Effects of Alpha Lipoic Acid Supplementation on Serum Levels of Oxidative Stress, Inflammatory Markers and Clinical Prognosis among Acute Ischemic Stroke Patients: A Randomized, Double Blind, TNS Trial

Sheyda Shaafi1,2*, Sorida Ebrahimpour-Koujan25, Mohammad Khalili4,2, Seyed Morteza Shamshirgaran5, Mazyar Hashemilar1,2, Aliakbar Taheraghdam1,2, Seyed Kazem Shakouri6, Elyar Sadeghi Hokmabadi1,2, Yaqoub Ahmad1, Mehdi Farnoudi1,2, Nasim Rezaeimanshahfar2,3, Daryoush Savadi Osgouei1,2

1Department of Neurology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
2Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
3Students Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran.
4Multiple Sclerosis Research Center, Neuroscience institute, Tehran University of Medical Sciences, Tehran, Iran.
5Healthy Aging Research Center, Neyshabour University of Medical Sciences, Neyshabour, Iran.
6Physical Medicine and Rehabilitation Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

$These authors had equally taken part.

Introduction
Stroke is the second leading cause of death across the world.1 It has various clinical, social, and economic burdens and its management demands a comprehensive effort by both basic scientists and clinicians.2 Ischemic stroke which is caused by either a sudden reduction in brain blood flow or complete blockage of it, accounts for 85% of all strokes.3 Despite sophisticated medical management and neurosurgical techniques, the mortality rate of stroke is remarkable.4 Wide lines of studies have focused on well-defined risk factors of stroke and its management strategies. Both life style and diet-related factors contribute to its high rate mortality.1 Better understanding of risk factors would improve treatment outcomes and prognosis of patients. It has been strongly clarified that oxidative stress is a fundamental mechanism causing brain injury in stroke patients.5 In fact, increasing levels of reactive

---

Abstract
Purpose: Stroke is one of the most common conditions causing death. There have been few studies examining the effects of alpha lipoic acid (ALA) on stroke patients. In this regard, the present randomized controlled clinical trial was conducted to examine the effects of ALA supplementation on serum albumin, and inflammatory and oxidative stress markers in stroke patients.

Methods: The present paralleled randomized controlled clinical trial involved 42 stroke patients who were over 40 years and under enteral feeding. The participants were randomly assigned into two groups and finally 40 patients completed the study. Patients in alpha lipoic acid group (n = 19) took 1200 mg ALA supplement daily along with their meal, and participants in control group (n = 21) underwent the routine hospital diet for 3 weeks. Fasting blood samples were obtained and albumin, oxidative stress, and inflammatory indices were assessed at baseline, as well as at the end of the trial.

Results: After 3 weeks, treatment of patients with ALA led to a significant decrease in tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) levels (P < 0.01) compared to baseline. But serum levels of albumin, total antioxidant capacity (TAC), malondialdehyde (MDA), high-sensitivity C-reactive protein (hs-CRP), IL-6 and TNF-α did not change significantly vs. control group (P > 0.05).

Conclusion: ALA did not significantly change the serum levels of albumin and inflammatory as well as antioxidant capacity indices in stroke patients compared with the control group. More clinical trials with large sample sizes and long duration are needed to clarify the effects of ALA on these patients.

---

Article info
Article Article History:
Received: 22 May 2019
Revised: 12 Aug. 2019
Accepted: 30 Sep. 2019
epublished: 18 Feb. 2020
Keywords:
• Alpha lipoic acid
• Inflammation
• Oxidative stress
• Stroke

