Original Article

The Comparison of the Effectiveness of Cognitive-Behavioral Stress Management Training and Acceptance and Commitment Therapy on Interleukin 12 in patients with Multiple Sclerosis

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Abstract

Introduction: The levels of Biomarkers such as interleukin 12 (IL-12) are elevated in patients with Multiple Sclerosis (MS). The aim of the present study was to compare the effectiveness of Cognitive-Behavioral Stress Management (CBSM) training and Acceptance and Commitment Therapy (ACT) on IL-12 in Multiple Sclerosis (MS) patients.

Methods: The present study was a quasi-experimental design with pretest-posttest and follow-up with control group. The statistical population included all female patients with Relapsing–Remitting MS who had referred to Multiple Sclerosis Research Center of Tehran University of Medical Sciences in Sina Hospital. 30 patients were selected by convenient sampling method and were replaced randomly into two experimental groups and one control group (each group included 10 patients). One of the experimental groups received the CBSM training and another experimental group received the ACT. To measure IL-12, the Enzyme-Linked Immunosorbent Assay (ELISA) was used. The data were analyzed using Analysis of Variance (ANOVA) with repeated measurement.

Results: The results showed that ACT had no significant effect on IL-12 ($p>0.05$), but CBSM training significantly reduced IL-12 and these results remained in the follow-up period ($p<0.001$).

Discussion: Relaxation techniques in CBSM can increase diaphragmatic breathing and decrease stress experience, including cortisol levels and stress. Subsequently, physiological symptoms reduce stress and thus affect the level of biomarkers like IL-12. Therefore, it can be useful in improving biological parameters in patients with MS.

Declaration of Interest: None

Key words: Cognitive-behavioral stress management training, Acceptance and commitment therapy, Interleukin-12, Multiple Sclerosis.

Introduction

Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system that destroys the myelin sheath in the brain and spinal cord (1). Women are approximately 2–3 times more likely to suffer from MS, and most patients are 20 to 50 years old (2). Residents of Eastern Europe are more likely to suffer from MS compared with residents of Asia, Africa and Latin America (3, 4). MS causes to the impairment of the sensory system, including numbness or paresthesia; impaired motor function including weakness or spasm; eye, bowel and bladder dysfunction, cognitive and fatigue disorders (5), and psychological disorders such as stress (6). MS can have an effect on the levels of biomarkers such as Interleukins 12. (7)

Interleukins (IL) are cytokines made by white blood cells that often affect other leukocytes (8). Cohen and Herbert (8) have suggested that assessing the concentration of cytokines is an appropriate method for examining the underlying mechanisms of immune disorders in stress. Biomarkers can identify disease progression or therapeutic effects (9). Researchers such as Alxander et al., 2010 & Van Boxel-Dezaire et al., 1999, have linked IL-12 levels to disease activity and changes in magnetic resonance imaging (10, 11). People with MS have been shown to have higher levels of Il-12, and this marker predicts correctly in 81% of patients (12). The findings of Özenci et al. (13) corroborated this system in MS patients. Van Boxel-Dezaire (11) showed that there is a significant increase in the expression of Interleukin-12 by peripheral blood mononuclear cells before recurrence. In the research of Losy et al. (7), there is significant increase in interleukin-12 in relapsing-remitting stage disease as well as in primary cases and secondary forms (14). Biological processes in MS can be influenced by psychological variables such as stress, psychological distress, or even exposure to disease such as acceptance, so psychological treatments may be effective on these biological processes of MS, Numerous studies have shown the association between physical stress or stressors and psychological distress with levels of interleukins (15,16,17,18).

Cognitive-behavioral Stress Management (CBSM) is one of the psychological therapies developed for people who are struggling with the stress of chronic and severe physical illness (19). CBSM can relax and reduce stress and effectively cope with problems through techniques such as relaxation training, meditation, and biofeedback (19). This program is a combination of relaxation and cognitive-behavioral techniques that are integrated into CBSM intervention (20).

