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Effect of alpha-lipoic acid on asymmetric dimethylarginine and disability in multiple sclerosis patients: A randomized clinical trial

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Abstract

Background: Multiple Sclerosis (MS) is an inflammatory and demyelinating disease of the central nervous system. Oxidative stress plays a major role in the onset and progression of MS. Asymmetric dimethylarginine (ADMA) formation is dependent on oxidative stress status.

Objective: We examined whether alpha-lipoic acid (ALA) as a potent antioxidant could improve the Expanded Disability Status Scale (EDSS) and decrease plasma level of ADMA in multiple sclerosis patients.

Methods: In a randomized, double-blinded clinical trial conducted at Sina Hospital in Tehran, Iran, from September 2009 to July 2011, 24 patients with relapsing-remitting MS were divided into a treatment group receiving ALA (1200mg/day) for 12 weeks and a control group receiving placebo. Then patients' EDSS and Plasma levels of ADMA were measured at baseline and 12 weeks later. Statistical analysis was done by SPSS software version 16 using the K-S test, Chi square, Mann–Whitney U-test and Wilcoxon test.

Results: The plasma levels of ADMA in the intervention group were decreased significantly (p=0.04). Also, no patient had increased EDSS score in the supplement group, where 2 out of 12 patients in the placebo group experienced so. Comparing the serum level of ADMA between the two groups failed to show any significant change in the supplement group compared with the control group.

Conclusion: Considering that ADMA is produced by oxidative stress in MS patients and leads to increase of inflammation, ALA may have the potential of beneficial effects in them, in part, by decreasing the plasma level of ADMA and stopping progression.

Trial registration: The trial was registered at the Iranian Registry of Clinical Trials (http://www.irct.ir) with the Irct ID: No. IRCT138812222602N2.

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Keywords: Lipoic acid, Multiple sclerosis, Inflammation, Asymmetric dimethylarginine

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1. Introduction

Multiple sclerosis (MS), an inflammatory and demyelinating disease, affects the central nervous system (CNS) by demyelization and destruction of nerve tissue (1). Therefore, inflammation and degenerative processes are the main cascades in the pathogenesis of MS (2). Nitric Oxide (NO), with different biological functions are produced from L-arginine via NOS activity. Asymmetric dimethylarginine (ADMA) is a major endogenous inhibitor of endothelial NO synthase (eNOS). Recently, a positive association between inflammatory response and ADMA levels had been found in cardiovascular diseases (3). It is proposed that tissue damage in MS is related to the high levels of NO (4, 5). In line with this hypothesis, investigations in MS (6, 7) and experimental allergic encephalomyelitis (EAE) (8, 9) have shown that increase in proinflammatory cytokines TNF-α and INF-g is related with consequent progress in iNOS activity and NO generation. Reactive oxygen species (ROS), direct consequence of neuroinflammation, play a major role in inception and development of MS (10). A new report has indicated that oxidative stress increases the ADMA concentration by enhancing the formation and decreasing the degradation of ADMA (11). Alpha-lipoic acid (ALA), a naturally occurring short chain fatty acid with Sulfhydryl groups, has a potent anti-oxidant activity (12). The beneficial effects of lipoic acid on MS patients have been reported in several investigations (13-15). In addition, consumption of ALA led to a drop in plasma ADMA levels in diabetic end-stage renal disease (16). Yet, experimental studies have reported inconsistent roles of NO in the development of neurological immune-pathogen diseases such as multiple sclerosis (MS) (17, 18), leaving open the role of NO in this field. In the present study, we assessed whether ALA could improve the Expanded Disability Status Scale (EDSS) and decrease the plasma level of ADMA in multiple sclerosis patients.

2. Material and Methods

2.1. Trial design and participants

This study was a randomized clinical trial that was conducted from September 2009 to July 2011. This study is a pilot study and, to the best of our knowledge, is the first assessing effect of ALA on ADMA in MS patients. The sample size was assumed to be twenty subjects in each group. The MS patients (n=40) with relapsing-remitting course with disease duration more than one year were recruited from a multiple sclerosis clinic at Sina Hospital in Tehran. Diagnosis of MS was done according to McDonalds criteria (19).

2.2. Selection criteria

Excluding criteria were ongoing clinical relapse, pregnancy and lactation, the use of corticosteroids, occurrence of relapse attack during the study, and other major medical disorders. Regular consumption of antioxidants or vitamin supplements was also considered as exclusion criteria.

2.3. Interventions

The current study was carried out as a randomized double-blinded clinical trial. During the three months of study, from thirty-one patients allocated to interventional groups (ALA group; n=15 and placebo group; n=16) two patients in the lipoic acid group and one in the placebo group were exposed with relapse and excluded from the study. In addition, a patient in the placebo group not attending the complete study, was excluded. Finally, we finished the study with thirteen patients in the ALA and fourteen patients in the placebo group. At endpoint of study, we lost two blood samples in the placebo group and one blood sample in the supplement group. Therefore, results are presented with twelve participants in each group (Figure 1). While the placebo and ALA capsules were of the same shape and color, participants in ALA and placebo group took 1200 mg of ALA and placebo as two capsules respectively. The EDSS with scores from 0 and 10 units in half units was used to measure the intensity of MS symptoms and to assess the disease status and treatment. On start point and after three months, all participants underwent EDSS evaluation by the same neurologist. Weight was recorded using a Seca Electronic Weighing Scale (Seca, Hamburg, Germany) to the nearest 100 gr wearing light clothing. Height was measured without shoes, using a non-stretchable tape with accuracy of 0.5 cm. Body mass index (BMI) was determined by dividing the weight (kg) by the square of height (m^2). After overnight fasting, blood samples (8 ml) were obtained at baseline and at week twelve with subjects seated, in accordance with the standard protocol. Serum ADMA was detected by HPLC methodology (20) on HPLC apparatus (Agilent) with our condition modified fluorometric detection.

