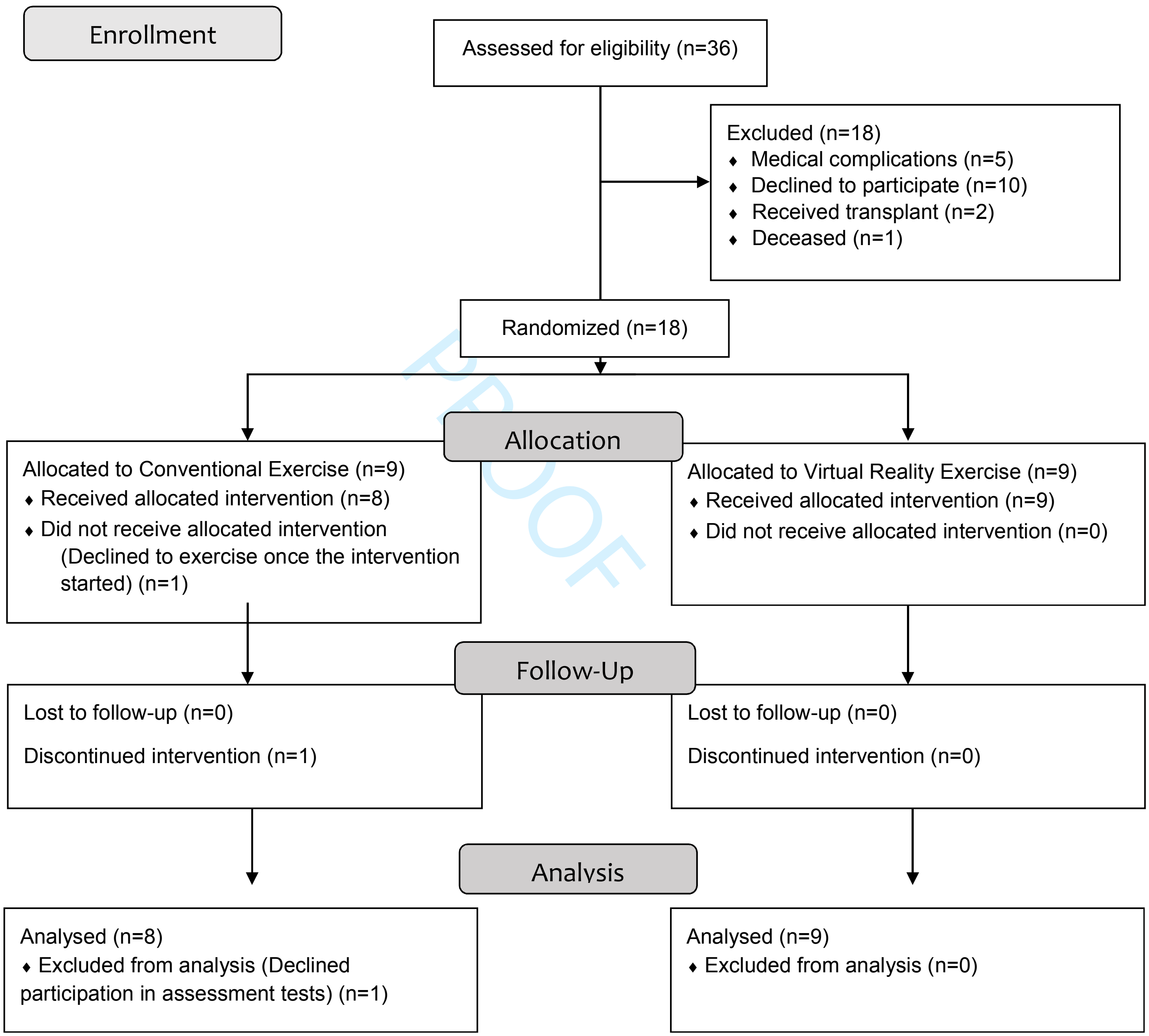
Table 2. ANOVA significance for the physical function tests, combined exercise group versus virtual reality group