Other therapies that have been effective in patients with MS, are Acceptance and Commitment Therapy (ACT) (21). Research has shown that ACT has been effective in improving the psychological problems of patients with MS and these improvements have been sustained (22, 23). ACT was first developed by Steven Hayes in 1986 (24). This method is part of the third wave of behavioral therapies followed by the second wave of these therapies, such as Cognitive-Behavioral therapy (CBT) and it is one of the recent expanded models whose key therapeutic processes differ from traditional CBT (25). ACT is a third-wave behavior therapy that explicitly embraces this approach of changing thoughts and feelings rather than their content or frequency, and the underlying principles include: 1- Acceptance, or willingness to experience pain or other disturbing events without attempting to inhibit them. 2. Value-based action or commitment with a desire to act as meaningful personal goals rather than eliminating unwanted experiences in

interacting with other nonverbal attachments in a way leading to healthy functioning (25). This method includes exposure-based experiences and exercises, linguistic metaphors, and techniques such as mental relaxation (25). The main goal of acceptance and commitment therapy is to provide some kind of psychological flexibility. Psychological flexibility means the ability to choose the action that is most appropriate among the various options, rather than doing something that is only to avoid disturbing thoughts, feelings, memories, or desires (26).

Some studies of the effects of CBT on the reduction of inflammatory cytokines such as Interleukin-6 in patients with major depressive disorder (27) and inflammatory cytokines in insomnia patients (28) as well as the effect of CBSM. A CBSM training done by phone has revealed a decrease in inflammatory cytokines including IL-13 (29). ACT has been associated with reduced anxiety, depression, and stress in patients with Multiple Sclerosis (30). Stress, depression, and anxiety and levels of interleukins are related (31, 32, 33). Therefore, ACT may also decrease interleukin-12 levels by reducing stress, anxiety, and depression. Although these studies have revealed the effects of these two therapies on biomarkers and psychological distress, there is no research that directly examines these two therapies on interleukin 12 in MS patients. Therefore, this study was the first to address the general question of whether CBSM training and ACT can influence biomarkers such as Interleukin 12 in MS patients, and whether there is a difference between the two treatments in the effectiveness of this biomarker.

Method

The present study was a quasi-experimental design with pre-test, post-test and two-month follow-up with control group. The statistical population consisted of all female patients with relapsing-remitting MS who referred to MS Research Center of Tehran University of Medical Sciences in Sina Hospital between January 2019 to June 2019. The McDonald Criteria (2017) was the basis for the Diagnosis of Multiple Sclerosis (34). Patients were selected and randomly assigned to the first experimental group (n = 10), the second experimental group (n = 10), and the control group (n = 10). The first experimental group underwent 8 weekly sessions (90 minutes each session) of CBSM training based on therapeutic guidelines of Anthoni, Ironson & Schneidermann (20), the second experimental group received eight 90-minute sessions of ACT Based on Hayes (24), and the control group was placed on the waiting list. The sessions were held at the Sina Hospital of Neuroscience Research Center of Tehran University of Medical Sciences. Inclusion criteria included definitive diagnosis of Relapsing-Remitting MS by a neurologist, failure to receive psychological treatment for the past 3 months, receiving the same medical treatment, no psychiatric disorders, no use of psychotropic drugs, no other physical illnesses affecting patients, and informed consent to participate in the study. Exclusion criteria included having psychiatric illnesses and other physical ailments, not attending training sessions for more than two sessions, refusing to participate in research and receiving psychological therapies for any reason. CBSM Training was summarized as follows in Table 1.

Table 1: Summary of CBSM intervention performed for the first intervention group

Session	Summary
First session	Introduction, introducing the first component of stress management (including being aware of physical responses to stress) and progressive muscle relaxation training for 16 muscle groups
Second session	Training on the impact of stress on thinking patterns, emotional conditions, behavior, physical sensations, stress, and patient relationships
Third session	Teaching the interplay of thoughts, emotions, and physical senses together, and learning how to change your "assessments" in stressful situations, and learning how to use imaging for relaxation
Fourth session	Introduce common types of negative thinking and cognitive distortions
Fifth session	Emphasize replacing logical thoughts with irrelevant thoughts and teaching five steps to replace logical thoughts
Sixth session	Learning to use the techniques learned in life and defining "coping" and introducing effective and ineffective coping strategies
Seventh session	Introducing and training steps for an effective
Eighth session	Program subjects became aware of their raw anger responses and patterns and learned better ways to manage anger, post-test.

Patients in the second intervention group participated in 8 sessions of ACT. Table 2 presents a description of these 8 sessions.

