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Effectiveness of virtual reality on cognition and motor outcomes in patients with multiple sclerosis: A systematic reviews

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Abstract:

Purpose: The study was conducted to produce the best evidence of Virtual reality Therapy's effectiveness in improving motor for gait, motor for hand function, and cognition in patients with multiple sclerosis disease.

Methods: Intensive search was made by electronic databases such as PubMed, Cochrane Library, and Pedro was conducted. We also double-checked the bibliographies. The goal of this search was to find RCTs that compared virtual reality therapy to traditional rehabilitation for multiple sclerotic patients . After that, the data was retrieved, and the methodological quality of each included trial was reviewed. Finally, the data of between pre and post intervention scores were pooled, and the aggregate standard mean differences by 95% confidence of interval were calculated.

Results: Sixteen studies were included in the analysis. It was all about multiple sclerosis. Virtual reality may have not a significant effect on cognition, balance, or weariness. Only seven research reported on the outcomes of improving motor in gait and two studies on improving motor hand function in people who received the intervention during a less than three-month follow-up evaluation, and the difference was significant.

Conclusion: Evidence of virtual reality's effectiveness on motor outcomes in patients having multiple sclerosis may be found in the included RCTs.

Keywords : Virtual Reality Therapy , RCT, Multiple Sclerosis .

1. Introduction:

Multiple sclerosis is an autoimmune disease in which myelin in the central nervous system sis lost. It typically affects young adults. Multiple sharply marked zones of demyelination across the white matter of the central nervous system are pathologic findings.

Fatigue, loss of vision, dysarthria , sensitivity disorders, balance, and coordination issues, causing parasthesia, extraocular movement synonyms, loss of sensation, weakness, spasticity, ataxia, and bladder dysfunction, as well as cognitive and emotional disturbance, are some of the clinical signs (1).

Virtual reality is a popular, widely available modern technology that is becoming more beneficial in biomedical and health applications. It provides real-time visual feedback for movements while also encouraging participation in enjoyable rehabilitation activities (2).

Virtual reality rehabilitation systems provide three sorts of information to participants having Multiple

Sclerosis: visualisation of movement, feedback performance and context of information. Virtual reality therapy can aid in the processing and integration of sensory information, making them a feasible alternative to traditional motor therapy (3,4).

Virtual reality offers alternative rehabilitation programmes with unique and effective treatment strategies, as such as goal-oriented tasks and repetitions, to enable wide spectrum of rehabilitation of patients having neurological deficits develop functional abilities (5).

Virtual reality offers a real chance for neurological patients suffering from a variety of neuropsychological symptoms for cognitive therapy which include memory, attention, problem-solving, and executive problems, in addition to behavioural disturbance (6).

2. Materials and Methods:

This review was conducted through electronic and manual search, from August 2020 to May 2021, to provide valid evidence regarding the virtual reality that affecting motor and cognition outcomes in multiple sclerotic patients, and it followed the following steps:

2.1 Inclusion criteria considering studies for this review:

2.1.1 Types of studies: This review comprise published Randomized Controlled Trials (RCTs) with or without blinding of participants, physiotherapists, and assessors, which compare different forms of Virtual Reality Therapy with Usual Care Therapy.

2.1.2 Types of participants:

• Adult patients diagnosed by multiple sclerosis, either relapsing and remitting or secondary progressive

• Studies on mixed populations of healthy individuals or patients with multiple sclerosis were included only if separated data for patients were gettable.

2.1.3 Types of interventions: Different forms of Virtual reality Therapy including Immersive, non-immersive, and semi-immersive.

2.1.4 Control/comparator: Comparing the intervention offered with control, placebo, or standard care, as well as comparison of alternative intensities and administration timing of the exact intervention, will be included in the studies.

2.1.5 Outcome: The primary outcome was the Motor and Cognition assessed post-intervention the outcomes were analysed to test the efficacy of the included intervention variations; measures were prioritized as follows:

Motor for Upper limb and hand function: Active actions , manipulation objects , dexterity, and reach to grasp, grip, or pinching are all assessed.

