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ORIGINAL ARTICLE

An intradialytic non-immersive virtual reality exercise programme: a crossover randomized controlled trial

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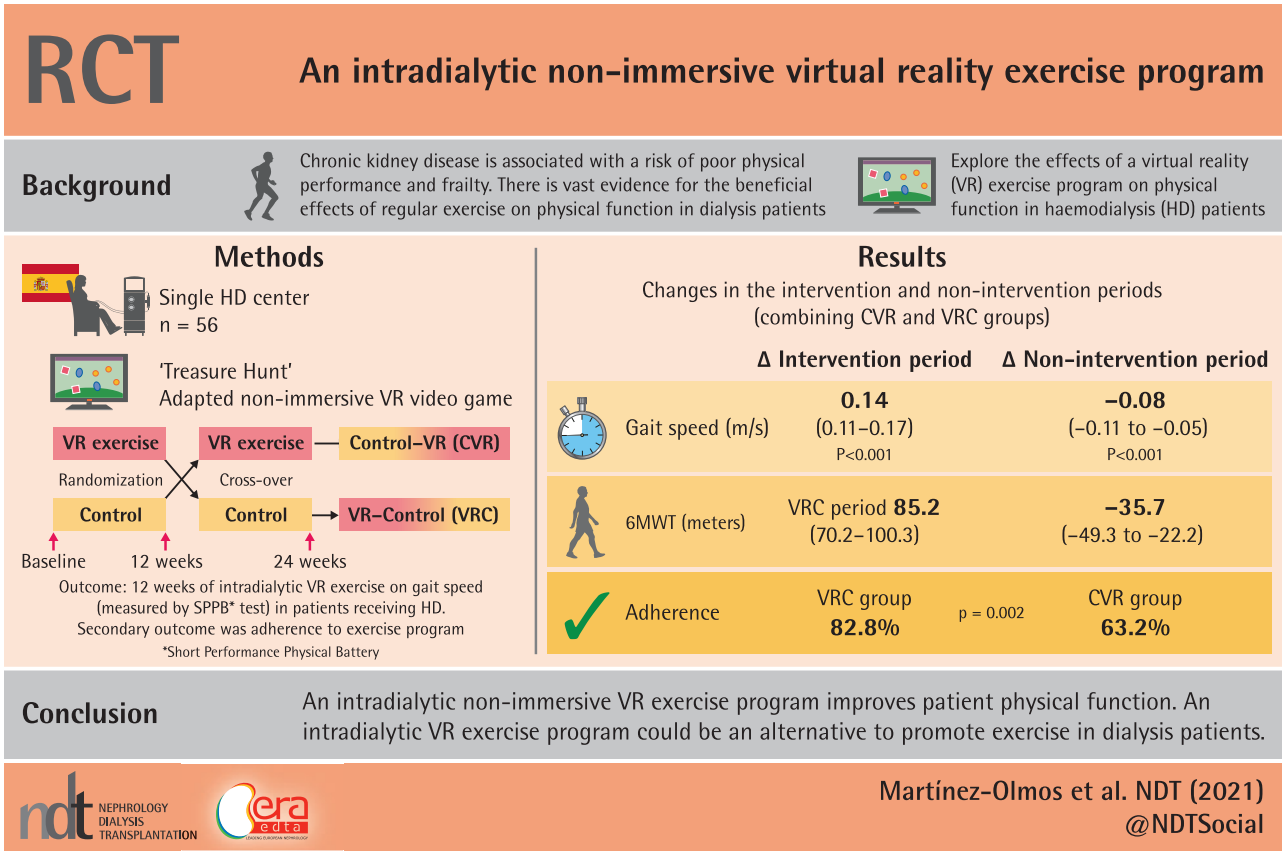
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What is already known about this subject?

- The present intradialytic virtual reality (VR) programme had a significant impact on physical function, which is of great importance in this cohort.

What this study adds?

- An intradialytic VR exercise programme could be an alternative to promote exercise in this population in video game format.

What impact this may have on practice or policy?

- An intradialytic VR exercise programme is an easy modality of intradialytic exercise that increases the chances of clinical applicability when the unit does not count on the expertise of a physiotherapist.

ABSTRACT

Background. Chronic kidney disease is closely related to a high risk of death and disability, poor physical performance and frailty. The main objective of this research was to analyse how intradialytic administration of a non-immersive virtual reality (VR) exercise programme would affect physical function and adherence to exercise in these patients.