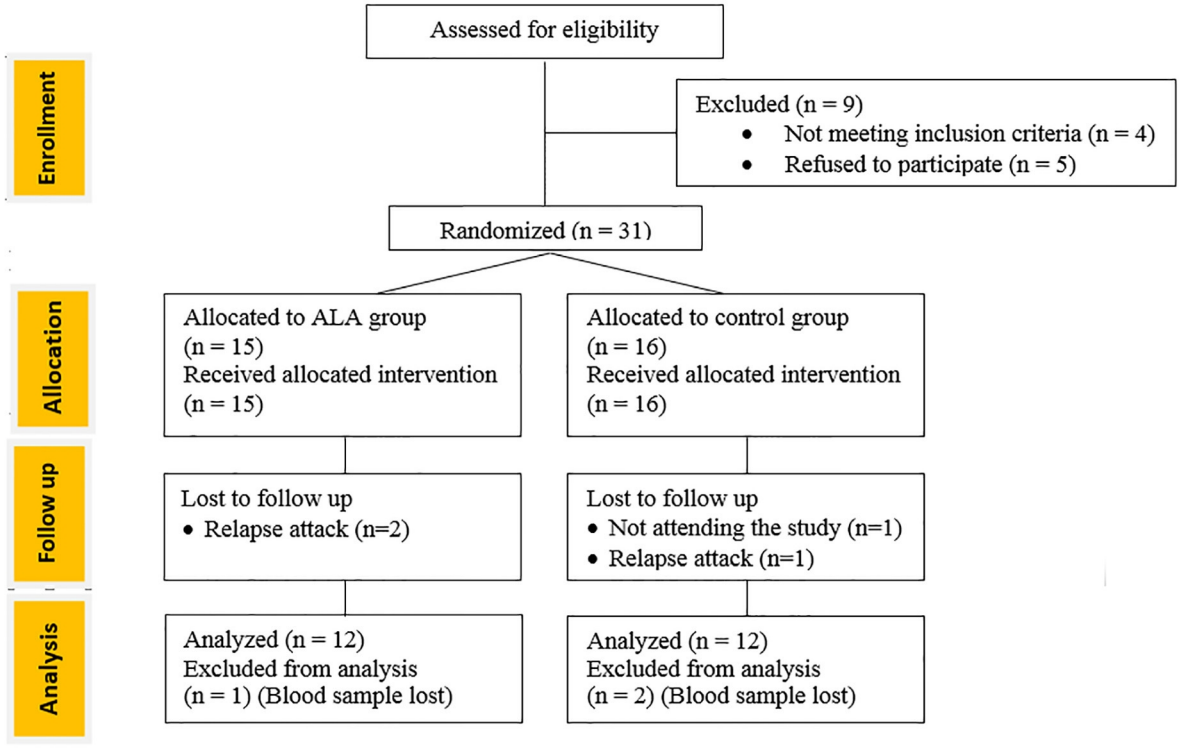

Figure 1. Subjects' disposition

2.4. Outcomes

The primary outcomes of our analyses were the mean variation of ADMA and EDSS score during study in the two groups. The secondary outcome was percent of patients exposed with rising of EDSS score in each group.

2.5. Randomization and blinding

In this clinical trial, using block randomization, participants were assigned randomly to receive either lipoic acid or placebo. We used computer generated randomization sequence through SPSS16 software (SPSS, Inc., Chicago, IL, USA) by one of the researchers who did not have a role in the treatment of the participants. A block size of four was provided for randomized sequence generation. Also, using numbered envelopes which contained the name of the intervention groups, the allocation hiding was done by the researcher who was responsible for the randomization.

2.6. Statistical methods

The mean and standard deviation were calculated using SPSS 16 software (SPSS, Inc., Chicago, IL, USA). The normality of the variables' distribution was examined using the K-S test. Chi square, Mann-Whitney U-test and Wilcoxon tests were used for variables analyzing. The significance level was established at p-value=0.05.

2.7. Research ethics

The study was approved by the Ethics Committee of Tehran University of Medical Sciences. The authors confirm that all ongoing and related trials for this intervention are registered. Prior to the study, all the participants were informed by the researcher about the objective and nature of the study, and provided written consent in Persian language. We were committed to keeping all the participants' information confidential.

3. Results

While, the supplement group had higher mean of EDSS than the control group, comparing baseline values of all parameters failed to show any significant difference between the two groups (Table 1). The mean plasma level of ADMA in MS patients was 0.37μmol/L, and baseline level of ADMA difference between supplement and control group was not so significant. In the treatment group, however, intake of ALA for 12 weeks significantly reduced the plasma level of ADMA, from a mean of 0.37 to 0.31 μmol/L (p=0.04). In the control participants, the plasma level of ADMA showed slight and non-significant increase during the study. Finally, comparing change of ADMA level

between the two groups did not show statistically significant variation in the ALA group compared with the control group (Table 2). During ALA treatment, EDSS scores in treated patients were slightly and not significant decreasing (at the beginning of the treatment EDSS score was 2.2±1.6, after 12 weeks 1.83±1.5). Instead, EDSS scores did not change significantly in the control group (Table 3). In addition, we compared disability progression manner to the number of patients with increased EDSS during intervention. Our findings indicated that in the ALA group, no patient had experience of increased EDSS, but in the placebo group 16.5% of patients were exposed with raised EDSS after 12 weeks. The correlation coefficients between base line level of ADMA and EDSS as well as the correlation of their changes during the study were not significant (data were not presented).

Table 1. Demographic characteristics at baseline (Mean±SD).

Variable	Supplement group (n=12)	Placebo group (n=12)	p-value
Age (year)	32.3±6.2	32.2±10.5	0.78
Sex (F/M) n	7/5	11/1	0.07
Duration of disease (month)	53.83±53.82	69.00±64.34	0.67
EDSS	2.20±1.60	1.54±1.32	0.31
BMI(kg/m^2)	24.1±2.9	23.9±2.3	0.73

Table 2. Baseline and end point level of ADMA and change after placebo or supplement application in patients (Mean±SD).

Variable	Supplement group (n=12)	Control group (n=12)	p-value
Base line ADMA(μmol/L)	0.37±0.08	0.35±0.10	0.41
End point ADMA (μmol/L)	0.31±0.06	0.37±0.14	0.19
Difference (μmol/L)	-0.06±0.09	0.02±0.19	0.29
p-value	0.04	0.96	

Table 3. Baseline and end point level of EDSS and change after placebo or supplement application in patients (Mean±SD).