Motor for Lower limb function: such as walking ability, stages of motor recovery, measures of disability and temporospatial gait characteristics .

Cognition measures that examine the five domains.

2.2 Exclusion criteria:

The studies that were excluded:

• Study designs that are not randomized controlled trials and quasi controlled trials.

• Review articles, surveys, case reports, and case series.

• Published abstracts with no full-text articles available.

• Trials that investigate one of the included interventions together with the application of other interventions .

• Studies with low quality of methodology (All studies with total PEDro scores that is less than 5).

2.3 Search methods identification studies:

Electronic database search was done in:

• PubMed(Medline) in http://www.ncbi.nlm.nih.gov/pubmeds.

• CENTRAL in http://www.thecochranelibrary.com.

• Physiotherapy Evidence Database (PEDro) in http://www.pedro.org.au/.

The following keywords will be used to search the electronic databases (PEDro, PubMed, CENTRAL (Cochrane) and Google Scholar): virtual reality, augmented reality , virtual environment , active video game , interactive game , exergame , Kinect , X-box , Nintendo , Wii . An additional search for Multiple Sclerosis was done using the following keywords : Multiple Sclerosis, Sclerosis, Disseminated ,disseminated sclerosis , Demyelinating disease , Acute Fulminating , transverse myelitis , neuromyelitis , encephalomyelitis, descriptor Myelitis.

Databases were searched from **August 2020** to **January 2021**, Reference lists of relevant publications was also reviewed in addition to search for the database.

2.4 Study selection criteria:

Two independent reviewers checked titles and abstracts records found through electronic search(Myra Yasser and Khaled Hussien). Manual search was done by checking the reference lists of relevant publications and tracking the newer studies through "Scopus". By Excluding Obvious Irrelevant trials, Also Obtaining a full text of the studies that are remaining and then by checking for eligibility against inclusion and exclusion criteria by excluding the studies that really don't fulfil the included criteria.

2.5 Data extraction:

Extracting a data collection form and then record the feature key of each trial by obtaining Participant's

details , Interventions, Outcomes, so the Results. One reviewer (Myra Yasser) had taken out the data from the included studies and a second reviewer (Khaled Hussien) cross-checked it.

2.6 Assessment of Methodological quality of the studies:

The methodological quality of the complete papers was assessed using the risk of bias evaluation procedure given in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. And by using the physical therapy evidence database scale (PEDro), which evaluates the eligibility criteria, Randomization and blinding methods, allocation concealment, baseline similarity of individuals in treatment groups, whether an intention to treat analysis will be carried out, and number of participants lost to follow-up and missing values are all factors to consider (Appendix I). If necessary, a third author (Prof. Nahed Salem) was brought in to help for the establishment of a consensus.

Studies with a score of 9-10 on the PEDro scale are considered outstanding, studies with a score of 6-8 on the PEDro scale are considered good, studies with a score of 4-5 on the PEDro scale are considered ordinary, and studies with a score of 0-3 on the PEDro scale are considered poor.

2.7 Measurement of treatment:

The primary and secondary outcome variables of interest were continuous outcomes. Data of change scores between pre-and post-intervention measures were evaluated and entered as means and Standard Deviations (SDs) and the Standardized Mean Difference (SMD) with 95% Confidence Intervals (CIs) for each trial was calculated. Data were pooled through calculation of the overall SMD and 95% CI.

2.8 Data analysis:

A comparison between the virtual reality and conventional therapy or placebo therapy was made, Moreover, as previously mentioned, the analysis that was pooled to primary and secondary outcomes was done., using a random effect model instead of a fixed effect model if heterogeneity of the studies was elevated. The analysis of subgroups was performed to determine the efficiency related to the use of outcome measures, (virtual reality and motor and cognition).