*Corresponding Author: Mohammad Khalili, Tel/Fax: +98 21 66348571, Email: khalilimh@tbzmed.ac.ir
© 2020 The Author(s). This is an Open Access article distributed under the terms of the Creative Commons Attribution (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, as long as the original authors and source are cited. No permission is required from the authors or the publishers.
oxygen species (due to lower levels of antioxidant defense and higher levels of oxygen after reperfusion), oxidizing lipids, and iron induce oxidative stress. Therefore, the increase in ROS production and consequently in oxidative stress, as well as the increase in inflammatory mediators are the earliest and the most potent mechanisms involved in brain damage during the stroke.\textsuperscript{1,3} Modulation of free radicals derived from metabolic processes is one of the most important strategies in preventing reperfusion injury during stroke. This process is mainly mediated by antioxidants of the body.\textsuperscript{6} Alpha lipoic acid (ALA, 1,2-dithiolane-3-pentanoic acid), a neuro-protective and neuro-restorative antioxidant, with the ability to cross through blood–brain barrier, is a strong free radical scavenger in the brain.\textsuperscript{7,8} There are recent interests to assess the effects of ALA in central nervous system diseases such as Parkinson’s disease, Multiple sclerosis, Alzheimer’s disease, and spinal cord injury.\textsuperscript{9-11} Lipoic acid protects the brain against reperfusion injury in the early stages of cerebral ischemia.\textsuperscript{12} Primary experimental evidence has revealed that treatment of rats in cerebral artery occlusion condition with lipoic acid protects the brain against ischemic stroke by modulating several inflammatory pathways.\textsuperscript{3,4,12-14} Despite the positive results from a clinical trial on protective effects of lipoic acid on clinical outcomes after acute ischemic stroke,\textsuperscript{6} there is no evidence confirming its role in modulating the inflammatory process and oxidative stress in stroke patients. It seems that some clinical trials with basic trends are required to clarify the effects of lipoic acid on the modulation of the levels of free radicals and oxidative stress as main mediators in stroke. It is especially important in Iran where the prevalence of stroke is rising and this severely affects the patients’ quality of life which is effective in controlling the complications of the disease. Therefore, this randomized controlled clinical trial was conducted to examine the effects of ALA supplementation on serum albumin, and inflammatory and oxidative stress markers in stroke patients.

\textbf{Material and Methods}

\textbf{Participants}

The target population of the present randomized clinical trial (RCT) was patients with acute ischemic stroke of cerebral hemisphere who had referred to Imam Reza hospital, Tabriz University of Medical Sciences, Tabriz, Iran (Tabriz stroke registry project). The patients were screened according to the inclusion and exclusion criteria and 42 individuals of them were involved to this study, among which 40 patients completed the study (Figure 1). The patients who met the following criteria were eligible to include in the study: those who were admitted for the first time or diagnosed with acute ischemic stroke, those over 40 years, those whose National Institutes of Health Stroke Scale (NIHSS) scores were less than 20, and those for whom the enteral or oral feeding was done in first 48 hours of admission. The exclusion criteria included, being in vegetative state, having chronic conditions (including kidney failure, undergoing dialysis, liver failure and cirrhosis in the admission, seizure, cancer, gastrointestinal bleeding, uncontrolled diabetes, having any history of heart attack during past three month, respiratory disease,
heart failure, and hematologic disease), any changes in diagnosis and feeding methods, taking enteral feeding less than 10 days, taking immune-suppressive medications, abusing alcohol and drugs, death in the first 10 days of admission, and lactose intolerance. Patients were assigned to intervention and control groups by block randomization method. Randomization was done by computer-generated random numbers. Allocation of participants into the groups was done by a third person who was not directly involved in the project. Intervention group took 1200 mg ALA supplement daily along with the ordinary meal and participants in control group underwent the routine hospital diet for 3 weeks. All participants received kitchen made feeding with composition of 1.5 g/day protein and 25 kcal/kg energy per day. The ALA supplement was produced by Caren co. We did all measurements both at baseline and at the end of the trial. We calculated the required sample size based on data from a previous study by considering serum interleukin 6 (IL-6) as a key dependent variable, type I error of 0.05, and study power of 80%. Based on suggested formula for clinical trials and taking into account a possible dropout of 20%, we came up with the sample size of 20 stroke patients for each group.