Methods. A total of 56 individuals participated in two 12-week periods in a crossover randomized controlled trial. Each patient underwent a functional capacity evaluation before and after each study period. The functional tests administered included the 4-m gait speed test, Short Physical Performance Battery (SPPB), timed up-and-go (TUG) test, one-legged stance test (OLST) for balance, sit-to-stand 10 (STS-10) and sit-to-stand 60 (STS-60) tests and 6-min walking test (6MWT). Adherence to the exercise programme was also recorded. To assess the effect of VR exercise on the functional test outcomes over time, the patients were analysed using a two-way repeated-measures analysis of variance with time and treatment as the within-participant factors.

Results. By the end of the 12 weeks of exercise, compared with the control period, 33 participants showed significant change in physical function as measured through the 4-m gait speed test (0.14 m/s), SPPB (1.2 points), TUG (−1.7 s), OLST (7.1 s), STS-10 (−5.8 s), STS-60 (5 repetitions) and 6MWT (85.2 m), with adherence rates exceeding 70%. There were no changes in the biochemical data or in the medications in the period of the study.

Conclusion. An intradialytic non-immersive VR exercise programme improves patient physical function.

Keywords: adherence, exercise, haemodialysis, physical function, virtual reality

INTRODUCTION

Chronic kidney disease (CKD) is associated with a high risk of death and disability, poor physical performance and frailty. The latter is an especially common problem among dialysis patients and evidence on the beneficial effects of regular exercise on physical function is overwhelming [1, 2].Gait speed is an important measure of physical function because it is strongly associated with the enjoyment of an active lifestyle, lifelong brain health and survival in older adults [3–5]. In previous work, physical function and muscle power and strength were all found to improve in patients on haemodialysis (HD) after engaging in resistance training [6].

However, despite the effectiveness reported in these previous studies, exercise intervention programmes have not yet been firmly established as a useful clinical intervention for patients on HD. Some of the reasons these patients give for not engaging in exercise include a lack of motivation, tiredness after HD sessions and an unexplained fear of exercise [7–10]. Although patient-related exercise barriers are important, barriers related to the health system and dialysis provider resources are equally significant, for example in terms of cost, staff, equipment, time, expertise, space and safety considerations [11–13].

The use of virtual reality (VR) in clinical practice has become more popular in recent years to increase the amount of physical activity patients perform and to overcome some of patients' complaints about exercise programmes [14]. Moreover, the variety of non-immersive VR systems developed by the entertainment industry for home use has made this technology less costly and more accessible for use in potential rehabilitation interventions [15]. VR has been used to improve mobility, balance and walking speed in several populations suffering from different diseases, including patients on HD, with Parkinson's disease, or affected by stroke or cerebral palsy [8, 16–18].

Our group previously published a feasibility study that also used non-immersive VR to help HD patients perform exercises over a period of 4 weeks after first having performed a 16-week combined intradialytic exercise programme [18]. This present study explores whether these earlier positive results could be confirmed in a larger sample over a longer period. This non-immersive VR intervention was very easy to apply at the clinical level since it did not require the use of VR glasses; it required

the participants to interact with a computer through a camera, which translated their lower-limb movements into corresponding movements on the screen [19, 20].

The primary aim of this study was to assess if completing 12 weeks of intradialytic VR exercise improved gait speed in patients receiving HD. The secondary aim was to assess the impact of the VR programme on other functional measurements as well as on adherence to the intervention.

MATERIALS AND METHODS

This was a randomized, crossover, controlled trial. Eligible participants were randomly allocated either into a group that received the VR intervention for 12 weeks followed by the control treatment for 12 weeks, 'VR–control' (VRC), or vice versa, 'control–VR' (CVR) (Figure 1).

Participants were assessed for eligibility and were recruited from the HD unit at 'Hospital de Manises' in Valencia (Spain). Patients receiving HD treatment for more than 3 months and with a stable medical condition were included. The exclusion criteria were (i) myocardial infarction (in the 6 weeks prior), (ii) amputation of a lower limb below the knee, (iii) cerebrovascular disease, (iv) patients suffering from chronic cardiac or respiratory diseases that presented chest pain, dyspnoea or others after exertion and (v) inability to perform the functional tests.

All the participants gave their written informed consent to participate in the study, which was approved by the Ethics Committee at 'Hospital Universitario y Politécnico la Fe' (registration number 2017/0638). This study was registered at www.clinicaltrials.gov (NCT03456414) and conformed to the CONSORT (Consolidated Standards of Reporting Trials) guidelines for randomized controlled trials (RCTs). The study was undertaken from April to September 2018.

All the participants performed a physiotherapist-supervised intradialytic VR exercise programme for 12 weeks. The patients were randomized into the CVR or VRC group based on their age and sex by blocked randomization using www.randomization.com. An external investigator generated the random numbers and assigned participants to each group. Allocation was concealed from all the research group staff members involved at every stage of the study, as well as the outcome assessors and data analysts. However, the physiotherapists administering the interventions could not be blinded to each patient's allocated study arm.