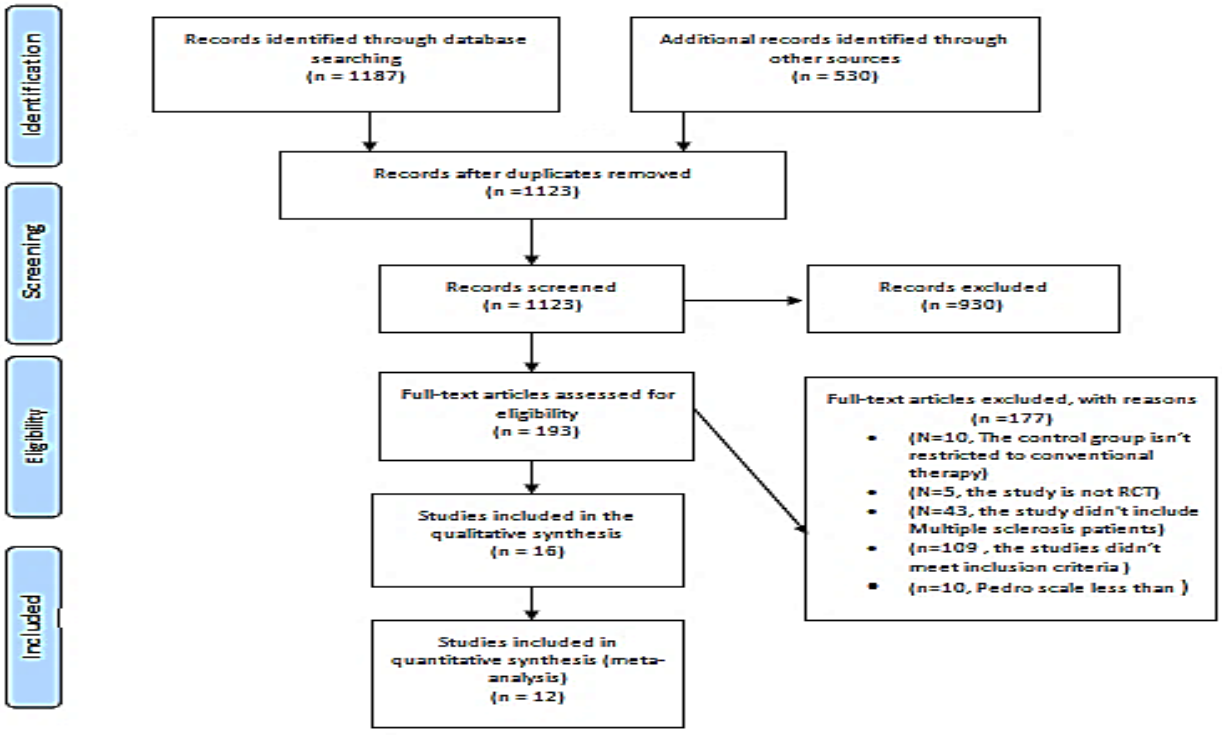

Fig. (1): Results of the search

3.Results:

3.1 Results of the search:

1187 studies A search in PubMed, Cochrane, and PEDro databases yielded the following findings. Total number of 1123 studies were examined after all duplicate studies were removed.

930 studies have been excluded and the full-text articles of 193 studies which appear to meet the eligibility criteria have been assessed. Results of the search are displayed in (**Fig. 1**).

3.2 Sample size and participants:

A total of 514 people took part in the 16 studies. The sample sizes of the trials that were found ranged from 5 to 30. In this section, you will find detailed descriptions of the patient's characteristics **(Table 1).**

The average age of participants in the studies considered was 43.3 years, with a range of 26.39 to 53.9 years. Females made up 64% of the participants, while men made up 36%.