Variable	Group	Mean (SD)			Mean differences (95% CI); Baseline-16 weeks	Mean differences (95% CI);Baseline-20 weeks	Mean differences (95% CI); 16-20 weeks
		Baseline	16 weeks	20 weeks			
STS-10 (seconds)	CG	27.6 (9.0)	22.8 (7.6)	19.5 (5.5)	4.8 (0.0 – 9.5)**	8.1 (2.3 – 13.9)**	3.3 (0.3 – 6.3)**
Mean (SD)	VRG	29.5 (15.0)	25.5 (17.3)	22.8 (17.2)	4.0 (-0.5- 8.4)	6.7 (1.2- 12.2)	2.7 (-0.1- 5.5)
STS-5 (seconds)	CG	12.4 (2.8)	11.8 (3.2)	9.7 (2.7)	0.6 (-2.4- 3.5)	2.7 (0.5- 5.0)**	2.2 (0.5- 3.8)**
Mean (SD)	VRG	14.4 (7.5)	13.2 (10.0)	11.6 (9.3)	1.2 (-1,5- 4.0)	2.9 (0.8- 5.0)	1.6 (0.1-3.2)
Gait Speed (m/s)	CG	0.96 (0.12)	1.12 (0,23)	1.29 (0.32)	0.17 (0.00– 0.35)**	0.34 (0.13– 0.55)†	0.17 (0.00– 0.34)**
Mean (SD)	VRG	1.03 (0.40)	1.18 (0.41)	1.38 (0.46)	0.15 (-0.01- 0.32)	0.35 (0.15- 0.54)	0.19 (0.03- 0.35)
STS-60 (repetitions)	CG	22.0 (7.7)	26.1 (9.8)	29.0 (10.2)	4.1 (-1.3 – 9.6)*	7.0 (0.2 – 13.8)*	2.9 (-0.7 – 6.4)
Mean (SD)	VRG	23.9 (13.3)	28.4 (13.5)	28.8 (11.8)	4.6 (-0.6- 9.7)	4.9 (-1.5- 11.3)	0.3 (-3.0- 3.7)
OLHR D (repetitions)	CG	16.2 (12.1)	17.6 (6.9)	23.6 (3.1)	1.4 (-11.7– 14.5)	7.4 (-8.0 – 22.8)	6.0 (-1.9 – 13.9)
Mean (SD)	VRG	14.5 (11.1)	19.2 (7.4)	22.8 (5.3)	4.7 (-7.3- 16.7)	8.3 (-5.7- 22.4)	3.7 (-3.5- 10.9)
OLHR I (repetitions)	CG	20.6 (7.4)	15.6 (9.0)	23.0 (4.5)	-5.0 (-15.7– 5.7)	2.4 (-10.1 – 14.9)	7.4 (-1.1 – 15.9)*
Mean (SD)	VRG	13.3 (10.6)	17.2 (6.4)	23.5 (3.7)	3.8 (-5.9- 13.6)	10.2 (-1.2- 21.6)	6.3 (-1.4- 14.1)
6MWT (meters)	CG	382.0 (79.8)	395.6 (95.5)	454.3 (42.3)	13.6 (-35.0 – 62.3)	72.3 (24.4 – 120.1) †	58.6 (13.0 – 104.2)**
Mean (SD)	VRG	369.7 (121.4)	413.9 (127.9)	454.6 (118.7)	44.2 (-1.7- 90.1)	84.9 (39.7- 130.0)	40.7 (-2.3- 83.7)
Adherence (%)	CG	-	60.3 (19.3)	81.2 (16.7)			13.6 (-4.1 – 31.3)*
Mean (SD)	VRG	-	56.6 (19.6)	70.1 (32.5)			20.9 (3.2- 38.6)

†p<0.001; ** p<0.01; *p<0.05 Overall time effect for both groups. No group per time interaction effect was found.

(CG) Combined exercise group; (L) Left; (OLHR) One Leg Heel Rise; (OLST) One-Leg Standing Test; (R) Right; (SPPB) Short Performance Physical Battery; (STS) Sit to stand to sit; (VRG) Virtual Reality exercise group; (6MWT) 6-Minute Walk Test

Figure 1. Flow Diagram Combined Exercise VS. Virtual Reality



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