**Study design**

This project was done in accordance with the guidelines laid down in the Declaration of Helsinki (1964). Individual questionnaires including demographic characteristics, past medical and drug history, as well as socio-economic status were completed for each patient by their family through comprehensive face-to-face interviews.

**Biochemical measurements**

Prior to the intervention and at the end of the trial, after at least 8 hours overnight fasting, 7 mL of venous blood samples were obtained from each patient. Blood samples were immediately centrifuged at 4000 rpm for 15 minutes in aseptic condition. Serum samples were separated in 1 mL micro-tubes and were immediately stored at -80°C. Serum levels of albumin, total antioxidant capacity (TAC), malondialdehyde (MDA), IL-6, high-sensitivity C-reactive protein (hs-CRP), and tumor necrosis factor alpha (TNF-α) were measured using enzyme-linked immunosorbent assay (ELISA) kits at the baseline and endpoint of the trial.

**Clinical prognosis measurements**

NIHSS is a systematic method that provides a quantitative measure of stroke-induced neurological damage and is generally designed for patients with acute stroke. The scale is comprised of 15 items and covers the results of stroke patients’ neurological examination and assesses the effect of acute stroke on the level of consciousness, language, eye movements, motor force, ataxia, and sensorium. Each item is scored either on a 3 or 5 point scale, where zero represents the normal state and upper limit is 42. Also, modified Rankin Scale (mRS) is comprised of 6 levels and evaluates independence rather than the performance of specific tasks. The scale consists of 6 grades, ranging from 0 to 6, where zero is associated with no symptoms, five represents severe disability, and 6 means death.

**Statistical analyses**

Statistical analyses of all data were performed using SPSS software version 21. Data results were expressed as mean ± standard deviation (±SD). We used the one-sample Kolmogorov-Smirnov test for assessing the normality of the data distribution. Baseline characteristics of the patients in the alpha lipoic acid and control groups were compared using independent sample t test and chi-square test for quantitative and qualitative variables, respectively. Paired t test analysis (following the intention to treat principle) was used to identify any differences between the two groups after intervention. The P value <0.05 was considered statistically significant.

**Results**

All 40 patients (19 patients in alpha lipoic acid group and 21 patients in control group) completed the 3-week trial. No patient reported adverse effects or symptoms with ALA supplementation during the trial. In lipoic acid group, 68.4% of the participants were men and 31.6% were women (13 males and 6 females). In control group 81.0% of the participants were men and 19.0% were women (17 males and 4 females). The demographic characteristics and anthropometric measures of the participants are shown in Table 1. There were no significant differences between the two groups regarding baseline variables including age, sex, marital status, education, smoking, co-morbidities, and lesion location at the beginning of the study (P>0.05).

The serum levels of albumin, TAC, MDA, TNF-α and hs-CRP before and after the intervention and their variations are shown in Table 2. There were just significant differences in term of MDA between two groups at the
Effects of alpha lipoic acid supplementation in acute ischemic stroke patients

Table 2. Serum oxidative-stress and inflammatory parameters of stroke patients at the baseline and after 3 weeks intervention with alpha lipoic acid

| Variable       | Measurement period | Alpha lipoic acid group (n=19) | Control group (n=21) | P value for between groups |
|----------------|--------------------|-------------------------------|---------------------|---------------------------|
| Albumin (mg/dL) | Baseline           | 2.94±0.78                     | 3.32±0.79           | 0.13⁺                    |
|                | After intervention | 2.92±0.62                     | 3.4±0.07            | 0.08³                    |
|                | Change, MD (95% CI), P value | -0.01 (-0.14,0.11), 0.79 | 0.10 (-0.15,0.36), 0.41 | 0.61 ³                  |
| TAC (mmol/mL)  | Baseline           | 3638.31±860.30                | 3835.14±881.83      | 0.48                     |
|                | After intervention | 3817.95±888.13                | 3842.19±938.21      | 0.99³                    |
|                | Change, MD (95% CI), P value | 199.63 (24.27,423.54), 0.07 | 7.05 (-1533,1394.42), 0.91 | 0.11 ³                  |
| MDA (nmol/mL)  | Baseline           | 1.02±0.14                     | 1.82±0.32           | 0.01⁺                    |
|                | After intervention | 2.05±0.26                     | 1.83±0.38           | 0.03³                    |
|                | Change, MD (95% CI), P value | 0.03 (-0.08,0.15), 0.57 | 0.01 (-0.12,0.14), 0.88 | 0.91³                  |
| hs-CRP (mg/dL) | Baseline           | 3.32±1.81                     | 3.58±1.56           | 0.63⁺                    |
|                | After intervention | 3.16±1.51                     | 3.47±1.43           | 0.51⁺                    |
|                | Change, MD (95% CI), P value | -0.16 (-0.37,0.4), 0.11 | -0.11 (-0.25,0.03), 0.11 | 0.92⁺                  |
| TNF-α (pg/mL)  | Baseline           | 20.50±13.91                   | 18.09±11.14         | 0.57⁺                    |
|                | After intervention | 16.49±9.63                    | 15.95±9.03          | 0.85⁺                    |
|                | Change, MD (95% CI), P value | -4.00 (-7.10,-0.91), 0.01 | -2.14 (-5.51,1.23), 0.20 | 0.21⁺                  |
| IL-6 (pg/mL)   | Baseline           | 8.39±6.05                     | 7.31±8.81           | 0.57⁺                    |
|                | After intervention | 3.85±4.62                     | 3.78±4.44           | 0.98⁺                    |
|                | Change, MD (95% CI), P value | -4.54 (-4.74,5.3), 0.01 | -3.43 (-7.41,1.62), 0.01 | 0.54⁺                  |

TAC: total antioxidant capacity; MDA: malondialdehyde; hs-CRP: high sensitivity C-reactive protein; TNF-α: tumor necrosis factor-α; IL-6: interleukin 6. The results are described as mean ± standard deviation (SD).

Table: The results are described based on the analysis of independent sample t test.¹ MD (95% CI), P value is reported based on the analysis of paired sample t test.

Baseline (P=0.01) and endpoint (P=0.03) of study. Supplementation with lipoic acid resulted in no significant changes on antioxidant capacity compared with control group. Also, in term of other inflammatory factors the changes after 3 weeks were not significantly different between study groups (P>0.05).

After 3 weeks, treatment of patients with ALA in intervention group, led to a significant decrease in TNF-α and IL-6 (P=0.01) and not significant increase in TAC (P=0.07) serum concentrations. There were no significant differences between baseline levels of albumin, MDA, and hs-CRP, and endpoint concentrations in alpha lipoic acid group (P>0.05).

Table 3 provides the mean changes in clinical measurements of patients from the baseline to the end point. During study, there was a significant decrease in NIHSS and mRS in lipoic acid (7.10 ± 4.34 vs. 5.52 ± 3.58, P=0.01), (1.73 ± 1.09 vs. 1.47 ± 0.96, P=0.02) and control groups (5.28 ± 4.57 vs. 3.42 ± 1.07, P=0.02), (1.85 ± 1.49 vs. 1.47 ± 1.28, P=0.04), respectively. However, there were no changes regarding the clinical prognosis indices between two groups.

Discussion

Our study demonstrated that ALA supplementation for 3 weeks led to a significant decrease in serum TNF-α and IL-6 in intervention group, but no significant differences were founded on inflammatory and antioxidant biomarkers variation between intervention and control groups. To the best of our knowledge, this is the first clinical trial on the effects of ALA supplementation on inflammatory and oxidative stress biomarkers in stroke patients.

