

## Article

# Conventional Cervical Exercises Compared with a Mixed-Reality-Based Game in Asymptomatic Subjects: An Exploratory Crossover Pilot Study

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**Abstract:** Mixed reality presents itself as a potential technological tool for the management of people with musculoskeletal disorders, without having as many adverse side effects as immersive virtual reality. The objective of this study was to explore the possibilities of a mixed-reality game, performing task-oriented cervical exercises compared to conventional therapeutic exercises in sensorimotor outcome measures in asymptomatic subjects. A randomized crossover pilot study was performed with two intervention groups: a mixed-reality group (MRG) and a conventional exercise group (CEG). The cervical joint position error test (CJPET) and deep cervical flexor endurance test (DCFET) were measured as sensorimotor outcomes. Statistically significant differences were found in the pre–post comparison in the DCFET for both groups (MRG:  $t = -3.87$ ,  $p < 0.01$ ; CEG:  $t = -4.01$ ,  $p < 0.01$ ) and in the extension of the CJPET for the MRG ( $t = 3.50$ ,  $p < 0.01$ ). The rest of the measurements showed no significant differences comparing both groups pre- and postintervention ( $p > 0.05$ ). Mixed reality has apparently the same positive effects as conventional exercises in sensorimotor outcomes in asymptomatic subjects. These results could help in future studies with mixed virtual reality in the management of people with musculoskeletal disorders.

**Keywords:** virtual reality; mixed reality; cervical spine; HoloLens

## 1. Introduction

Technology-based rehabilitation is a new training approach that allows therapists to develop patient-centered approaches [1,2]. Adding new technologies to the rehabilitation process can allow for its improvement, and the main reason for this is due to the data obtained with the device's software and the ability to individualize the therapy. Likewise, the patient's motivation and engagement significantly increase with this training [1]. Moreover, technology offers users an appropriate context, providing them with a recognizable environment that allows them to perform therapy while also taking into account the patient's personal preferences [1].

The most used technologies in rehabilitation are virtual reality (VR), augmented reality (AR), and mixed-reality (MR) devices [3]. The “boom” in these devices in recent years is due to the increase in VR games and head-coupled immersive virtual reality devices since 2006. However, international experts agree on the differences between VR, on the one hand, and AR–MR, on the other hand [4]. VR does not interact with the real environment, and the user’s interactions are always with a virtual environment [3–5]. AR and MR allow the user to see real objects and the environment in which they are placed, adding virtual and responsive objects on top of it. Some experts believe that the addition of MR on AR, among other things, gives virtual objects perspective and depth [3–5]. Nevertheless, public accessibility to MR is limited because of the high prices of the devices, among other limitations [3]. An example of MR, according to some experts, is the “Microsoft© HoloLens” headset device [4].

The side effects of VR, specifically immersive VR, were described many years ago [6]. Currently, despite advances in technology and new virtual reality devices, these adverse effects have not changed [7]: dizziness, headache, and motion sickness, among others. However, MR does not have these disadvantages, because the subject is always aware of their surrounding environment and reality. This opens up possibilities for its use in the management of musculoskeletal disorders in rehabilitation.

In rehabilitation research, the use of VR applications in combination with other therapies has increased and offers the possibility of obtaining more precise and repeatable control of each session in comparison with conventional treatments. Moreover, it allows for the adaptation of interfaces to the user’s limitations and for recreating safe virtual environments to improve and practice skills that have potential risk in the real world [8,9]. Likewise, it enables the development of tele-rehabilitation platforms in which clinicians can remotely follow the evolution of patients from the data recorded during each session, goal-oriented challenges, and daily tasks [8,9]. The latter being a key point of development in physical rehabilitation after the COVID-19 pandemic [10,11]. In addition, for users, this can increase motivation by adapting exercises to the user’s daily life. Not only that, but it enhances their entertainment and sports activity by adding new technologies to conventional treatments such as videogames or virtual reality [12].

Different studies indicate that subjects with neck pain may present coordination alterations in the synergy between the activity of the deep and superficial cervical flexor musculature as well as a decrease in the activity of this deep musculature, accompanied by fatigability and a delayed activation of the same, which may result in a diminished capacity in the control of the deep flexor and extensor muscles [13]. Alterations in cervical movement and motor control appear more frequently in patients with neck pain than in healthy subjects [14]. On the other hand, a previous pilot study concluded that adding virtual reality to kinesthetic exercises did not further improve range of motion, speed, and accuracy of movement [15]. Other work has shown that virtual reality increases improvement in the rotational range of motion in both healthy subjects and patients with neck pain [16]. This opens the possibility of using VR, MR, or AR with the aim of improving these outcomes.

