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Neuroprotective Effects of Citicoline in Diffuse Axonal Injuries

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Abstract

Citicoline is a neuroprotective agent and fundamental item of phospholipid biosynthesis in cell walls. In this study, we aimed at examining the effect of citicoline in patients suffering from traumatic brain injury with Glasgow Coma Score (GCS) ≤ 8, and diffuse axonal injury (DAI) diagnosis. Efficacy of citicoline was evaluated by measurement of malondialdehyde (MDA) plasma levels as a marker of oxidative stress. Forty patients were randomly divided into two groups of cases (treated with citicoline) and controls (treated without citicoline). The duration of study was 15 days and blood samplings were performed on the 1st, 10th and12th days of admission to evaluate the plasma levels of MDA. Citicoline was administered intravenously with dosage of 500mg/6h. In the control group, the mean plasma levels of MDA were 2.54±0.83, 2.43±0.79 and 2.39±0.97 ng/dL in first, second, and third blood samplings, respectively (P=0.85). In the case group, the mean plasma levels of MDA were 2.46±1.08, 1.99± 0.81 and 1.60±0.6 ng/dL in first, second and third blood samplings, respectively (P=0.01). The mean total plasma levels of MDA were comparable in the case (2.64±1.08 ng/dL) and control groups (2.54±0.83 ng/dL) (P=0.78). The results of this study suggest that citicoline is an effective neuroprotective agent which might be used in order to reduce MDA levels.

Keywords: Citicoline; malondialdehyde; traumatic brain injury

1. Introduction

Nowadays, trauma is one of the most important causes of mortality and morbidity around the world. Among the different types of trauma, head trauma plays a main role in the morbidity and mortality of victims. In the US, the annual number of victims of traumatic brain injury (TBI) reaches more than 1400000, of which

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50000 die (1). