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The effect of exercise therapy on cognitive functions in multiple sclerosis patients: A pilot study

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Abstract

Background: The positive impacts of exercise therapy on patients' cognitive problems still remain unknown. This study was a pilot intervention to examine the effects of combined exercise on the cognitive problems of patients with multiple sclerosis (MS) in Iranian MS Society over 2012 to 2013.

Methods: This quasi-experimental research was carried out in the form of a pretest/posttest study. Forty two patients with MS were selected from those visiting the rehabilitation center of Iranian MS Society, using non-probability convenience sampling. The Expanded Disability Status Scale (EDSS) of each patient was recorded before the intervention and Brief Repeatable Battery of Neuropsychological (BRB-N) test was administered before and after the intervention. The data were analyzed using the analytical tests such as Wilcoxon test.

Results: Of 21 participants, 17 subjects (82%, n=14) female with mean (±SD) age of 37 (±9.98) years and mean (±SD) EDSS of 2.35 (±0.90) completed all stages of the study. Changes in long-term storage and permanent long-term retrieval of information after the intervention were statistically significant ($p<0.001$). In addition, the change in the average of total delay after the intervention was also significant by 1.11 ($p<0.001$).

Conclusion: Our study confirmed the possibility of change in the cognitive abilities of MS patients through physical interventions. This finding emphasizes the necessity of more clinical examinations and increases the hopes for new rehabilitation methods for the disorder.

Keywords: Exercise Therapy, Cognitive Functions, Multiple Sclerosis.

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Introduction

Multiple sclerosis (MS) disease affects the central nervous system in a way that the rate of neural conduction of electrical impulses in the patient decreases due to the damage to the neurons' myelin which, in turn, leads to a variety of symptoms and problems (1). Currently, over 1.3 million people are infected with MS, globally (2).

According to the statistics by World Health Organization (WHO), its prevalence in Iran is 20-60 individuals per 100,000 populations and its prevalence is 3-4 times higher among women (3). The major prob-

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lems associated with MS are fatigue, depression, muscular spasms, pain, overactive bladder, and sexual impairments. MS-induced fatigue is actually caused by the unnatural lack of energy instigated by the illness which, in turn, considerably limits the patient's physical and mental ability, regardless of his/her level of neurological disability. This lack of energy affects the patient's motor and cognitive skills and can surface in the form of energy decline, feeling of illness, motor weakness, and difficulty in concentration. One of the most serious difficulties facing MS patients is their cognitive impairment (4) .Based on different reports, 40-60% of MS patients face some degrees of cognitive difficulties in their daily lives (5). These problems are related to long- and short-term memory, visual and auditory memory, working memory, and logical functions of the brain with different intensities depending on the type of the disease (6). The results of the previous research indicate the existence of a reduction in the rate of processing of information, as well as a decrease in the concentration and attention span in about 30% and 25% of MS cases, respectively, which in comparison to executive functions, with 19% frequency, are more prevalent (7). Considering the fact that the majority of MS patients are young and middle-aged people, cognitive problems can have devastating effects on their professional, social, and family lives. All this suggest the importance of finding solutions to improve the cognitive faculties of those afflicted with this disease (8) .As pointed out by some studies, such problems can also be regarded as the primary symptoms in early stages of the disease (9) .In the case of cognitive problems, pharmacological interventions have not proven to be successful (10, 11). It seems that making use of alternative types of rehabilitation techniques, such as mental and/or physical ones, can be a more appropriate substitute for such treatments (12-14). Physical activities aiming for the improvement of patients' cognitive faculties are among the recommended remedies in the literature (15, 16). In the past, the effects of physical exercises on the improvement of physical abilities such as strength, endurance, and fatigue, as well as mental and psychological aspects like quality of life, depression and anxiety have been investigated with the results in favor of such interventions (17-19) .Most of the studies on MS patients have focused on physical aspects, ignoring the cognitive and psychological dimensions (20). For example, in 2004 Oken et al. examined 69 MS patients performing aerobic and yoga exercises for six successive months, and concluded that these exercises had no impact on their mental functioning (21) .In contrast, Velikonja et al. (2010) in a comparison between only 20 MS patients, who were categorized into yoga and mountain climbing groups, concluded that yoga caused 17% improvement in brain function (22). Finally, Motl et al. (2008) in a meta-analysis on the effect of exercise on cognitive performance of MS patients found that there are not adequate clinical trials in this area to arrive at any firm conclusion, yet (23). Nevertheless, the existence of positive impact of physical exercises on cognitive problems and brain size in other diseases such as dementia, Alzheimer, Parkinson, as well as in old people has been confirmed (24-29). Based on the previous studies, it seems that multi-stage or compound exercises may have positive impacts on MS patients, minimizing the development of their disease and improving their life quality. This study was conducted due to the necessity for curing cognitive problems of MS patients. As stated in the literature review, due to the complexity of the disease, the current therapeutic techniques to remedy the cognitive impairment do not have enough variety and power. Therefore, some experts have proposed using physical interventions to evaluate their cognitive impacts.

This pilot study was conducted to identify whether physical exercises affect mental and cognitive impairments, and whether they can result in any significant changes in the cognition of MS patients. Basically, this study aims to examine whether a large clinical trial for this purpose is feasible. Considering the fact that a large-scale and rigorous experiment in this area will be quite costly, carrying out such pilot studies to reveal their obstacles and potential caveats seems indispensable. Therefore, this study, as a quasi-experimental pilot research, has been designed to investigate the effects of physical exercises on the cognitive problems of MS patients.

Methods

After obtaining the required permissions from the president of Iranian Multiple Sclerosis Society and making the preliminary arrangements, this quasi-experimental research was carried out in the form of a pretest/posttest pilot study. The study was carried out with the participation of 42 patients diagnosed with MS, who were selected from those visiting the rehabilitation center of Iranian Multiple Sclerosis Society (located in Tehran), within a 14-month period from September 2012 to December, 2013, using non-probability convenience sampling.

Patients and Methods

The total sample size for the study was determined to be 42 individuals -which based on the prior studies was calculated to render a 95% confidence level, d= 1, and σ2= 2.

Iranian Multiple Sclerosis Society :Iran Multiple Sclerosis Society -- located in Tehran, the capital city of Iran -- was established in June 1999 and later, in 2000, was registered as a non-governmental charity organization. Today, it has over 18,000 members across the country (30).

In this paper, the following data collection instruments were used:

-Demographic questionnaire asking about age, sex, disease flow (i.e. recurrence, recovery, and progression types - whether primary or secondary).

-Expanded Disability Status Scale (EDSS) that estimates the amount of disability in MS patients. This scale investigates the eight Functional Systems (FS) including the pyramidal and cerebellar areas, brainstem, sensory, bowel and bladder, visual and the cerebral; then, the patient receives an score ranging between 0 (normal neurological function) to 10 (death due to MS). The scale was chosen by a neurologist and divided into three categories of mild (0-3), moderate (3.5-6.5), and severe (7 and above), based on Jones classification criterion (31).

-The Rao Brief Repeatable Battery of Neuropsychological (BRB-N) Tests.

First, the patients were evaluated based on EDSS. Then, only those who were identified to be in the mild to moderate categories (i.e. EDSS= 1 to 4) were selected (31). The reason for this was that the researchers wanted to ensure patients are capable of performing the variety of exercises selected for them. The inclusion criteria were definitive diagnosis with MS of relapse and recovery, secondary progression types, the use of disease modifying drugs (DMD) such as interferon, and an EDSS lower than 5.0. All patients who had gone through rehabilitation or had had any type of MS attack over the last three months prior to the intervention were excluded from the study. The majority of the participants had relapse-recovery courses of MS, and some of them were inflicted with the secondary progressive type of the disease (9). In this study, both genders, regardless of their educational levels, were included. All members of this group consumed anti-depression, fatigue-relievers, and DMD drugs. One reason for the exclusion of primary progressive patients was that they did not take DMDs (16, 32). However, the dosage and injection days were not constant for all patients. In addition, patients' capability in commuting to and from the rehabilitation center was also taken into consideration for proper planning of exercise sessions. In sum, 21 subjects including 4 (19%) males and 17 (81%) females began the training program. It is worth noting that before conducting the study, the objectives of the program were explained to all participants. Medical examinations and questionnaires were completed after obtaining written consent from the volunteers. All patients took the Rao cognitive test to screen cognitive status one week before and after the interventions. Rao cognitive test is repeatable cognitive test in which the amount of concentration and attention span, short- and long-term retention of vocabulary items received through the auditory channel, short- and long-term visual memory, and semantic memory are evaluated.

It is noteworthy to mention that the content validity of the Rao Brief Repeatable Battery of Neuropsychological (BRB-N) test was evaluated in this study first by the confirmation of 10 faculty members of medical faculty based on the latest professional texts and reliability of this tool was confirmed by test-retest method. In this method, BRB-N test was administered twice, within a 14-day interval to 34 individuals who were qualified to enter the study. Finally, the correlation coefficients of 0.88 and Cronbach's alpha coefficient of 0.93 were achieved for BRB-N test.

The BRB-N test contains five separate sections as follows:

1. Selective Reminding Test (SRT): This is a short- and long-term word memorization test, used for the evaluation of short- and long-term memory. A list of 12 irrelevant questions is given to each patient and they are immediately asked to repeat the words they have heard. This procedure is repeated for six times, allowing the patient to memorize all the items. The examinee is then re-asked to retrieve the memorized words after 11 minutes. In this test, the scores for permanent long- and short-term memory are estimated.

2. 10/36 Spatial Recall Test (SRT): This test evaluates the visual memory. In this test, a card (similar to a chessboard) with 36 squares is given to the examinee. Ten out of 36 squares on the card are filled with black color. After 10 seconds, the test-taker is asked to replicate the pattern using 10 pieces on a blank 6*6 card, similar to the original one. The test may be repeated for the second or third time in case the patient fails to complete the task. The subject is again asked to repeat the task after 7 minutes; this way his/her visual long-term retention is also assessed. Finally, the correct and incorrect answers in long- and short-term trials are recorded.

3. Symbol Digit Modalities Test (SDMT): This test evaluates the brain's capability in connecting numbers and symbols. In other words, the data processing rate and the working memory are evaluated. In this test a set of numbers and symbols which are matched together are given to the test-taker. He/she, then, is asked to match the numbers with their corresponding symbols by looking at the symbols. The number of correct answers given in 90 seconds is recorded as the test score.

4. Paced Auditory Serial Addition Test (PASAT): In this test, hearing, the ability in concentrating on what is heard, the rate of information processing, and working memory are examined. In this procedure the test taker listens to two separate sets of numbers uninterruptedly for two times (i.e. first for three minutes and then for two minutes). The subject must then add every two consecutive numbers with each other and report the result. The total number of correct answers is taken as the test score for both the stages.

5. Word List Generation: This is a sensitive test for measuring cognitive problems for several types of brain damage. In this test, the subject is asked to create as many words as he/she can with a certain letter in 90 seconds. This task is then repeated with two other letters. The total number of words correctly made with the three given letters is taken as the test score (33).

Intervention

The exercise program for the group included a set of compound physical movements in three-step form which is assigned to each patient to be performed individually or in group. After the initial evaluation, each patient received a program including aerobic exercises in the first step. These exercises were performed using stationary bikes and treadmills. Each patient started the exercise with the treadmill and the stationary bike, spending 10 minutes on each. This period increased gradually based on the subject's ability until he/she could preform 20 minutes on the treadmill and 20 minutes on the bike. To provide patients with more comfort and less tiredness, the bikes chosen for the experiment were of the type with recumbent seats. The difficulty level and the revolution rate of the bike, as well as the speed and slant of the treadmill were adjusted based on the unique characteristics of each participant. Every patient was reminded to take a rest in case of tiredness. They were also recommended to have a 10-minute interval between the bike and treadmill exercises. Each patient undertook 24 therapeutic sessions in eight weeks. One of the inclusion criteria was participating in at least 20 therapeutic sessions. In some cases make-up sessions were provided to those who had missed some sessions so that they could continue as participants in the study. In case of missing the sessions for 10 successive days, the subject was removed from the study.

In each session the participants were given 30 minutes of different balance exercises. The types of exercises used for this purpose included 10 minutes of trampoline, 10 minutes of tilt board, and 10 minutes of various individual and group exercises such as weight shift via standing on one leg with open and closed eyes, walking modification, and walnut cracking. Every patient would get a rest between these exercises to prevent fatigue. In addition, the participants performed isometric and stretching exercises which targeted their lower muscles and vertebral column two times per week for 15 minutes. All of these exercises were carried out under the supervision of an experienced physiotherapist and two experts in physical education. The training programs were decided based on individuals' physical conditions. Every session was recorded on a certain schedule and rechecked every 10 days. After the completion of the eight-week training program, the cognitive tests were given to the participants, again.

Three-step exercises are compound exercise programs which are used with MS patients. In three-step exercises, instead of performing only balance, aerobic or resistance exercises, patients work with a combination of the three types. Here, a combination of aerobic, strength, and balance trainings was used. The underlying reason for the employment this type of trainings is 15 years of research into how MS patients should exercise. Today, this method is known (or at least it is supposed) to be a reasonable way in helping MS patients in different tasks such as improving their strength, walking quality, balance, and feeling of fatigue. In fact, this three-step intervention is not meant to separate these exercises, but to combine their benefits for the patients. As mentioned earlier, this training method is the most up-to-date therapeutic technique for the rehabilitation of MS patients.

Ethical Considerations

Ethical considerations (such as plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely followed by the authors. The Ethics Committee of Kerman University of Medical Sciences approved the study protocol with Code No: K/92/398. Written Informed consent from all participants was obtained and the Declaration of Helsinki was followed throughout the study.

Statistical Analysis

After data collection and codification, the normality assumption for the data was first examined by Kolmogorov-Smirnov test which did not verify data normality. Then, the descriptive statistics including frequency, mean, and standard deviation, as well as analytical statistics like Wilcoxon Signed Ranks Test were used to compare the main variables before and after the intervention. The significance level was set to 0.05. The researcher could control for the confounding variables by comparing the posttest results of each patient with his/her own pretest results.

Results

In this quasi-experimental study, 17 (81%) out of 21 subjects completed the test. Two (9%) patients dropped out of the study because of commuting problems, and one (5%) had an attack during the fourth session. Also, one (5%) subject was withdrawn from the study due to his absence at final evaluation session which made it impossible for the researchers to obtain information from him. Therefore, 17 patients undertook the final assessment. Overall, 82.4% (n=14) and 17.6% (n=3) of the subjects were female and male, respectively. The mean (±SD) age of the participants was 37.1 (±9.98) years (Range: 23-51 years), and all of them were living in Tehran. In addition, 88% (n=15) and 12% (n=2) of them had relapse-recovery, and secondary progressive types MS, respectively. Moreover, the mean (±SD) of EDSS was estimated to be 2.35 (±0.90), and the subjects participated in 22.5 training sessions, on average. Research data were tested using Wilcoxon nonparametric test and the results showed that there was a significant difference in long-term memorization between pretest and posttest ($p<0.05$) which means an improvement in the long-term retention of the participants from 42.94 to 54.65 ($p<0.001$). In addition, there was a significant difference in sustainable long-term retrieval between posttest and pretest, indicating an increase in long-term retrieval of the patients from 36.94 to 49.88 ($p<0.001$). Moreover, the average total delay increased from 8.47 to 9.58, implying a significant difference ($p=0.010$). The average SDMT scores increased from 26.35 to 29.76 also suggesting a significant change ($p=0.028$). In the 3-minute-PASAT, the average score changed by 7.54 points in posttest showing a significant difference ($p=0.047$), however this change was not statistically significant in the 2-minute version of the test. In addition, no significant differences were spotted in 10/36, word generation, and Wilcoxon tests.