Table 2: Summery of ACT intervention performed for the second intervention group

Session	Summary
First session	Getting to know the research subject, examining the disease in each individual, presenting homework
Second session	Exploring the inner and outside worlds in act, developing a desired ineffective program (behavior change), changing and understanding that problem control is not a solution, and introducing alternatives to control, introducing homework
Third session	Identifying people's values, defining values, defining goals and defining obstacles, explaining the concept of acceptance and differing from the concepts of failure, despair, denial and resistance, acceptance is a perpetual, not a cross-cutting, process. On the challenges of acceptance, summary, and homework assessment
Fourth session	Assign and continue the discussion of clarifying value and behavioral commitment, and presenting homework.
Fifth session	Demonstrate self-separation, internal experiences and behavior, introduce and conceptualize self-conceptualized fault and fault, apply cognitive fault techniques, fusion and fault techniques homemade.
Sixth session	Commitment and self-observation, identifying patients' living values and reflecting on these values, summarizing and presenting homework
Seventh session	Mindfulness and emphasis on the present time, investigating the values of each person and deepening previous concepts, listing the most important values of the subjects and possible barriers to their follow-up, summarizing and homework presentation
Eighth session	Understanding the nature of willingness and commitment (commitment to action training), identifying values and commitment behavior plans, investigating life and commitment action stories, completing treatment, and post-test.

In order to adhere to the research ethics, participants were asked to participate in research and training sessions willingly and were told that their information would be kept confidential by the researchers. In this research, repeated measure Analysis of Variance was used for data analysis in SPSS-22 software.

Measurement In this study, a laboratory instrument was used to measure interleukin 12.

Measurement of IL-12 (ELISA): ELISA is a biochemical technique mainly used in immunity to measure interleukin 12 in experimental and control groups in pre-test, post-test and follow-up stages. Oncology is used to identify the presence of an antibody or antigen in a sample, ELISA is based on the binding of the antibody and the antigen, and this process is performed on a bed of a material with a high binding ability to the protein and having an adsorbing role. This bed is a 96-sheet pallet with 12 * 8 matrix, each one centimeter high and 0.7 centimeter in diameter. The advantages of ELISA are its high sensitivity, its quantitative and repeatability. Primary IL-12 levels were calculated by the device as well as after the intervention and after the 60-day follow-up period. Serum IL-12 levels were measured from the blood samples of patients with MS participating in the present study in pre-test, post-test and follow-up. In this method, blood samples were separated by serum centrifugation and stored in a freezer at -18°C. Then IL-12 levels were analyzed and analyzed only on the duplicate samples taken prior to each of the three stages (pre-test, post-test, and follow-up). IL-12 levels were recorded in all three stages of pre-test, post-test and follow-up.

Results

Demographic Characteristics was shown in Table 3

Table 3: Demographic Characteristics

Group	Age		Marital Status			Academic Studies			Age of onset of disease		Duration of illness	
	M	SD	Unmarried	Married	Divorced	High School	Bachelor	Master & Higher	M	SD	M	SD
CBSM	31.6	6.74	3	7	-	4	4	2	24.3	3.47	7.3	4.83
ACT	36.2	9.31	2	8	-	4	5	1	28.9	7.45	۸/۳۰	5.44
Control	33.9	6.08	4	6	-	4	6	-	27.6	5.19	6.3	3.27

The mean and standard deviation of the IL-12 dependent variable in the pre-test, post-test and follow-up in the experimental and control groups are presented in Table 4.

Table 4: Mean and standard deviation of pre-test, post-test and follow-up of IL-12 variable follow-up by experimental and control groups.

Variable	Groups	Pre-test		Post-test		Follow-up	
		Mean	Standard Variation	Mean	Standard Variation	Mean	Standard Variation
IL-12	CBSM	55.6	6.77	36.76	5.98	37.17	5.77
	ACT	54.05	6.64	51.61	7.27	52.01	7.15
	Control	58.52	16.27	57.7	16.23	58.79	16.28

According to Table 4, which shows the mean and standard deviation of the study groups in the three stages of pre-test, post-

test, and follow-up, the mean IL-12 scores at post-test (36.76) and follow-up (37.17). Compared to the pre-test (55.61) in the CBSM training group. Also, IL-12 scores in posttest (51.61) and follow-up (52.01) compared to pre-test (54.05) did not change significantly in ACT group. The mean scores of the control group were equal in pre-test, post-test, and follow-up on this variable.

