INPLASY PROTOCOL

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None declared.

Effects of Different Exercise Therapies on Balance Function and Functional Walking Ability in Multiple Sclerosis Disease Patients—A Network Meta-Analysis of Randomized Controlled Trials

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Review question / Objective: **PICOS tool: (Population) Population: people with multiple sclerosis; (I) Intervention: exercise; (C) Comparator: control group with usual care and usual rehabilitation measures only; (O) Outcomes: tests of motor function for people with multiple sclerosis; (S) Study type: RCTs**

Eligibility criteria: **2.2. Inclusion criteria(1) Experimental group: use of an exercise as an intervention to treat multiple sclerosis disease; (2) control group: Treatment of multiple sclerosis dis-ease using only daily care and conventional rehabilitation (no other types of exercise interventions, just the more popular and commonly used balance re-habilitation exercises; no training, just daily living care); (3) clinical randomized controlled trial; (4) outcome indicators including at least one of the following: Berg Balance Scale (BBS) score, Timed-Up-and-Go (TUG) score. 2.3. Exclusion criteria(1) Studies with incomplete or unreported data; (2) studies from non-randomized controlled trials (including quasi-randomized controlled trials, animal studies, protocols, meeting abstracts, case report correspondence).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 June 2022 and was last updated on 08 June 2022 (registration number INPLASY202260035).

INTRODUCTION

Review question / Objective: **PICOS tool: (Population) Population: people with multiple sclerosis; (I) Intervention: exercise; (C) Comparator: control group with usual care and usual rehabilitation measures only; (O) Outcomes: tests of motor function for people with multiple sclerosis; (S) Study type: RCTs.**

Rationale: **In addition to traditional meta-analysis, researchers have invented a new evidence-based medical technique, network meta-analysis (NMA), which, in contrast to the original technique, allows**

one to compare and rank the effects of multiple interventions for a disease at the same time [14]. Therefore, in this study, we use network meta-analysis to compare different exercise programs (aquatic exercise, aerobic exercise, yoga, Pilates, virtual reality exercises, whole-body vibration exercises, and resistance exercises) in order to assess the effect of these programs on physical function in people with MS and to pro-vide patients and clinicians with appropriate evidence-based recommendations.

Condition being studied: Multiple sclerosis is one of the most common disabling neurological diseases worldwide and has an average age of onset of 29 years. As of 2017, there are 2.5 million people with multiple sclerosis worldwide, and this number is increasing [1][2]. The disease has many adverse effects on patients, including, but not limited to, physical symptoms such as muscle weakness and reduced mobility and balance as well as mental symptoms such as fatigue and cognitive decline [3,4]. This has a considerable impact on not only the patients themselves and their families, but also on public health and safety [5]. Due to the combination of reduced physical and mental function, approximately 75% of people with MS experience balance and walking-related impairments in the early stages of the disease as well as in the later stages of the disease [6], increasing the risk of falls and injuries [1]. The physical injuries and psychological fears associated with falls may further affect the patient's physical and mental health, creating a vicious cycle that further affects the patient's quality of life [7,8]. More and more research is focusing on the rehabilitation of pwMS, and in addition to traditional measures such as daily care and rehabilitation, different forms of exercise are increasingly being used in clinical non-pharmacological treatment and rehabilitation [9]. A number of randomized controlled trial studies have shown that exercise produces beneficial effects on mental aspects such as fatigue and cognitive performance in patients that exceed those of traditional rehabilitation measures. In addition, there are meta-analyses comparing one exercise intervention alone versus traditional rehabilitation measures for physical and mental functioning in MS patients [10,11] as well as network meta-analyses comparing multiple exercise interventions versus traditional rehabilitation measures for mental functioning in MS patients [12,13], both of which provide considerable clinical evidence-based recommendations.

METHODS

Search strategy: Table 1. Search strategy on Pubmed.

#1 Search “Multiple Sclerosis” [MeSh]

#2 Search (Multiple Sclerosis [Title/Abstract]) OR (MS [Title/Abstract]) OR (Relapsing-remitting Multiple Sclerosis [Title/Abstract]) OR (RRMS [Title/Abstract]) OR (Multilocular Sclerosis [Title/Abstract])

#3 Search #1 OR #2

#4 Search “Exercise” [MeSh]

#5 Search (exercise[Title/Abstract]) OR (exercise intervention[Title/Abstract]) OR (exercise training[Title/Abstract]) OR (training[Title/Abstract]) OR (physical training[Title/Abstract]) OR (physical exercise[Title/Abstract]) OR (sports training[Title/Abstract]) OR (nurse intervention[Title/Abstract]

#6 Search #4 OR#5

#7 Search #3 AND #6.