Discussion

The results from this study indicate that 24 training sessions (3 sessions per week) allow significant changes in the scores of different sections of RAO cognitive test in patients suffering from MS. The average changes in all parts of SRT were significant. In addition, the scores from SDMT and PASAT-3' version also showed a significant increase, implying an improvement in the concentration, working memory, and information processing rate of MS patients. These results are compatible with Velikonja et al., which reported a 17%-increase in the concentration capability of MS patients after 10 weeks of aerobic and yoga trainings (22) .In contrast, Oken et al., after a six-month yoga program, concluded that these exercises had no impact on cognitive problems of patients with MS (21). These divergent results can be attributed to the differences in the types of exercises used. Due to the lack of adequate studies on MS, several other studies in other areas can be mentioned, in which aerobic, balance, resistance, and strength training programs have been administered to the elderly, as well as patients with MS, dementia, and even Parkinson, resulting in improvements in their cognitive faculties. Among those studies, the reviews and meta-analyses by Heyn (27), Smith (26), and Erickson (34) are examples in which the positive effects of training, especially those of aerobic exercises, on cognition has been discussed. Liu-Ambrose has also reported the effect of balance and resistance exercises on the improvement of cognition, particularly with respect to concentration and working memory, in the elderly (28). In addition, it has been shown that the rate of decrease in the brain size of animals with Parkinson intensifies after halting physical activities (14). All these evidence suggest that physical activities may improve the brain functions of MS patients. Here, the vital and essential questions are: what are the most effective exercises? What mechanisms of those exercises are causing these changes? Which cognitive problems are improved by which exercises? And, to what extent these changes are stable. Rao (1991) argued that although cognitive problems facing MS patients are very divergent, a certain number of difficulties are seen in all of them that include problems in memorization, information processing, and concentration as the most frequent ones. Also, as pointed out by Rao, functional memory problems are relatively rare in MS patients (7). The results of this study are consistent with the other results reported before, indicating higher recovery rate for the problems enumerated above. Unsurprisingly, the scores from the word generation, 36/10, and PASAT-2' version tests did not show significant changes. These results may be because of the higher severity of the problems in memorization and concentration of individuals' or maybe the types of exercises used here have caused more improvement in these areas of cognitive circle of MS patients. However, the lack of accurate measures for these variables in the case of MS patients makes precise confirmation of this claim difficult.

Among other reasons attributable to the considerable effect of exercises on the reduction of cognitive problems, is the decrease in such problems as MS induced fatigue, depression, and anxiety. Researchers such as Landro (35), Krupp (36), Engel (37), Arnett (38), and Chiaravalloti (39) have suggested the existence of a relationship between affect and cognitive problems. Learmonth et al. (2011) has also referred to the effect of exercise on the reduction of cognitive problems (40). Therefore, any minor or major improvement of mental and cognitive performance of the patients may be attributable to the improvement in their affective states. Consequently, it seems that controlling for this factor, before initiating such studies, is essential.

It is worth mentioning that patients participating in this study were members of Iranian MS Society which had come from various socioeconomic classes in Tehran and there was no orientation on the part of the researchers in this regard. One of the limitations of this study was nonexistence of the Persian version of Selective Reminding Test. There are 15 different lexical lists used in the original version of this test, however only one of them had been translated into Persian and could be employed here. In addition, access to the research participants was very difficult due to their disease and commuting problems. Moreover, considering that this study was a pilot, there was no control group for making comparisons, although this limitation was partly tackled by comparing each person's final results with his/her pretest outcomes.

Conclusion

Finally, it is recommended to perform RCTs with larger sample sizes, longer durations, different exercise types, and longer and broader evaluations, and more comprehensive tests for a better assessment and understanding of patient problems to answer questions such as: Do physical exercises improve MS patient's mental capability? What aspects of these problems are affected by those exercises? What results should be expected from different exercises?

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