ANOVA with repeated measures was used to compare the means of the groups in the three stages of pre-test, post-test and follow-up. Prior to performing the analysis of variance with repeated measures, the tests of MBB, Kravitz and Levine tests were performed to observe the assumptions. The results of these tests to compare the efficacy of two therapeutic interventions on Interleukin 12 showed that the non-significant results of boxing tests ($p < 0.05$, $F = 1.48$) and Levin in pre-test (0.09). Post-test ($p = 0.10$, $F = 2.53$), and follow-up ($p = 0.08$, $F = 2.75$) ($p = 0.08$) ($p = 0.05$) confirms the assumptions of homogeneity of variance-covariance matrices and intergroup variance homogeneity

Also, the significant results of the Mokheli Sphericity test on the homogeneity of intra-group variances for Interleukin 12 showed no sphericity. Therefore, the Gaussian Greenhouse Modification was used to report on the intra-group effects. According to confirmation of the hypotheses, repeated measures Analysis of Variance was used to compare the effectiveness of the two interventions on research variables and the results are presented in Tables 5, 6 and 7.

Table 5: Results of repeated measures analysis of variance for intergroup effects of time and group interaction on IL-12

Variable	Source	Test	Value	F	the first rate of freedom	Error rate of Freedom	Significance	Eta
IL-12	Time of measurement	Wilks Lambda	0.03	497.55	2	26	0.001	0.98
	Interference of Time and Group	Wilks Lambda	0.02	88.7	4	52	0.001	0.87

According to the results of Table 5, the results of Lambda Wilks test showed that the effect of time and group interaction on IL-12 was significant ($p < 0.001$, $F = 88.70$). The variance of group scores is related to group membership. According to the results of the above test, repeated measures analysis of variance can be used to evaluate the effectiveness of CBSM and ACT on IL-12.

Table 6: Intra-group and inter-group effects test results using repeated measures analysis of variance on IL-12 levels

Effects	Variable	Variation Sources	Sum of Squares	Degree of Freedom	Mean of Squares	F	Significance	Eta
Inter-group	IL-12	Time of Measurement	950.39	2	475.19	865.01	0.001	0.97
		Time×Group	1403.18	4	350.8	638.56	0.001	۰.98
		Error	29.67	54	0.55			
Intra-Group	IL-12	Constant Value	238403.79	1	238403.79	679.4	0.001	0.96
		Group	3653.47	2	1826.74	5.21	0.01	0.28
		Error	3090.03	27				

Table 6 presents the results of the effects of CBSM training on ACT on IL-12. Based on these results, the intra-group effects of measurement time (p = 0.001, F = 865/01) and time and group interaction (p = 0.001, f = 638.56) as well as the intergroup effects (P <0.01, F = 5.21) for the Interleukin 12 variable showed a significant difference in Il-12 scores at least between one or both groups of CBSM and ACT with the group There is evidence and the chi-square values indicate acceptable intra-group effect size of measurement time (ηƞ2 = 0.97) and time-group interaction (ηƞ2 = 0.98) and intergroup (ηƞ2 = 0.28). (ηƞ2 >14) (Table 6).

Bonferroni post hoc test was used to evaluate the difference between the effectiveness of the intervention on IL-12, the results of which are presented in Table 6.

Table 7: Bonferroni follow-up test results for pairwise comparisons of mean IL-12 scores

Variable	Basis Group	Compare Group	Mean Differences	Standard Error	Significance
IL-12	CBSM	ACT	-9.37	4.84	0.19
		Control	-15.49	4.84	0.01
	ACT	CBSM	9.37	4.84	0.19
		Control	-6.12	4.84	0.65
	Control	CBSM	15.49	4.84	0.01
		ACT	6.11	4.84	0.65

Table 7 shows the results of paired comparison of the mean IL-12 scores between the experimental and control groups. The results showed that there was a significant difference between the mean scores of IL-12 in the CBSM training group and the control group (p <0.01). But there was no significant difference between the IL-12 scores of the ACT group and the control group (meandiff = -12.12, p <0.05). That is, IL-12 scores were significantly reduced only in the CBSM training group compared to the control group, and these changes remained in the follow-up period. The results also showed that there was no significant difference between the effectiveness of the two interventions (meandiff = 9.37, p <0.05).

Discussion and Conclusion

The present study compared the effectiveness of CBSM with ACT based on IL-12 for the first time. Repeated measures ANOVA were used to evaluate the effectiveness of CBSM and ACT on Il-12 levels. The results showed that only CBSM intervention resulted in a decrease in Il-12 and there was no significant difference between their efficacies. Also, these changes remained stable over time.

MS is a disease in which stress plays a major role, and evidence suggests that assessing the concentration of cytokines is an appropriate method for examining the underlying mechanisms of immune abnormalities in stress (8). People with AMS have higher levels of IL-12, and this biomarker predicts correctly in 81% of patients (12). Also, evidence has shown that there is a significant increase in Il-12 in the recurrent stage of STD (7) as well as in primary cases and secondary forms (14).