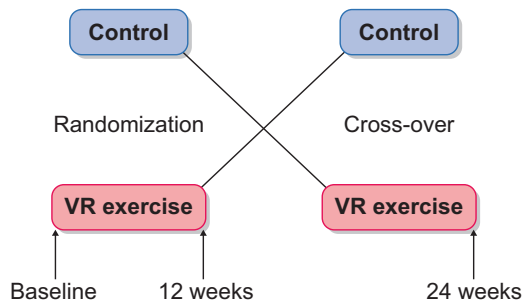


FIGURE 1: Study design. VR: Virtual Reality.

During the 12-week exercise period, all the participants were offered three VR sessions per week, on the day they received their dialysis treatment, during the first 2 h of the dialysis session with standard monitoring of blood pressure and heart rate. The warm-up and cool-down consisted of free hip, knee and ankle flexion and extension movements for 5 min before and after the VR exercise programme. Participants engaged in VR sessions lasting a maximum of 40 min, depending on their reported rate of perceived exertion (RPE), which ideally fell between 'somewhat hard' to 'hard' (12–15 out of 20 on the RPE scale). The intensity of the exercises was increased as the patients progressed by increasing the number of exercise sets (each lasting 3–6 min) and ranged from one to six sets, with 1-min rest intervals between them.

The intradialytic exercise formed part of an adapted non-immersive VR video game called 'Treasure Hunt' in which the participant must try to catch targets and avoid obstacles by moving their lower limbs (hip flexion, abduction and adduction, and knee flexion and extension) [20]. The difficulty level of the game graduated according to the characteristics of each player and the patients were able to change the leg they used during the game when they felt tired [18]. The general hardware set-up comprised affordable and simple equipment (Figure 2), a standard computer, a TV (which most HD units already have) and a Microsoft Kinect® as a motion tracking system.

The administering physiotherapist defined the VR intervention at the beginning of each session, via a management tool that allowed them to easily add in-game break periods and configure their duration. The physiotherapist also set up the initial exercise difficulty levels and could activate the adaptive difficulty feature, which allowed the system to automatically increase or decrease the level of difficulty of the game, depending on the participant's performance. Before their first session, each patient received basic instructions on the use of the system and completed a test session. Moreover, this system had already been demonstrated as suitable for this cohort through a 'Suitability Evaluation Questionnaire' [21].

A detailed description of the functional tests is available in a previously published study [22]. Gait speed was measured by using the Short Physical Performance Battery (SPPB), which

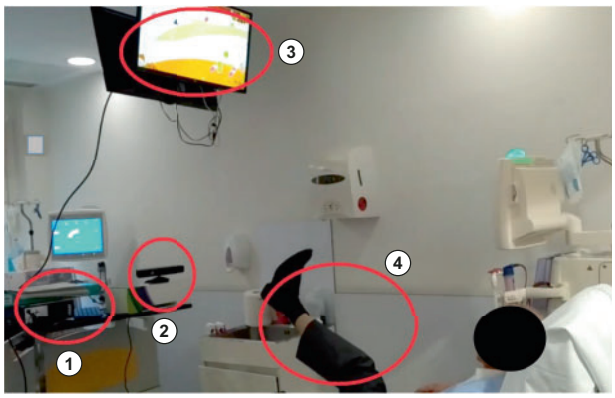


FIGURE 2: A computer connected to a camera. TV: Television.

has also been extensively reported upon elsewhere [23]. Furthermore, these tests were used in a previous multicentric study that assessed the relative and absolute test–retest reliability in CKD patients [24]. The sit-to-stand 10 (STS-10), sit-to-stand 60 (STS-60) and 6-min walking test (6MWT) were previously used to calculate the minimal detectable change (MDC) scores in people undergoing HD [25].

The SPPB was performed prior to the first weekly dialysis session. Before the second weekly dialysis session, the STS-10 and STS-60 tests were carried out to assess the participant's capacity to stand up from a chair. The reliability of these tests was high for this cohort with an intraclass correlation coefficient (ICC) of 0.88–0.97 [25]. Because of its high cardiovascular demands, the 6MWT was assessed prior to the third weekly dialysis session. This test registered the longest distance (in metres) the patient could walk up and down along 30-m corridor, and had an ICC of 0.94 [25].

Clinical and anthropometric characteristics and physical function were assessed at baseline, 12 weeks and 24 weeks. The tests were performed prior to a programmed dialysis session by trained physiotherapists who were blinded to the individuals' allocation. In a previous study, we developed detailed scripts for all the functional tests in order to standardize this procedure [22]. Each physiotherapist had specific assigned patients, so that each of them assessed always the same patients. Adherence was defined as the percentage of sessions the participant performed from the total number of sessions offered.