	Experimental group					Control group				
	N	Male	Female	Age	Duration (in years)	N	Male	Female	Age	Duration (in years)
Brichetto et al.,2013 (7)	18	8	10	40.7	11.2	18	6	12	43.2	12.3
Kramer et al.,2014 (8)	21			47.0		20			47.0	
Lozano-Quilis et al.,2014 (9)	6	3	3	48.33	14.00	5	4	1	40.60	4.70
Robinson et al.,2015 (10)	20	6	14	52.6		15	7	12	53.9	
Kalron et al.,2016[(11)	15	5	10	47.3	11.6	15	6	9	43.9	10.4
Peruzzi et al.,2016 (12)	14	6	8	43.6	11.8	11	4	7	42.0	12.4
Calabro et al.,2017[(13)	20	7	13	44	11.5	20	8	12	41	11.5
Khalil et al.,2018 (14)	16	4	12	39.88	8.38	16	6	10	34.87	10.43
Russo et al.,2018 (15)	30	14	16	42	11.40	15	5	10	41	12.27
Waliño-Paniagua et al.,2019 (16)	8	4	4	46.75		8	4	4	46.13	
Cuesta-Gómez et al.,2020 (17)	16	7	9	49.86	15.20	14	5	9	42.66	10.91
Maggio et al.,2020 (18)	30	18	12	51.9		30	13	17	48.2	
Munari et al.,2020 (19)	8	3	5	57	17.7	9	4	5	51.7	13.9
Norouzi et al.,2020 (20)	15	-	15	26.39		15	-	15	26.39	
Ozdogar et al.,2020 (21)	21	5	16	39.2	7.5	19	6	12	43.6	6.43
Ozkul et al.,2020 (22)	13	4	9	29	4	13	2	11	34	4

4. Interventions:

Using Virtual reality (VR) is a relatively new way of treatment that a 3Denvironmental world that is being created digitally. It helps in interacting, supplying sensory information. VR create a fully immersive mode. (high-immersion environmental level) or non-immersive mode (low immersion environmental level) (23,24).

VR gives an immersive practice, a sensation of being involved in the virtual environment by apparatus with an interactive display device (e.g., a head-mounted display) and (e.g. joystick, glove). Virtual reality has been utilized for both rehabilitation and health care and for educational purposes (25,26).

This innovative tool is used for applying a rehabilitation strategy to reduce the negative effect of a non-communicable diseases on individuals and community.

4.3 Risk of bias in included studies:

In **Fig. (2) and (table 2),** all information of the methodological of quality of the included studies are provided using the risk of bias assessment tool (7) and the PEDro Scale.

Outcome: Cognition:

Also the measures for primary outcome for Cognition outcome the three studies that used Digit Symbol Modalities Test conducted by (Munari et al.,2020) (19), used Paced Auditory Serial Addition Task also conducted by (Munari et al.,2020 ; Ozdogar et al.,2020) (19), (21) also Montreal Cognitive Assessment conducted by (Maggio et al.,2020) (18).

Outcome: Motor function:

For measuring the primary outcomes in motor function of Lower extremity , A seven studies was used by Timed up and go test for lower extremity (Gait) (Hanan Khalil et al.,2018 ; Agnese Peruzzi et a.,2016 ; Margherita Russo et al.,2018 ; Rocco Salvatore Calabrò et al.,2017 ; Jose-Antonio Lozano-Quilis et al.,2014 ; Cagla Ozkul et al.,2020 ; Maria Grazia Maggio et al.,2020) (14), (12), (15), (13), (9), (22), (18).

And to analysis the primary outcome, motor function for upper extremity by two studies (hand function) and the studies used Nine-Hole Peg Test conducted by (Ozdogar et al.,2020) (21) and also used Grooved Pegboard Test and Purdue Pegboard Test are conducted by (Waliño-Paniagua et al.,2019) (16).

4.1 Effects of interventions:

4.1.1 Outcome Motor function (Gait):

In a pooled analysis on motor function we included 7 studies in gait (14), (12), (15), (13), (9), (22), (18), we performed an analysis of change scores between pre-and post-assessment.

Virtual reality rehabilitation in patients with multiple sclerosis on improving motor gait has an significant effect measured less than 3 months compared with conventional therapy(SMD= -0.11,95%CI= -0.56 to 0.33).Heterogeneity was significant in the pooled result (Chi square value= 16.91; I^2= 65% and p= 0.010) **Fig. (3).**