Neuro-protective effects of ALA had been studied frequently in central nervous system diseases.¹⁰ It is demonstrated that reactive oxygen scavenging capacity and ability to regenerate endogenous antioxidants necessary for repair systems relate to neuro-protective and neuro-restorative roles of lipoic acid, respectively.¹⁰ Our results, as the first study which examined the effects of ALA supplementation on anti-oxidant profile in stroke patients, are inconsistent with previous studies conducted on related issues. We did not observe significant effects of ALA supplementation on serum concentrations of TAC and MDA. It has been reported that TAC levels were improved in multiple sclerosis patients through ALA supplementation. However, in line with our results, they did not observe significant changes in MDA levels.¹⁰ It seems that the ischemic reperfusion in stroke patients leads to over production of ROS and consequently increase in the levels of oxidative stress mediators, several months after stroke.¹²,¹⁰ Therefore, short term supplementation with ALA may not be able to affect body anti-oxidant profile. It is recommended that all treatment procedures should be followed at least for 3 months.

Three-week supplementation with ALA led to a significant decrease in serum concentration of TNF-α and IL-6 in intervention group. However, there were no significant differences between two groups in terms of TNF-α, IL-6, and hs-CRP as well as serum levels of albumin (as a negative acute phase protein). Our results...
are not consistent with the findings of the previous trial on supplementation with ALA which showed a significant decrease in serum inflammatory cytokines in MS patients.29 The serum inflammatory markers usually remain high over months after stroke.20,21 Due to acute inflammation, the levels of negative phase proteins including albumin are also low in stroke patients over a month. Hypoalbuminemia is frequently reported among stroke patients and correlates with the pro-inflammatory pattern of serum protein electrophoresis.22,23 It seems that examining the changes in serum inflammatory indicators needs relatively long-term trials. It should also be mentioned that stroke patients suffer from various co-morbidities including hypertension, diabetes, etc, which are basically accompanied with chronic inflammation and increased levels of pro-inflammatory cytokines that interrupt their treatment. Therefore, comprehensive therapeutic strategies with long-term interventions should be developed.

There are numerous studies on stroke models that have examined its potential action mechanisms.24 As ROSs cause tissue injury leading to ischemic reperfusion in stroke, ROS scavengers are considered in CNS-protecting therapies.25 It has been shown that protective effects of ALA against cell death following stroke are mediated by increasing the antioxidant enzyme levels and scavenging ROS.12,13 Immediate injection of ALA decreases the infarct size in the rat partially via insulin receptor activation.4,26 Experimental evidence suggested that inhibition of peripheral TNF-α and down-regulation of brain microglial activation by ALA protect rat brain against ischemic stroke.14 It seems that expressions of nuclear factor erythroid 2-related factor 2 and heme oxygenase-1 are induced by ALA treatment that consequently decreases the intracellular ROS, infarct volume, brain edema, and oxidative damage, and promotes neurologic recovery in rats.1 ALA had a significant positive effect on NIHSS and mRS values but no statistically significant differences were found at baseline and after potential cofounder adjustment between two groups.

No side effects were reported for ALA supplementation in the present study. There are some limitations that should be considered in interpretation of our results. Although all patients were on the same hospital diet, individual intakes of patients were not considered. Therefore, the dietary intakes and nutritional status of patients were not evaluated which are important confounders affecting the inflammatory and oxidative stress indicators. Moreover, it seems that duration of supplementation was not long enough to examine the changes reported here. The small sample size was other factor affecting the findings. Thereafter, more clinical trials with large sample sizes in this regard are required.

**Conclusion**

In conclusion, 3 weeks of supplementation with ALA did not have any significant effects on serum albumin, and oxidative stress and inflammatory biomarkers compared to control group in stroke patients. However, more clinical trials with large sample sizes and long duration are required to clarify the effects of ALA on stroke patients.