The sample size was calculated based on our ability to detect changes in physical function, as measured by the gait speed test. We considered an alpha error of 0.05, a statistical power of 90% and the mean difference and standard deviation (SD) of the result from previously published work [18], and used G*Power software to calculate that a minimum of 16 participants would be required to detect an effect size of 0.459 [by repeated measures analysis of variance (ANOVA) with within-between interactions]. The expected patient attrition rate was 30%, and so at least 11 patients would be required per group.

Baseline differences between the groups were tested using chi-squared and Mann–Whitney *U*-tests to ensure successful randomization. The carryover effect was checked using a *t*-test by adding the scores measured in the CVR and VRC sequence groups compared across the two groups. To assess the effect of VR exercise on the functional tests over time, we used two-way repeated-measures ANOVA with time (baseline and after 12 weeks of exercise) and treatment (VR exercise versus control) as within-participant factors. The sequence in which the VR exercise period was competed (CVR versus VRC) was considered a between-participant factor [26].

The data are presented as the mean ± SD and all the statistical analyses were performed using SPSS software for Windows (version 24.0; IBM Corp., Armonk, NY, USA) with the cut-off for statistical significance set at $P \leq 0.05$.

RESULTS

A total of 56 patients on HD were enrolled and randomized into the CVR and VRC groups, with crossover treatment starting after 12 weeks. The median participant age was 68.9 years in the VRC group and 69.5 years in the CVR group, and there were 17 men and 11 women per group; these baseline clinical characteristics and demographics of this population are summarized in Table 1. The biochemical data and the medications are described in Tables 2 and 3, and there were no changes during the period of the study.

As shown in Figure 3, some participants dropped out of the study at different times; by the end of the study, a total of 33 patients had been analysed. However, because of the blocked random allocation, there were no significant differences between the groups at the beginning of the study and those that finally completed the whole study in terms of the functional test results.

Table 4 shows the average physical function test results for the baseline, 12-week and 24-week examinations in the CVR and VRC groups. It also shows the changes achieved during the intervention period based on the difference between the 12-week and baseline examinations for the VRC group and the difference between the examinations of the CVR group at 24-weeks and 12-weeks. Finally, it shows the results for the

Table 1. Baseline clinical characteristics and demographics

Variable	CVR ($n = 28$)	VRC ($n = 28$)
Age (years)		
Mean (SD)	66.5 (14.8)	68 (13.5)
Median (min–max)	69.5 (31.7–86.4)	68.9 (31.6–90.8)
Time on HD (years)	4.9	4.4
Median (min–max)	4 (0.3–15.9)	3.7 (0.7–18.6)
Sex, *n* (%)		
Male	17 (60.7)	17 (60.7)
Female	11 (39.3)	11 (39.3)
Weight (kg)		
Mean (SD)	72.5 (16.3)	68.5 (13.54)
Median (min–max)	70.2 (49.2–108.6)	63.6 (50.8–104.5)
Height (cm)		
Mean (SD)	164.1 (10.7)	160.5 (9.5)
Median (min–max)	164 (143–178)	160.3 (144–178)
Body mass index (kg/m^2)		
Mean (SD)	27.09 (6.31)	26.88 (6.24)
Median (min–max)	25.72 (17.84–41.41)	25.1 (16.97–40.99)
Albumin (mg/dL)		
Mean (SD)	3.76 (0.37)	3.83 (0.27)
Median (min–max)	3.80 (2.90–4.30)	3.80 (3.30–4.30)
Haemoglobin (g/dL)		
Mean (SD)	11.02 (1.16)	11.86 (1.58)
Median (min–max)	11.10 (8.50–13.00)	11.80 (9.30–16.40)
Diagnosis CKD, *n*		
Diabetes mellitus	6	4
Glomerulonephritis	8	6
Polycystosis	2	3
Others	12	15
Diabetes, *n*		
No	15	18
Type I	10	8
Type II	3	2
Smoking habit, *n*		
No	20	18
Yes	8	10
Charlson's comorbidity		
Mean (SD)	6.83 (3.10)	6.35 (2.81)
Median (min–max)	7.00 (1.00–12.00)	6.00 (2.00–12.00)

min, minimum; max, maximum.