Currently, there are systematic reviews and meta-analyses on the use of VR for musculoskeletal disorders in the cervical region and spine [17,18]. These studies beforehand support the use of VR, but studies with better methodological quality should be conducted. Studies that measure range of motion as a motor variable currently exist [19,20]. However, there are no studies with other sensorimotor variables such as joint position error or deep flexor strength. To the authors’ knowledge, there are no international published studies applying MR in the cervical region and spine. Therefore, there is a need to study the future potential of mixed reality in the physical rehabilitation of people with musculoskeletal disorders, specifically in the cervical spine.

For this purpose, the primary objective of this study was to explore the possibilities of a mixed-reality game, performing task-oriented cervical exercises compared with conventional therapeutic exercises in sensorimotor outcome measurements in asymptomatic

subjects. Added to this, the study aimed to assess the usability and satisfaction of the program and the setup used for performing task-oriented cervical exercises in asymptomatic subjects.

## 2. Materials and Methods

In order to achieve the abovementioned objectives, a randomized single-blind crossover pilot study was carried out, conducted in accordance with the CONSORT statement [21].

### 2.1. Description of Participants

Based on the sample size of other pilot studies, 15 asymptomatic subjects between 18 and 40 years were recruited from “La Salle University Centre for Advanced Studies”, Madrid (Spain), from October 2018 to March 2019. Subjects had to meet the following inclusion criteria in order to participate in the study: no neck or upper limb symptoms; no significant history of chronic pain disorder; not taking any medication; the ability to understand, write, and speak Spanish fluently. Moreover, they were not able to present the following exclusion criteria: craniocervical pain, peripheral neuropathy, history of migraine or headache, endocrine disorders, epilepsy, any psychiatric disorder, any neurological disorder, surgery or a history of traumatic injuries to the upper limb. In addition, participants who were unable to see clearly without glasses and those who missed an evaluation session once the study began were excluded.

### 2.2. Randomization and Blinding

After meeting the eligibility criteria for the study, an external researcher randomly allocated the participants to a sequence of groups. This was performed using a computer-generated program list. A second researcher who was in charge of applying the treatments, knew the sequence of the subjects. This sequence was blinded for the third researcher, who was in charge of performing the measurements. Therefore, it was a simple blind due to the fact that the researcher who carried out the measurements did not know which group the subjects belonged. The researchers were trained for approximately 300 min each on how to perform the measurements and the intervention for each group.