Although no research has been conducted on the effectiveness of CBSM on biomarkers such as interleukin 12 and this study first examined the effects of this intervention on IL-12 in MS patients, the results of some studies are consistent with our results. Cognitive-behavioral stress management influenced IL-12 depletion. For example,

Hall showed that CBSM training could reduce IL-6 in people with chronic fatigue syndrome (35). Moreira showed that CBT was able to decrease inflammatory cytokines such as IL-6 in patients with major depressive disorder (27). Lattie showed that treatment of CBSM treatment by phone reduced IL-13 (29). Berk showed that CBT was able to reduce stress-related biomarkers such as interleukins 4, 6, and 10 in patients with major depression and chronic medical conditions (36). A research by Chen et al., 2011, reported that CBT reduced inflammatory cytokines such as IL-18 in hemodialysis patients (37).

Although no research has been done on the efficacy of acceptance-based therapy on IL-12, but inconsistent with the results of the present study, one study found that Acceptance-based therapy improved biomarkers such as heart rate, blood pressure, fasting blood sugar, Salivary telomere length, Il-6, cortisol and alpha amylase were found in breast cancer patients (38). Also, another study showed that ACT improved biological parameters such as systolic and diastolic blood pressure and cortisol in patients with major hypertension (39). However, this study found that ACT had no role in reducing IL-12, and only CBSM was able to decrease IL-12. Thus, these results can be said to play a key role in stress disorder, and also that stress and psychological distress are correlated with levels of interleukins (31, 32, 33), CBSM may have reduced IL-12 in MS patients through its effect on stress reduction. Numerous studies have shown the association between stresses or physical and psychological stressors with levels of interleukins (15, 16, 40, 41 and 42). CBSM leads to relaxation and stress reduction and effective coping with problems, through techniques such as sedation training, meditation, and biofeedback (19). Stress as a multidimensional and multidimensional phenomenon can be a complication of EMAS as well as a factor in the exacerbation and recurrence of symptoms due to illness (15). Stress management training may be provided by empowering patients with MS to cope with their illness, learning about sources of stress, and training effective coping skills, including problem solving training, muscle relaxation skills and modifying maladaptive cognitive assessments using cognitive reconstruction may help modulate stress-affected biomarkers. CBSM program enhances individuals' ability to reduce stress and adapt to stressful situations (19).

Stress Management interventions, CBT, or CBSM training may be appropriate strategies for positive change in patients with MS (43) and reduction of inflammatory cytokines (28, 44). Research has shown that stress-reduction therapies such as CBSM training and mindfulness-based stress reduction have improved biological markers such as interleukin 6 reduction in people with essential hypertension (45). Given that immune system dysfunction is one of the most important etiologic factors in this disease, it has recently been suggested that stress may exert an adverse effect on the course of these diseases through exacerbation of cognitive immune dysfunction and impact on the cytokine network. And intensifies disease activity (46, 47). CBSM training is taught to participants in the relaxation techniques group. Training in relaxation techniques enables individuals to recognize physical symptoms of stress and to learn how to control physical symptoms of stress by mastering the relaxation and use of these techniques (48). Because physiological responses to stress can occur in a wide range of physical symptoms, training in relaxation techniques can increase diaphragmatic breathing and decrease stress experience, including cortisol levels and stress.

Subsequently, physiological symptoms reduce stress (49) and thus affect the level of biomarkers.

This study has some limitations. First, current study is done only with women with MS disease , thus the results may not be generalizable to men with MS disease Secondly, this research has been performed on Recurrent-Remission type of MS and is not generalizable to other types of the disease such as progressive primary, progressive secondary, and recurrent progressive disease. Moreover, this research is not controlled for, and long-term illness can contribute to increased interleukin levels.

Despite these limitations, the present study showed that acceptance and commitment therapy had no significant effect on interleukin 12, but CBSM training reduced interleukin 12, and these results remained consistent in the follow-up period. Based on these results, applying CBSM training can be effective in regulating biomarkers in MS patients and it is suggested that this treatment should be used alongside drug therapy. It is suggested that future researches be conducted with a larger sample size and in a wider population, also future studies can be assessed on other types of MS including primary-progressive MS, secondary-progressive MS and progressive Relapsing MS and other auto immune diseases such as psoriasis and rheumatoid arthritis, The effectiveness of both interventions can be examined regarding other important biomarkers in MS

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Conflict of interest statement

The authors declare no conflict of interest.

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