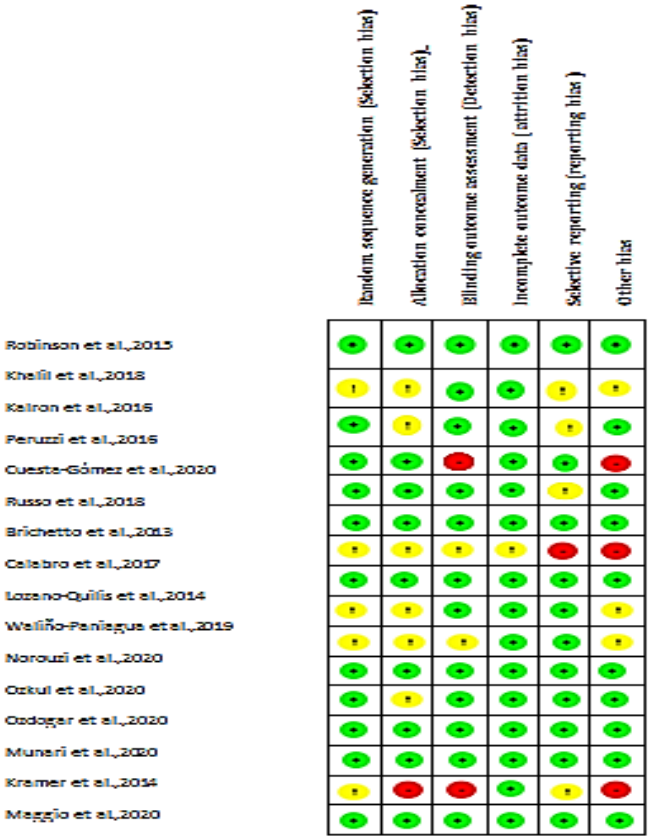

Fig. (2): Risk of bias summary.

4.1.2 Outcome Motor hand function

Two studies were used in a pooled analysis on Motor function in gait (21), (16) we performed an analysis of change scores between pre-and post-assessment.

Virtual reality rehabilitation in patients with multiple sclerosis on improving motor hand function has an significant effect measured less than 3 months compared with conventional therapy(SMD= -1.99,95%CI= -4.95to 0.98).Heterogeneity was significant in the pooled result (Chi square value= 43.14; I^2= 95% and p=0.0001) **Fig (4).**

4.1.3 Outcome Cognition

Including 3 studies in a pooled analysis in Motor function in gait (19), (18), (21), we performed an analysis of change scores between pre-and post-assessment.

virtual reality rehabilitation in patients with multiple sclerosis on improving cognition has an significant effect measured less than 3 months compared with conventional therapy(SMD= 0.54,95%CI= 0.20 to 0.89).Heterogeneity was not significant in pooled result (Chi square value= 2.54; I^2= 0.0 and p= 0.47) **Fig. (5).**

Table 2: Pedro scale

Pedro scores for Virtual reality Therapy Studies

9-10 points excellent 6-8 points good 4-5 points average 0-3 points poor

Article	1	2	3	4	5	6	7	8	9	10	11	Total	Classification
Robinson et al.,2015	Yes	1	1	1	0	0	0	1	1	1	1	7	Good
Khalil et al.,2018	Yes	1	1	1	0	0	1	1	1	1	1	8	Excellent
Kalron et al.,2016	Yes	1	1	1	0	0	1	1	1	1	1	8	Excellent
Peruzzi et al.,2016	Yes	1	1	0	0	0	1	0	1	1	1	6	Good
Cuesta-Gómez et al.,2020	Yes	1	1	1	0	1	1	1	1	1	1	9	Excellent
Russo et al.,2018	Yes	1	1	1	0	0	1	1	1	1	1	8	Good
Brichetto et al.,2013	Yes	1	1	1	0	0	1	1	1	1	1	8	Good
Calabro et al.,2017	Yes	1	0	1	0	0	1	1	1	1	1	7	Good
Lozano-Quilis et al.,2014	Yes	1	0	1	0	0	1	1	1	1	1	7	Good
Waliño-Paniagua et al.,2019	Yes	1	0	1	0	0	1	0	0	1	1	5	Average
Norouzi et al.,2020	Yes	1	1	1	0	0	1	1	1	1	1	8	Excellent
Ozkul et al.,2020	Yes	1	1	1	0	0	1	0	0	1	1	6	Good
Ozdogar et al.,2020	Yes	1	1	1	0	0	1	1	1	1	1	8	Excellent
Munari et al.,2020	Yes	1	1	1	0	0	1	1	1	1	1	8	Excellent
Kramer et al.,2014	Yes	1	1	1	0	0	1	1	1	1	1	8	Excellent
Maggio et al.,2020	Yes	1	1	1	0	1	1	1	1	1	1	9	Excellent