Variable	Supplement group (n=12)	Control group (n=12)	p-value
Base line EDSS	2.20±1.60	1.54±1.32	0.31
End point EDSS	1.83±1.51	1.54±1.48	0.67
Difference	-0.37±0.77	0.01±0.1	0.34
p-value	0.10	0.95	

4. Discussion

This study is the first to assess the effects of ALA on the plasma level of ADMA in multiple sclerosis patients. In this study, we found that supplementation of ALA (1200mg/day) for 12 weeks, leads to a significant reduction in the plasma level of ADMA in MS patients. It is clear that MS is accompanied by inflammatory process as pathogenesis mechanism. This condition is mediated by activated specific and nonspecific immune cells infiltrating CNS tissue. It has been observed that NO generation is due to induction of inducible nitric oxide synthase (iNOS) in macrophages, increasing NO level is a critical component in the onset and development of MS (7, 21). This mechanism is a reason for high levels of NO and iNOS in CNS of both MS (18) and EAE (6). For example, the high levels of NO metabolites in the blood and CSF of MS patients have been observed in independent manner to neurological signs (22). It is believed that reactive nitrogen species, with cytotoxic effects on nerve and glial cells, provoke myelin and oligodendrocytes damage (22). ADMA, a natural amino acid, exits in plasma. It is known that the increase of ADMA, results in a suppression of the NO production by inhibition of NOS activity. Stojanovic and collogues reported that plasma concentration of ADMA in healthy people and MS patients is less than 1 μmol/l (23). Similarly, in our study the ADMA level in MS patients is found in less than 1 μmol/l. In another investigation, in patients suffering from multiple sclerosis, CSF ADMA levels were elevated (24). Positive correlation of ADMA levels with intensity of clinical severity was reported in inflammatory bowel disease (25). Furthermore, during interferon-β1b treatment in multiple sclerosis patients, ADMA levels were significantly increased compared to the baseline levels which were accompanied by decrease in EDSS level in treated patients (23). Regarding our results, treatment with ALA led to a decrease in ADMA levels as well as a halt in disability progression. These facts are in correlation with literature data from an experimental model of MS, reporting that ALA slows down the ICAM-1 and VCAM-1 and suppresses the infiltration of T cells through the blood brain barrier (26-28). Mentioned evidence found that ROS are important factors mediating injury in EAE and that generation of ROS can be decreased by

ALA. Also, ALA decreased the migration of monocytes through the blood brain barrier, which was correlated with the clinical improvement in EAE. However, there is no clear evidence evaluating direct correlation of ADMA level with clinical severity of MS. This study showed that ALA decreases circulating ADMA concentrations in patients with multiple sclerosis. Similarly, Chang and colleagues found that consumption of LA (600mg/day) decreased ADMA levels in a treated group of diabetic end-stage renal disease (16). ALA, as a potent antioxidant and anti-inflammation supplement, has been used in treatment of MS and suppressed proinflammatory cytokines levels such as TNF-α and INF-g in EAE models and MS patients (28, 29). In agreement with our results, researchers indicate that ALA decreases ADMA level in diabetes mellitus (30). ADMA is excreted via the kidneys and mainly metabolized by the enzyme dimethylarginine dimethylamino hydrolase (DDAH) (31), which is sensitive to oxidative stress (32). It is proposed that ALA via antioxidant properties could influence DDAH. Hence, accumulation of ADMA in nerve cells due to produced proinflammatory cytokines, such as TNF-α (33) as well as suppressing effect of ALA on TNF-α level in MS patients (15, 29) may be explanations for our results.

5. Limitation

The limitation of this study is that it does not show the clear mechanism by which ALA decreases the plasma level of ADMA. In addition, this study did not consider the potential for NO generation by the ADMA or give information on the activity of the DDAH enzyme that degrades ADMA.

6. Conclusions

Regarding our findings, ALA supplementation decreased ADMA levels and led to observe no patient with increased disability score during the study. But decrease of disability score in the ALA group was not significant. Considering that ADMA is produced by inflammation, however, ALA could have the potential to have beneficial effects on MS patients. We think that further studies with large samples and extended duration are needed to prove the effectiveness of ALA on the progression of multiple sclerosis.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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