Table 2. Biochemical data of HD session

Haemodialysis session	Pre-intervention ($n = 33$) Patients (%)	Post-intervention ($n = 33$) Patients (%)	P-value
Arteriovenous fistula	29 (87.9)	29 (87.9)	1.000
High-flow HD	20 (60.6)	20 (60.6)	1.000
Online haemodiafiltration	11 (33.3)	11 (33.3)	1.000
Low-flow HD	2 (6.1)	2 (6.1)	1.000
	Dose mean (SD)	Dose mean (SD)	
Session duration (min)	233.5 (12.0)	233.2 (9.5)	0.763
Blood flow (mL/min)	379.7 (20.9)	378.5 (20.1)	0.640
Dialysate flow (mL/min)	580.8 (64.2)	584.2 (63.1)	0.182
Kt/V sp	1.80 (0.16)	1.81 (0.17)	0.625

P-value is the difference between baseline and the end of the intervention.

Table 3. Biochemistry data of haemodialysis patients

Medications	Pre-intervention ($n = 33$) Patients (%)	Post-intervention ($n = 33$) Patients (%)	P-value
Folic acid supplements	17 (51.5)	15 (45.5)	0.423
Potassium binders	6 (18.2)	6 (18.2)	1.000
Phosphorus binders	24 (72.7)	24 (72.7)	1.000
Insulin	12 (36.4)	12 (36.4)	1.000
Statins	20 (60.6)	19 (57.6)	0.325
Calcium antagonists	13 (39.4)	16 (48.5)	0.083
ACEI/ARA2	10 (30.3)	9 (27.3)	0.325
Furosemide	11 (33.3)	13 (39.4)	0.160
Vitamin D supplements	17 (51.5)	17 (51.5)	1.000
Beta-blockers	15 (45.5)	15 (45.5)	1.000
Doxazosin	10 (30.3)	10 (30.3)	1.000
Antiaggregants (acetyl salicylic/ clopidogrel)	17 (51.5)	17 (51.5)	1.000
Anticoagulants (acenocoumarol or LMWH)	10 (30.3)	10 (30.3)	1.000
Proton-pump inhibitor	21 (63.6)	21 (63.6)	1.000
Psychopharmaceuticals	13 (39.4)	13 (39.4)	1.000
Analgesics	10 (30.3)	10 (30.3)	1.000
	Mean dose (SD)	Mean dose (SD)	
Epoetine alfa or equivalent dose (U)/week	6181.8 (4857.0)	6439.4 (7305.6)	0.782
Cinacalcet (mg)/week	95.0 (157.1)	93.2 (153.7)	0.851
Iron sucrose (mg)/month	151.5 (182.2)	165.9 (160.9)	0.595
Paricalcitol (μg)/week	2.9 (3.1)	2.9 (3.3)	0.934

P-value is the difference between baseline and the end of the intervention; ACEI/ARA2, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists; LMWH, low molecular weight heparin and U, international unit.

non-intervened period as the difference at 12-weeks compared with the baseline examinations in the CVR group and between the 24-week and 12-week tests in the VRC group. Repeated-measures ANOVA was performed for gait speed and revealed a significant time by treatment interaction ($F = 59.70$, $P < 0.001$, partial $\eta^2 = 0.658$). The main effect of treatment was an increase in gait speed (by 0.14 m/s) after the VR exercise programme after 12 weeks compared with baseline as well as a significant decrease after the control period.

In terms of overall adherence, the study participants attended 74.4% (19.1 sessions) of all the sessions offered; the VRC group attended 82.8% (16.2) of the sessions offered, while the CVR group attended 63.2% (17.0) of these sessions ($P = 0.002$).

Our results also showed a statistically significant time by treatment interaction for the SPPB, timed up-and-go (TUG), one-legged stance test (OLST), STS-5, STS-10, STS-60 and 6MWT, as shown in Table 4. After the VR exercise programme, the results for SPPB improved by 1.2 points ($F = 24.03$, $P < 0.001$, partial $\eta^2 = 0.437$), while there was a significant decrease after the control period. Similarly, the results for the TUG decreased by −1.70 s ($F = 24.76$, $P < 0.001$, partial $\eta^2 = 0.444$) and significantly decreased after the control period. The OLST results improved by 7.1 s ($F = 29.51$, $P < 0.001$, partial $\eta^2 = 0.552$) and there was a significant decrease after the control period.