**Ethical Issues**

The main goals of study were described for the first grade relatives of patients and written consent was obtained. The study was registered on the Iranian Registry of Clinical Trials website (identifier: IRCT2016061428450N1; http://www.irct.ir). The trial was approved by the bioethics committee of the Tabriz University of Medical Sciences (TBZMED.REC.1395.55).

**Conflict of Interest**

Authors declare no conflict of interest in this study.

**Funding**

This study received its financial support from Vice-Chancellor for Research of Tabriz University of Medical Sciences, Tabriz, Iran.

**References**

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation 2018;137(12):e67-e492. doi: 10.1161/cir.0000000000005558

2. Deb P, Sharma S, Hassan KM. Pathophysiologic mechanisms of acute ischemic stroke: an overview with
emphasize on therapeutic significance beyond thrombosis. Pathophysiology 2010;17(3):197-218. doi: 10.1016/j.pathophys.2009.12.001
3. Lv C, Maharjan S, Wang Q, Sun Y, Han X, Wang S, et al. alpha-Lipoic acid promotes neurological recovery after ischemic stroke by activating the Nrf2/HO-1 pathway to attenuate oxidative damage. Cell Physiol Biochem 2017;43(3):1273-87. doi: 10.1159/000481840
4. Choi KH, Park MS, Kim HS, Kim KT, Kim HS, Kim JT, et al. Alpha-lipoic acid treatment is neurorestorative and promotes functional recovery after stroke in rats. Mol Brain 2015;8:9. doi: 10.1186/s13041-015-0101-6
5. Moustafa RR, Baron JC. Pathophysiology of ischaemic stroke: insights from imaging, and implications for therapy and drug discovery, Br J Pharmacol 2008;153 Suppl 1:S44-54. doi: 10.1038/sj.bjp.0707530
6. Choi KH, Park MS, Kim JT, Kim HS, Kim JH, Nam TS, et al. Lipoic acid use and functional outcomes after thrombolysis in patients with acute ischemic stroke and diabetes. PLoS One 2016;11(9):e0163484. doi: 10.1371/journal.pone.0163484
7. Akbari M, Ostadmohammadi V, Tabrizi R, Mobini M, Lankarani KB, Moosazadeh M, et al. The effects of alpha-lipoic acid supplementation on inflammatory markers among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. Nutr Metab (Lond) 2018;15:39. doi: 10.1186/s12986-018-0274-y
8. Odabasoglu F, Halici Z, Aygun H, Halici M, Atalay F, Cakir A, et al. alpha-Lipoic acid has anti-inflammatory and anti-oxidative properties: an experimental study in rats with carrageenan-induced acute and cotton pellet-induced chronic inflammations. Br J Nutr 2011;105(1):31-43. doi: 10.1017/s0007114510003107
9. Khalili M, Soltani M, Moghadam SA, Dehghan P, Azimi A, Abbaszadeh O. Effect of alpha-lipoic acid on asymmetric dimethylarginine and disability in multiple sclerosis patients: a randomized clinical trial. Electron Physician 2017;9(7):4899-905. doi: 10.19082/4899
10. Seifar F, Khalili M, Khaledyan H, Amir Moghadam S, Izadi A, Azimi A, et al. alpha-Lipoic acid, functional fatty acid, as a novel therapeutic alternative for central nervous system diseases: a review. Nutr Neurosci 2019;22(5):306-16. doi: 10.1080/10715769.2017.1386755
11. Mohammadi V, Khalili M, Eghtesadi S, Dehghani S, Jazayeri S, Aghababaei SK, et al. The effect of alpha-lipoic acid (ALA) supplementation on cardiovascular risk factors in men with chronic spinal cord injury: a clinical trial. Spinal Cord 2015;53(8):621-4. doi: 10.1038/sc.2015.35