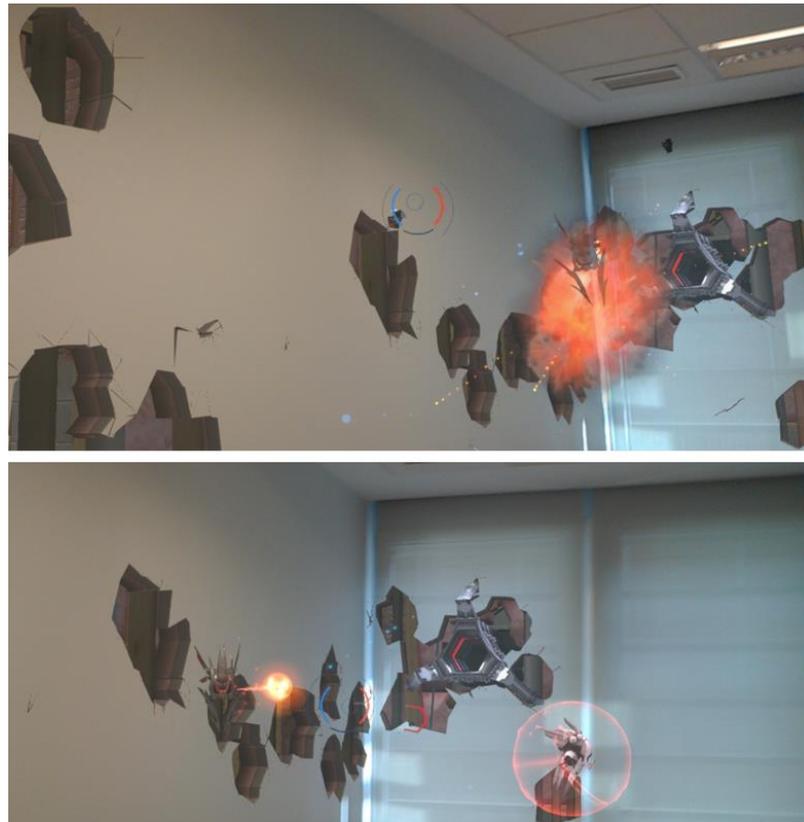
### 2.3. Interventions

Both intervention groups received a total of 6 sessions of treatment: 2 sessions per week, with an interval of 48–72 h between them, for 3 consecutive weeks. All sessions were one-to-one, subject–researcher sessions. Three weeks of motor training were considered sufficient to perceive changes in the outcomes under study [22,23]. Moreover, three weeks were considered sufficient time for the subject to assess satisfaction, usability, and the occurrence of adverse effects.

#### 2.3.1. Mixed-Reality Group (MRG)

The MRG participants received 6 exercise sessions over 3 weeks, using the Microsoft HoloLens “RoboRaid” game. The model used in this study was the “Microsoft HoloLens 1”, which is a mixed-reality, goggle-type device with a number of specialized components. For example, multiple sensors, advanced optics, and a custom holographic processing unit allows the user to go beyond the screen. The technology enables the users to see holograms superimposed on reality and interact with them. Participants in this group could leave the game at any time. The application used was RoboRaid software; a first-person “shooter” game, for general users, which requires cervical movements to move the pointer. This application was chosen among others because it allowed free movement of the cervical spine in all 3 planes of motion in addition to the free movement of the rest of the body, making the subject perform movements during the study as functional as possible. There were four levels of difficulty. On day one, subjects started at “level 1”. From there, subjects selected a level of difficulty they were comfortable with, and in each session, they should be playing for 10 min.

In this mixed-reality first-person shooter game, the user must defend the room (in this study, it was  $4 \times 2$  m) from a robot invasion. As these robots pass through the walls of the room, the participant must move his head and body to avoid the enemy fire and eliminate the invaders (see Figure 1). Glances as well as head and cervical spine gestures are used to aim at enemies, as well as to dodge their fire as they approach the user. To eliminate them, participants must press the button on the controller with their hand after pointing with their gaze [24]. Therefore, cervical spine movement is indispensable here (see Supplementary Material Video: S1\_session\_type).



**Figure 1.** Screenshots of the RoboRaid software while a participant was in a session.

### 2.3.2. Conventional Exercise Group (CEG)

The CEG participants received 6 exercise sessions over 3 weeks using an exercise protocol that was previously shown to be effective on motor outcome measurements [25]. This protocol was based on stabilization exercises of the cervical region, including exercises targeted at the deep neck flexors and extensors to provide them with strength and resistance.

The researcher was in charge of teaching and supervising the performance of these exercises. In addition, it was explained to participants that all exercises should be performed without pain, and if they experienced pain, they should stop the activity. As the sessions went on, if the subject was able, the difficulty of the exercises was increased. Each session lasted for approximately 8–10 min.

## 2.4. Outcome Measures

### 2.4.1. Cervical Joint Position Error Test (CJPET)

The aim of this test was to assess the participant's ability to return to the starting position after a cervical movement. The patient had to sit in a chair with a backrest and locate a headband with a laser pointer on the head. At 90 cm, a stitch (a type of target) had to be placed. Then, the participant had to close their eyes, perform a cervical movement, and return to the starting position as precisely as possible without any feedback. The difference

had to be measured between the center of the target (i.e., starting position) and the point where the laser was aimed (i.e., ending position) [26,27]. Below 4.5° denoted normal cervical proprioception. Participants performed the test in the following movements: flexion, extension, and left and right rotations.

#### 2.4.2. Deep Cervical Flexor Endurance Test (DCFET)

The deep cervical flexor endurance test provided the resistance time in seconds for the deep flexor muscles. To perform it, the therapist lifted the patient's head and neck until the occipital bone was approximately 2.5 cm from the table, keeping the chin tucked into the chest. Before the test, the verbal command, "keep your chin in and breathe", was given, but no verbal commands were given during the test. The test stopped whenever participants lost the chin position or if they needed to stop due to the fact of fatigue or pain. To prevent participant's fatigue, only one measurement was taken. This test showed moderate reliability in pain-free participants of 25 ( $24.51 \pm 15.92$ ) and 20 ( $20.18 \pm 8.8$ ) seconds for men and women, respectively [28]. Immediately after this test, participants were asked to rate their experienced fatigue intensity with a visual analogue fatigue scale, which contained a 100 mm long line marked with "no fatigue" on the left and "worst fatigue ever experienced" on the right [29].