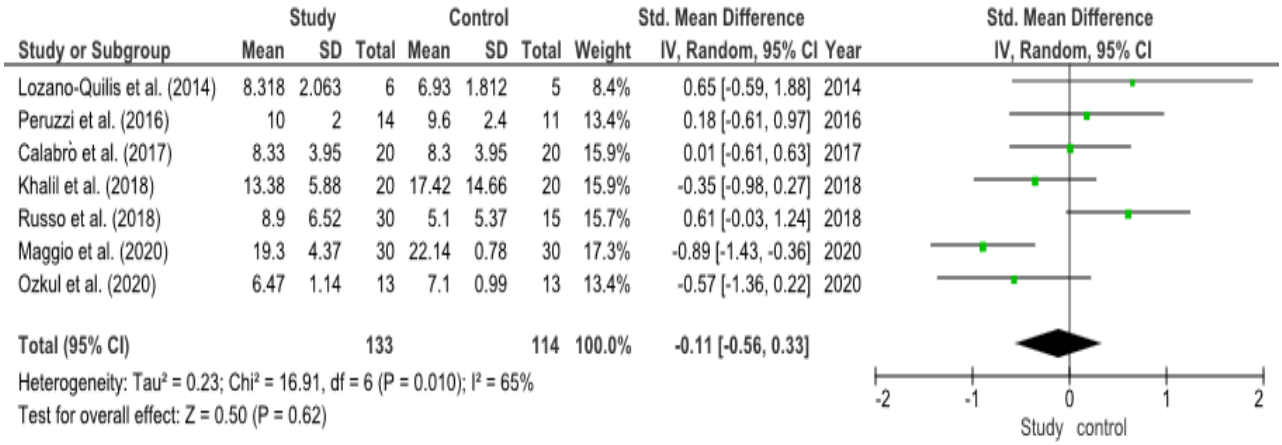

Figure (3) effect of virtual reality rehabilitation in improving motor gait in both study and control group.

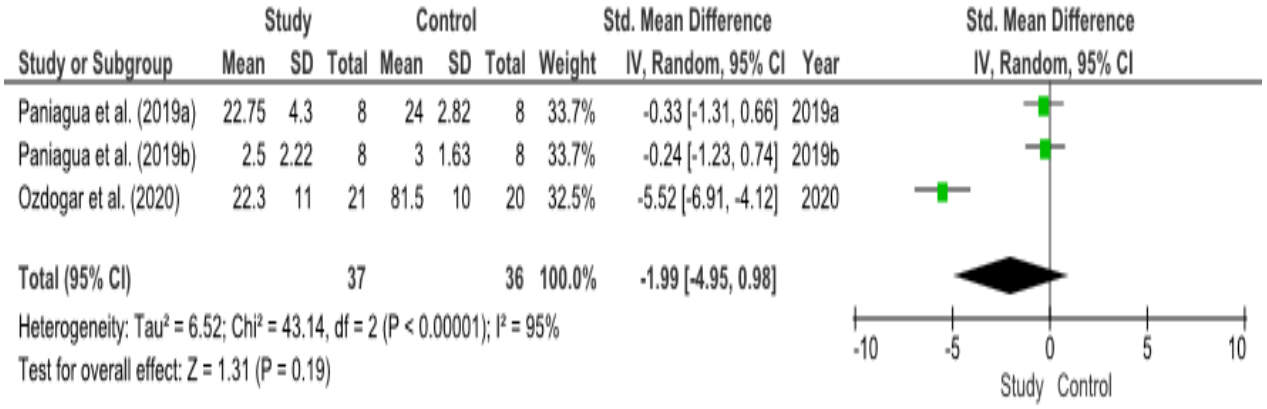

Figure (4) Effect of virtual reality rehabilitation in improving motor hand function in both study and control group.