The time taken to perform the STS-5 and STS-10 tests decreased by −2.6 and −5.8 s, respectively, representing significant improvements in both cases ($F = 35.30$, $P < 0.001$, partial $\eta^2 = 0.558$ and $F = 70.77$, $P < 0.001$, partial $\eta^2 = 0.717$), with a significant decrease in both these results after the control period. The STS-60 results also improved by 5 repetitions

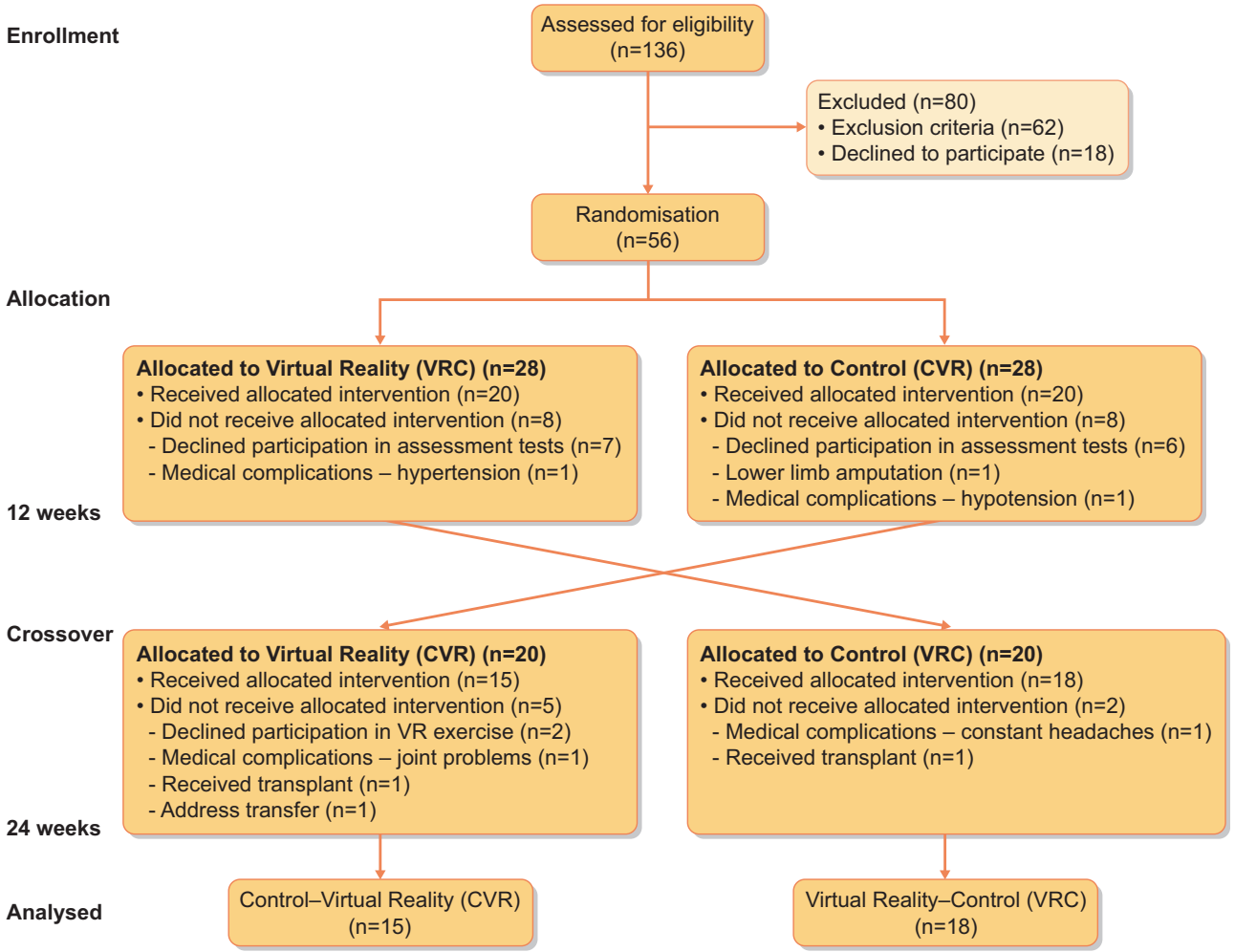


FIGURE 3: CONSORT Flow Diagram Virtual Reality. CVR: Control Virtual Reality VRC: Virtual Reality Control.

($F = 121.93$, $P < 0.001$, partial $\eta^2 = 0.808$), with a significant decrease in this metric recorded after the control period. Finally, the 6MWT results improved ($F = 89.03$, $P < 0.001$, partial $\eta^2 = 0.742$) by 85.2 m over the baseline values and also significantly decreased after the control period.

There were no adverse events during the HD sessions related to the VR programme.

DISCUSSION

This study shows, for the first time, that a 12-week VR exercise programme administered to patients with CKD during their dialysis treatment positively impacted their physical function. The length of the present study is longer (12 versus 4 weeks) and the sample size was larger (33 versus 18 participants) than used in our previous feasibility study [18]. Similar to the results obtained in this current work, our previous study showed that a VR-based programme performed for 4 weeks was beneficial in this population compared with a conventional intradialytic exercise programme. These present results also concur with previous studies, which indicated that conventional exercise improved physical function in HD patients [10, 27]. In the current work, all the tests we performed showed the same pattern of improvement after completing the VR exercise programme for 12 weeks. Thus, all of our results suggest that use of non-immersive VR as an exercise modality can help patients undergoing HD to achieve better function.