Participant or population: People with multiple sclerosis.

Intervention: Different exercise interventions.

Comparator: usual care (no exercise).

Study designs to be included: RCTs.

Eligibility criteria: 2.2. Inclusion criteria(1) Experimental group: use of an exercise as an intervention to treat multiple sclerosis disease; (2) control group: Treatment of multiple sclerosis dis-ease using only daily care and conventional rehabilitation (no other types of exercise interventions, just the more popular and commonly used balance re-habilitation exercises; no training, just daily living care); (3) clinical randomized controlled trial; (4) outcome indicators including at least one of the following: Berg Balance Scale (BBS) score, Timed-Up-and-Go (TUG) score. 2.3. Exclusion criteria(1) Studies with incomplete or unreported data; (2) studies from non-randomized controlled trials (including quasi-randomized controlled trials, animal studies, protocols, meeting abstracts, case report correspondence).

Information sources: Five electronic databases (Pubmed, EMBASE, the Cochrane Central Register of Controlled Trials, Web of Science, andCNKI).

Main outcome(s): outcome indicators including at least one of the following: Berg Balance Scale (BBS) score, Timed-Up-and-Go (TUG) score.

Additional outcome(s): None.

Data management: Data extraction A table with seven sections was used to extract detailed data from the included papers: (1) author (abbreviations), (2) year of publication, (3) country in which each study was conducted, (4) sample size in each study, (5) details of the experimental group; (6) details of the control group, and (7) outcome indicators.

Quality assessment / Risk of bias analysis: Risk of bias of individual studies Two authors independently assessed the risk of bias (ROB) in accordance with the Cochrane Handbook version 5.1.0 tool for assessing ROB in RCTs. The following seven domains were considered: (1) randomized sequence generation, (2) treatment allocation concealment, the blinding of (3) participants and (4) personnel, (5) incomplete outcome data, (6) selective reporting, and (7) other sources of bias. Trials were categorized into three levels of ROB accord-ing to the number of components for which high ROB potentially existed: high risk (five or more), moderate risk (three or four), and low risk (two or less). All of the studies would, by default, be classified as having a high ROB with respect to the category "blinding of participants" because it was impossible to the blind participants to group assignment in exercise intervention protocols [18,19].

Strategy of data synthesis: Data analysis First, because we are studying the efficacy of exercise for a particular dis-ease, we have chosen to use continuous variables for statistical analysis. In order to calculate the results more conservatively, we used the immediate post-intervention value minus the baseline value to express the size of the intervention effect. As the results that we analyzed were all in uniform units, we chose to use standard difference (SD) rather than standardized mean difference (SMD) for our calculations. There is bound to be variation between each original study, and to make the results more scientific, we chose to calculate a random effects model rather than a fixed effects model [14]. Secondly, Stata software was used to present the network graphs, which are important in NMA. In a network diagram, different graphs have different meanings: (1) each node represents an exercise intervention; (2) the size of the node indicates the sample size of the subjects who performed this intervention; (3) if there are no line segments between each node, it means that indirect comparisons will be made between the nodes, and if there are line segments, it means that direct comparisons will be made between the nodes; (4) the thick-ness of the line segments between the nodes indicates the original study sample size; and (5) the size of the nodes and the thickness of the line segments are positively correlated with the number [20]. Again, we used Stata software to summarize and analyze the NMA us-ing Markov chain Monte Carlo simulation chains in a Bayesian-based framework. Thus, in a ranking table, treatments were ranked from best to worst along the leading diagonal. Above the leading diagonal were estimates from pairwise meta-analyses, and below the leading diagonal were estimates from network meta-analyses. [21,22]. Finally, we calculated the SUCRA ranking in Stata software and used it as a criterion for evaluating the effect of the exercise interventions, which is a percentage with a maximum value of 1 and a minimum value of 0. The closer to 1, the better the intervention effect; the closer to 0, the worse the intervention effect. A funnel plot will also be generated to examine possible publication bi-as [20].

Subgroup analysis: None.

Sensitivity analysis: Looking at the parallelism of the horizontal line in the funnel plot to the x-axis, we concluded that there was no publication bias among the original studies that would have affected the NMA (Figure 4).

Language: None restriction.

Country(ies) involved: China.

Keywords: rehabilitation; yoga; aquatic exercise; multiple sclerosis disease; network meta-analysis.

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