#### 2.4.3. Suitability Evaluation Questionnaire

The suitability evaluation questionnaire (SEQ) assessed the participant's satisfaction, acceptance, and security of use regarding virtual rehabilitation systems. The SEQ is composed of 14 questions, one of which is an open-ended question. For the remaining questions, the participant had to select the number that best fit his or her answer, from 1 to 5 (in which 1 indicates "not at all" and 5 "very much", or 1 "very easy" and 5 "very difficult"). The first 6 questions evaluate experience with the system as well as the instructions on handling it; the next 4 questions evaluate associated problems such as dizziness, nausea, and disorientation; the last 3 represent information on the usefulness and difficulty of using the device [30]. The total SEQ score can be between 13 and 65. The higher the score, the higher the degree of satisfaction [30]. Previous research has used the SEQ to evaluate the suitability of virtual rehabilitation in adults [31].

#### 2.4.4. Evaluation of User Satisfaction with Auxiliary Device Technology

The QUEST 2.0 questionnaire was used to measure user satisfaction with the device used in therapy and has shown to be a valid and reliable tool [32]. It consists of 12 items, 8 related to the device and the experience perceived during its use, and the last 4 evaluating the assistance and repair services for the device. The items are valued with scores from 1 to 5 (in which 1 is "dissatisfied" and 5 is "very satisfied"). In this study, only the first 5 items of the questionnaire were used, referring to the experience satisfaction, usability, the dimensions, and weight of the device as well as the ease of adjusting the device on the head during the task. For this study, the QUEST score was between 6 and 30 points, indicating 25 as the highest satisfaction and usability.

### 2.5. Procedure

Each participant signed a copy of an informed consent form, and demographic data were collected including age, weight, and height. Then, subjects were randomly allocated to one of the 2 intervention sequences: MRG-CEG or CEG-MRG.

When participants had finished the first intervention group, they waited for a 4 week washout period, and then they began the other intervention group. All participants were evaluated 5 times using motor tests: (1) pre-treatment on day 1; (2) post-treatment at week three; (3) at week seven (post-washout period, prior to the beginning of the second intervention group); (4) at week ten (3 weeks after the second intervention started); (5) at week fourteen (4 weeks after the end of the second intervention). The questionnaires were only evaluated at the time (5) to prevent losing the blind.

### 2.6. Data Analysis

All statistical tests were performed with the Statistical Package for Social Sciences (SPSS, Inc., Chicago, IL, USA) with a significance level of  $p < 0.05$ . Demographic data were analyzed with descriptive statistics and presented as the mean  $\pm$  standard deviation (SD) for each of the measurements. The Shapiro-Wilk test was used to verify the normal distribution of the data. Because of the crossover design, it was necessary to analyze the difference in the measurements of interest within each of the interventions as well as the residual effect, period effect, and sequence effect of the intervention process. The Student's *t*-test was used for the following purposes, in this order: (1) to determine the effect of the interventions by performing, for each intervention, the Student's *t*-test for related samples comparing pre- and postintervention; (2) to check that the interventions had a short effect in time, the residual effect was analyzed using the Student's *t*-test comparing the initial measurement with the measurement after the washout period; (3) to verify the existence of a period effect, the Student's *t*-test was used to analyze the difference between the result at the end of the first period and the result at the end of the second period; finally, (4) to check the sequence effect, both intervention sequences (MRG-CEG and CEG-MRG) were compared, analyzing variables of interest.

### 3. Results

A total of 15 healthy individuals were recruited for the study, however, only 14 (nine women and five men) finished the trial; 1 was dropped for not attending mid-study measurements. The flow chart of the study is represented in Figure 2.