It is especially important to integrate exercise engagement into the clinical routine of HD units so that their users can continuously enjoy its benefits. Based on our work, we believe that non-immersive VR could easily be applied in clinical routines to achieve this goal, because its implementation does not require deep knowledge of exercise physiology. The non-immersive VR exercise programme we tested in this present study only requires a computer connected to a camera that captures the participant's movements (Figure 2). Compared with previous aerobic and/or strengthening exercise implemented by our group [28, 29], we found that this system was feasible for application in HD units by staff, including nurses, without any exercise implementation skills, and the use of this system is not time-consuming or expensive.

Additionally, although the materials are shared by patients on HD, using the system does not require interpersonal contact and so, potential contamination will be minimal, meaning that its use in the current context of the COVID-19 pandemic remains feasible. We believe that it is critically important to

Table 4. Average physical function tests for the baseline, 12-weeks and 24-weeks examinations in group CVR and VRC

Variable	Group	*N*	Mean (SD)			Changes		Intervention period difference (95% CI)	Non-intervention period difference (95% CI)
			Baseline	12 weeks	24 weeks	Intervention period	Non-intervention period		
Gait speed (m/s)	CVR	15	0.97 (0.33)	0.95 (0.29)	1.07 (0.33)	0.12 (0.07)	−0.03 (0.08)	0.14 (0.11–0.17)***	−0.08 (−0.11 to −0.05)***
	VRC	18	0.96 (0.38)	1.13 (0.41)	0.99 (0.37)	0.16 (0.10)	−0.13 (0.09)		
SPPB (points)	CVR	15	9.4 (3.0)	9.6 (3.1)	10.6 (2.5)	0.9 (1.0)	0.3 (0.8)	1.2 (0.8–1.6)***	−0.7 (−1.1 to −0.2)**
	VRC	18	8.4 (3.3)	10.0 (3.0)	8.4 (3.1)	1.6 (1.3)	−1.7 (1.6)		
TUG (s)	CVR	15	11.57 (7.60)	11.56 (7.77)	9.59 (5.61)	−1.59 (2.98)	−0.02 (0.94)	−1.70 (−2.49 to −0.92)***	0.64 (0.17–1.11)**
	VRC	18	12.35 (8.12)	10.54 (7.14)	11.82 (7.92)	−1.81 (1.21)	1.30 (1.57)		
OLST (s)	CVR	12	16.22 (12.11)	13.59 (12.53)	21.69 (12.19)	8.1 (7.4)	−2.6 (6.2)	7.1 (4.7–9.5)***	−3.7 (−5.6 to −1.9)***
	VRC	14	12.10 (15.77)	18.33 (16.22)	13.66 (15.29)	6.2 (4.3)	−4.9 (2.3)		
STS-5 (s)	CVR	13	13.5 (7.3)	14.1 (7.2)	11.2 (5.7)	−2.8 (2.4)	0.6 (2.2)	−2.6 (−3.3 to −1.8)***	1.6 (0.5–2.7)**
	VRC	17	13.9 (5.3)	11.5 (4.7)	13.6 (5.6)	−2.3 (1.5)	2.0 (1.9)		
STS-10 (s)	CVR	13	29.7 (10.9)	30.6 (10.5)	24.6 (9.0)	−6.0 (3.2)	0.8 (2.4)	−5.8 (−7.2 to −4.4)***	2.0 (1.1–2.9)***
	VRC	17	30.5 (11.7)	24.8 (9.5)	28.0 (10.1)	−5.6 (4.1)	3.2 (2.2)		
STS-60 (repetitions)	CVR	14	21.7 (9.7)	20.3 (8.7)	25.1 (9.2)	4.8 (1.8)	−1.4 (2.2)	5.0 (4.2–5.7)***	−2.9 (−3.9 to −2.0)***
	VRC	17	20.5 (8.5)	25.7 (9.4)	21.1 (8.9)	5.1 (2.1)	−4.4 (2.9)		
6MWT (m)	CVR	15	331.9 (119.0)	332.4 (115.8)	391.9 (116.7)	59.5 (29.4)	0.4 (36.7)	85.2 (70.2–100.3)***	−35.7 (−49.3 to −22.2)***
	VRC	18	344.9 (115.7)	455.8 (138.9)	383.9 (122.9)	110.9 (50.4)	−71.9 (39.0)		

***$P < 0.001$;

**$P < 0.01$.

Data are represented as means (SD) and mean change. P-values indicate the intervention effects, changes in the intervention and non-intervention periods (combining CVR and VRC groups) analysed using a two repeated measures ANOVA. Changes in the intervention period based on the 12 week – baseline examinations of group VRC and the 24 week – 12 week examinations of group CVR. Changes in the non-intervention period based on the 24 week – 12 week examination of group VRC and the 12 week – baseline examinations of group CVR. CI, confidence interval.

find imaginative solutions to make exercise part of the clinical routine in HD units, and we are convinced that this option is very promising and should be considered by clinicians.