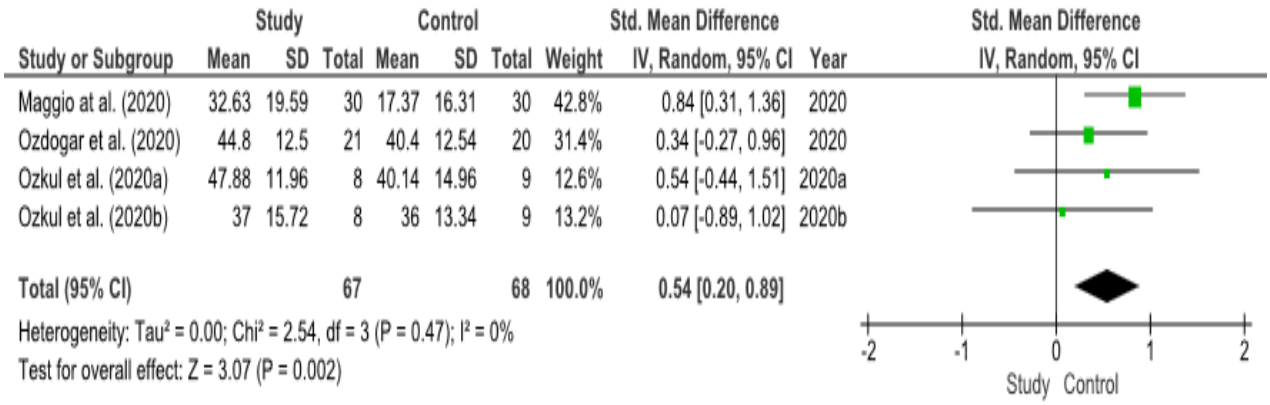

Figure (5) virtual reality efficiency in rehabilitation for improving cognition in both study and control group.

5. Discussion:

Overall completeness and applicability of evidence:

The goal of this systematic review was to see how virtual reality therapy is affecting motor and cognitive function in multiple sclerosis patients. Because the number of studies and participants for several outcomes was small, it was difficult to draw conclusions.

Only three research (Munari et al.,2020; Maggio et al.,2020; Ozdogar et al.,2020) (19), (18) and (21) measured the effectiveness of cognition in fewer than three months. Finally, only two research (Walio-Paniagua et al.,2019; Ozdogar et al.,2020) examined the effectiveness of hand motor function for shorter than three months (Walio-Paniagua et al.,2019; Ozdogar et al.,2020) (16), (21).

Because of the limited sample numbers and considerable variation between the observed outcomes, the overall quality of evidence was lowered. It is critical that future research is to be drawn to highest methodological quality possible.

Applicability of evidence:

The main goal of this review was to gain the best evidence in using virtual reality therapy in multiple sclerosis rehabilitation, in order to assist clinicians and policymakers in making clinical rehabilitation decisions.

Before applying any evidence, clinicians and policymakers should carefully consider the features of the trials formed in that review, particularly considering the therapeutic decision to be made, the relevance of the participant population, trial environment, therapies administered, and outcomes assessed When evaluating the possible applicability of findings, the dose of interventions is crucial. It's probably had an impact on effect size, and it is difficult to know whether the intervention dose administered in RCTs was sufficient.

5.Conclusion:

Few studies are robust enough and several studies included in this review are at risk of bias. At this point, it is difficult to conclude impact, because interventions and controls vary widely in different studies. Compared with conventional care, virtual reality programme after discharge have been shown to improve motor and have not shown an improvement in cognition function.

The studies which are existed consider that there is an effect of virtual reality therapy in multiple sclerosis patients, and they suffer from methodological problems such as small sample sizes within appropriate reporting. There is thus an urgent need for good RCTs with large sample size to give a high quality of evidence. Further research must give specific answers about frequency, dose, and duration of the interventions.

Abbreviations

Randomized Control Trial (RCT)
Virtual Reality (VR)
BTS-Nirvana System (BTS-N)
Standard Deviations (SDs)
Standardised Mean Difference (SMD)
Confidence Intervals (CIs)
Three Dimensional (3D)

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