12. Connell BJ, Saleh M, Khan BV, Saleh TM. Lipoic acid protects against reperfusion injury in the early stages of cerebral ischemia. Brain Res 2011;1375:228-36. doi: 10.1016/j.brainsci.2010.12.045
13. Gonzalez-Perez O, Gonzalez-Castañeda RE, Huerta M, Luquin S, Gomez-Pinedo U, Sanchez-Almaraz E, et al. Beneficial effects of alpha-lipoic acid plus vitamin E on neurological deficit, reactive gliosis and neuronal remodeling in the penumbra of the ischemic rat brain. Neurosci Lett 2002;321(1-2):100-4. doi: 10.1016/s0304-3908(02)00056-3
14. Wu MH, Huang CC, Chio CC, Tsai KJ, Chang CP, Lin NK, et al. Inhibition of peripheral TNF-alpha and downregulation of microglial activation by alpha-lipoic acid and etanercept protect rat brain against ischemic stroke. Mol Neurobiol 2016;53(7):4961-71. doi: 10.1007/s12051-9418-5
15. de Aguilar-Nascimento JE, Prado Silveira BR, Dock-Nascimento DB. Early enteral nutrition with whey protein or casein in elderly patients with acute ischemic stroke: a double-blind randomized trial. Nutrition 2011;27(4):440-4. doi: 10.1016/j.nut.2010.02.013
16. Khalili M, Eghtesadi S, Mirshafiey A, Eskandari G, Sanoobar M, Sahraian MA, et al. Effect of lipoic acid consumption on oxidative stress among multiple sclerosis patients: a randomized controlled clinical trial. Nutr Neurosci 2014;17(1):16-20. doi: 10.1179/1476830513y.0000000060
17. Olmez I, Ozyurt H. Reactive oxygen species and ischemic cerebrovascular disease. Neurochem Int 2012,60(2):208-12. doi: 10.1016/j.neuint.2011.11.009
18. Crack PJ, Taylor JM. Reactive oxygen species and the modulation of stroke. Free Radic Biol Med 2005;38(11):1433-44. doi: 10.1016/j.freeradbiomed.2005.01.019
19. Khalili M, Azimi A, Izadi V, Eghtesadi S, Mirshafiey A, Sahraian MA, et al. Does lipoic acid consumption affect the cytokine profile in multiple sclerosis patients: a double-blind, placebo-controlled, randomized clinical trial. Neuroimmunomodulation 2014;21(6):291-6. doi: 10.1159/000356145
20. Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J Leukoc Biol 2010;87(5):779-89. doi: 10.1189/jlb.1109766
21. Anrather J, Iadecola C. Inflammation and stroke: an overview. Neurotherapeutics 2016;13(4):661-70. doi: 10.1007/s13311-016-0483-x
22. Dziedzic T, Pera J, Slowik A, Gryz-Kurek EA, Szczudlik A. Hypoalbuninemia in acute ischemic stroke patients: frequency and correlates. Eur J Clin Nutr 2007;61(11):1318-22. doi: 10.1038/sj.ejcn.1602643
23. Dziedzic T, Slowik A, Szczudlik A. Serum albumin level as a predictor of ischemic stroke outcome. Stroke 2004;35(6):e156-8. doi: 10.1161/01.STR.0000126609.18735. be
24. Shay KP, Moreau RF, Smith EJ, Smith AR, Hagen TM. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. Biochim Biophys Acta 2009;1790(10):1149-60. doi: 10.1016/j.bbagen.2009.07.026
25. Cao X, Phillis JW. The free radical scavenger, alpha-lipoic acid, protects against cerebral ischemia-reperfusion injury in gerbils. Free Radic Res 1995;23(4):365-70. doi: 10.3109/1071769950062527
26. Prehn JH, Karkouly C, Noglish J, Peruche B, Kriegstein J. Dihydrolipoate reduces neuronal injury after cerebral ischemia. J Cereb Blood Flow Metab 1992;12(1):78-87. doi: 10.1038/jcbfm.1992.10