Interestingly, although the VR exercise programme significantly improved gait speed, it did not reach the 90% MDC confidence interval (MDC_{90}) calculated for patients receiving HD (0.26 m/s) [22]. These findings agree with previous work that found a 0.12 m/s increase in normal gait speed after completing a home-based exercise programme with high adherence rates [30]. Other research concluded that gait speed increased in stroke patients [15, 17], individuals with cerebral palsy [31] and even in a healthy population [32] after replacing a standard rehabilitation regimen with a VR-based programme. However, the design of the VR programme used in this work with patients receiving HD was limited because the participants were seated or lying down while exercising, which might have limited specific increases in their gait speed. Thus, future work should continue these programmes for periods exceeding 12 weeks and should aim to confirm whether the VR exercise programme length determines changes in gait speed.

Of note, although adherence was high in this study, it was significantly lower among individuals in the CVR group who had waited 12 weeks before starting the exercise programme. In a previous study of our group, a high dropout rate was observed in a group of patients that waited 6 months to start an exercise programme [22] and the present data support that motivation to participate in exercise is unstable among this cohort. Lack of motivation is a commonly reported barrier [33–36], and together with the unstable medical condition [33, 34, 36] leads to a recommendation for future studies of preventing waiting lists to increase exercise participation and engagement with the intervention in this cohort. We tried to limit the number of dropouts by not including a washout period between the exercise and control periods in this current work. Nonetheless, adherence to the VR exercise programme was higher in this study compared with another similar study [18].

An important limitation to exercise adherence is the high comorbidity levels of patients receiving HD [4, 11, 33, 34]. Therefore, future strategies should specifically design exercise regimens for patients with CKD with the aim of increasing their motivation to participate and adhere to these programmes. For some participants, the 'gaming' experience of intradialytic VR exercises was a motivating factor, which could help to explain the higher adherence levels seen in this programme compared with conventional interventions [18, 22]. It is also important to note that the non-immersive VR system we used had not yet been commercialized at the time of publication. Another limitation of the study is the sample size. Gait speed data were used to calculate sample size, but due to the high variability of this cohort, if we had chosen for example the 6MWT we would have required a larger sample size for the study. Since it is very difficult to enroll patients in exercise studies and there is a high dropout rate, it is really difficult to get large samples in intradialysis exercise studies. We believe that future multicentric studies or meta-analysis of published RCTs that share functional testing procedures would increase the power of exercise studies.

Finally, although significant results were achieved in all the physical function tests, only two tests reached the previously reported MDC_{90} thresholds: the STS-60 (4 repetitions) and 6MWT (66.3 m) [25]; these thresholds were not reached for the SPPB (1.7 points), TUG (2.9 s) or OLST (11.3 s) [24]. In addition, while the results of the STS-5 and STS-10 significantly improved, they also failed to achieve the MDC_{90} of 5.8 and 8.4 s [25], respectively. In this current work, we used a battery of tests that were very time-consuming, for both the patients and the assessors. Thus, it is important to identify which tests were sufficiently reliable, valid and sensitive to detect important changes in patients receiving HD. In future studies, we recommend including these patients in the decision-making process about which tests to use [19]. However, in our opinion, the STS-10 will be more useful than the STS-5 in future studies because stronger changes were observed for this test and because its data distribution was closer to normality.

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AUTHORS' CONTRIBUTIONS

F.J.M.-O., A.A.G.-C., A.G.-T., J.A.G.-G., R.G.-M. and E.S.-O. were involved in conceptualization and formal analysis. F.J.M.-O., A.G.-T., L.O.-P.-d.-V., N.V.-G. and E.S.-O. were responsible for investigation and methodology. F.J.M.-O., A.G.-T., L.O.-P.-d.-V., N.V.-G., R.G.-M. and E.S.-O. provided project administration and resources. F.J.M.-O., L.O.-P.-d.-V., N.V.-G. and E.S.-O. were involved in writing—original draft. F.J.M.O., A.A.G.-C., A.G.-T., J.A.G.-G., R.G.-M. and E.S.-O. were responsible for writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest in relation to the present study. They have nothing to disclose.

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