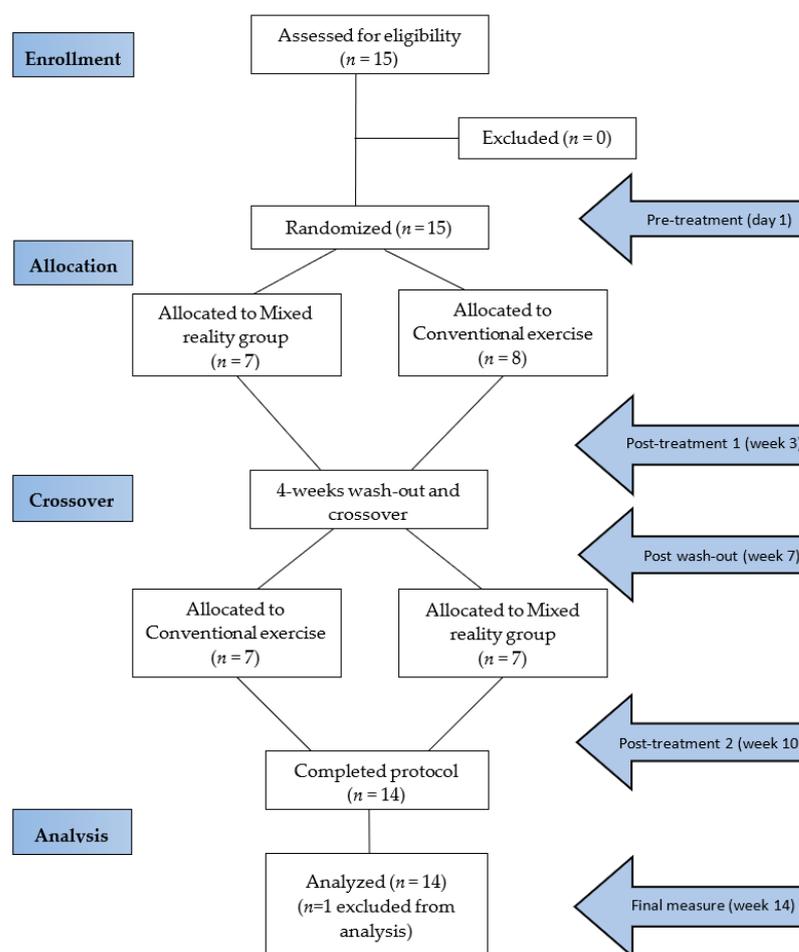


Figure 2. Flow diagram for crossover trial (arrows represent measurements).

### 3.1. Characteristics of Participants

The characteristics of the sample, expressed in mean  $\pm$  SD, were age (years),  $22.79 \pm 5.86$ ; weight (kg),  $66.96 \pm 13.73$ ; height (m),  $1.71 \pm 0.11$ ; BMI,  $22.72 \pm 2.60$ . All measurements showed a normal distribution with a  $p$ -value greater than 0.05 in the Shapiro-Wilk test, except for age ( $p < 0.01$ ). There were also no significant differences between the sequence groups at the beginning of the study.

### 3.2. Sensorimotor Outcomes

Regarding cervical variables, statistically significant differences were found in the pre–post comparison in the time of the DCFET for both groups (MRG:  $t = -3.87$ ,  $p < 0.01$ ; CEG:  $t = -4.01$ ,  $p < 0.01$ ) and in the extension of the CJPET for the MRG ( $t = 3.50$ ,  $p < 0.01$ ). The rest of the measurements showed no significant differences comparing both groups pre- and postintervention ( $p > 0.05$ ) (Table 1). No statistically significant differences were found in any measurement, comparing both groups postintervention.

**Table 1.** Measurements comparing pre- and postintervention in both groups and residual effect.

Measurement	Pre (Mean $\pm$ SD)	Group	Post (Mean $\pm$ SD)	Residual Effect (Mean $\pm$ SD)
DCFET (s)	16.46 $\pm$ 3.76	MRG	24.83 $\pm$ 7.96 **	24.45 $\pm$ 6.13 **
		CEG	22.17 $\pm$ 5.78 **	
Fatigue DCFET (cm)	3.29 $\pm$ 2.13	MRG	3.26 $\pm$ 2.47	3.67 $\pm$ 2.17
		CEG	3.20 $\pm$ 2.27	
CJPET Flexion (°)	3.28 $\pm$ 1.52	MRG	3.12 $\pm$ 1.72	4.80 $\pm$ 3.65
		CEG	3.51 $\pm$ 1.74	
Extension (°)	5.15 $\pm$ 1.81	MRG	3.64 $\pm$ 1.08 **	4.18 $\pm$ 1.49
		CEG	4.20 $\pm$ 2.48	
CJPET Rotation Left (°)	4.57 $\pm$ 2.07	MRG	3.56 $\pm$ 1.29	3.44 $\pm$ 1.88
		CEG	3.49 $\pm$ 1.23	
Rotation Right (°)	4.04 $\pm$ 1.56	MRG	3.37 $\pm$ 1.81	4.10 $\pm$ 1.72
		CEG	3.77 $\pm$ 1.89	

\*  $p < 0.05$ ; \*\*  $p < 0.01$ . DCFET, deep cervical flexor endurance test; s, seconds; cm, centimeters; CJPET: cervical joint position error test; °, degrees; SD, standard deviation; MRG, mixed-reality group; CEG, conventional exercise group.

The Student's  $t$ -test that was performed to determine the residual effect from the first period of intervention revealed statistically significant differences in the time of the DCFET in the comparison of the preintervention and the washout period ( $p < 0.01$ ) (Table 1). A secondary analysis was conducted to see which intervention was related to this difference. Based on a reduced sample size, a Wilcoxon test was applied to compare preintervention and washout measurements, subdividing in both intervention groups. The results obtained showed a mean difference of 4.02 ( $p = 0.06$ ) for the CEG and 11.94 ( $p = 0.02$ ) for the MRG.

Finally, there was no period effect or sequence effect in any measurement ( $p < 0.05$ ) as can be seen in Table 2.

### 3.3. Usability and Satisfaction

The data from the satisfaction and usability questionnaires, expressed in mean  $\pm$  SD, were SEQ:  $57.64 \pm 5$  out of 65 points and QUEST 2.0 (only five questions):  $19.29 \pm 3.89$  out of 25 points. This indicates that users had a high level of satisfaction and good handling and use of the mixed-reality device. There were no adverse events during the use of the program and the setup.

**Table 2.** Table showing data for the analysis of period and sequence effect. Expressed in mean  $\pm$  SD.

Measurement	Pre	Post-Period 1	Post-Period 2	<i>p</i> -Value	Sequence * MRG–CEG	Sequence * CEG–MRG	<i>p</i> -Value
DCFET (s)	16.46 $\pm$ 3.76	23.53 $\pm$ 8.16	23.47 $\pm$ 5.83	0.98	−2.88 $\pm$ 3.61	−11.11 $\pm$ 8.97	0.055
Fatigue DCFET (cm)	3.29 $\pm$ 2.13	3.32 $\pm$ 2.31	3.14 $\pm$ 2.44	0.64	0.60 $\pm$ 0.96	−0.30 $\pm$ 2.16	0.34
CJPET Flexion (°)	3.28 $\pm$ 1.52	3.45 $\pm$ 1.94	3.18 $\pm$ 1.51	0.54	0.12 $\pm$ 1.91	0.08 $\pm$ 2.30	0.98
CJPET Extension (°)	5.15 $\pm$ 1.81	4.29 $\pm$ 2.40	3.55 $\pm$ 1.20	0.19	1.42 $\pm$ 1.59	1.79 $\pm$ 1.79	0.69
CJPET Rotation Left (°)	4.57 $\pm$ 2.07	3.70 $\pm$ 1.20	3.36 $\pm$ 1.29	0.43	1.76 $\pm$ 2.60	0.68 $\pm$ 2.43	0.44
CJPET Rotation Right (°)	4.04 $\pm$ 1.56	3.88 $\pm$ 1.79	3.26 $\pm$ 1.88	0.26	0.84 $\pm$ 1.83	0.71 $\pm$ 1.79	0.89

\* Mean differences between pre- and post-period for each variable were used to analyze the sequence effect. DCFET, deep cervical flexor endurance test; s, seconds; cm, centimeters; CJPET: cervical joint position error test; °, degrees; SD, standard deviation; MRG, mixed-reality group; CEG, conventional exercise group.

#### 4. Discussion

This study is the first to explore the effects of using mixed reality for motor control performance of the cervico-craniofacial region in asymptomatic subjects. To summarize, the two main principal findings of this study are as follow:

1. Mixed reality and conventional exercises had positive effects in cervico motor control performance;
2. The participants of this study evaluated the use of mixed reality with high satisfaction and usability with no adverse effects.

First, the MRG showed greater improvement in the CJPET for the extension movement than the CEG. In addition, our results suggest that a mixed-reality-based exercise protocol could produce longer effects than the CEG according to the data obtained in the secondary analysis. Only the MRG showed statistically significant difference after the month of washout in the time of DCFET, and this may be related to the motivation generated with the technology during the intervention.

Several studies have examined the effectiveness of cervical exercises on motor control measurements, finding improvements in strength, endurance, and cervical proprioception [33–35]. However, no studies have involved mixed reality or evaluated changes in muscle endurance in the cervical region to our knowledge. There are currently numerous studies that show positive results of the use of VR on the cervical spine for the improvement of pain intensity, disability, fear of movement, GPE, patient satisfaction, and balance, among others [17–20]. Nevertheless, these studies only take into account cervical range of motion as a sensorimotor variable with contradictory results on whether there are improvements compared to conventional exercise [19,20].

The normative values of the CJPET can vary across studies [36,37]. In asymptomatic individuals, the results varied between 2.69° and 4.85° for flexion and extension movements and between 2.74° and 5.25° for right and left rotations. The data obtained in this study are within the normative data and are also in accordance with another study. In this one, the authors observed that cervical VR training generated improvements in the precision of cervical movements [38]. However, participants that did not use VR also obtained improvements in the precision of the movement. In this crossover study, although the MRG showed statistically significant changes in the extension movement, both groups improved. This difference could be due to the fact that cervical movements associated with the use of the MRG protocol were similar to those used in proprioceptive training programs, which involve eye stabilization exercises, eye–head coordination, and head repositioning exercises in a given position [39,40]. For this reason, the clinical use of MR should be presented as a program with greater specificity in the retraining of the articular position sensation.

In the present study, both groups showed improvements in the DCFET. These findings for the MRG are relevant due to the fact that there is no precedent for the use of mixed reality for this purpose. Previous studies only used specific exercises that have been shown to produce improvements in the variables of resistance and strength of the cervical muscles [33,34,40,41].

Finally, in terms of satisfaction, the results obtained on both questionnaires were positive. A pilot study conducted by Jasen-Kosterink et al. involved participants with chronic musculoskeletal pain and reported a high degree of usability, satisfaction, and motivation with the use of VR [42]. Another study compared VR with conventional treatments and both showed effectiveness. However, a greater degree of satisfaction with the therapy were obtained in the VR group as in this study [43].

#### 4.1. Applicability and Future Researches

The data presented in this study yield data for future researches using mixed reality as a new type of treatment for cervical dysfunctions and musculoskeletal disorders, based on the improvements obtained for motor measurements. In addition, this type of exercise could result in a better adherence and engagement with the treatment for those who like technology and videogames.

Future lines of research could add the creation of a more powerful game for mixed-reality platforms whose objectives will include the movement of the cervico-craniofacial region. It could be interesting to train the three planes of movement in order to be able to carry out more functional and global movements to improve.

#### 4.2. Limitations

This research has some limitations that must be considered. One of them is the lack of a control group with no exercise, although it did not affect the main objective of the study. Secondly, the sample size was small and future studies should include a major number of subjects. Thirdly, there was a significant residual effect in the first period of intervention, related to the MRG. This could be produced due to the fact that it was a new intervention, and we do not yet know the washout period needed in these kinds of interventions. For this reason, these findings should be taken into account in future studies. Finally, mixed reality is the newest of the artificial virtual realities that can be used in clinical practice; for this reason, mixed-reality devices are not accessible for everybody and could be expensive.

### 5. Conclusions

Mixed reality has apparently the same positive effects as conventional exercises in sensorimotor outcomes in asymptomatic subjects. The cervical joint position error test in extension improved only in the mixed-reality group, and the deep cervical flexor endurance test improved equally in both the conventional exercise group and the mixed-reality group. It obtained high satisfaction and usability with no adverse effects. These results could help in future studies with mixed virtual reality in the management of people with musculoskeletal disorders.

**Supplementary Materials:** The following are available online at <https://www.mdpi.com/article/10.3390/app12073657/s1>, Video: S1\_session\_type.

**Author Contributions:** Conceptualization, H.B.-A., M.G.-P., M.C.D.-S. and J.P.R.M.; methodology, G.N.-F., M.C.D.-S., J.F.-C. and M.G.-P.; data curation, M.C.D.-S., J.F.-C. and G.N.-F.; writing—original draft preparation, G.N.-F., M.C.D.-S., H.B.-A. and J.P.R.M.; writing—review and editing, H.B.-A., J.F.-C., J.P.R.M. and M.G.-P.; supervision, M.G.-P.; project administration, H.B.-A. All authors have read and agreed to the published version of the manuscript.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

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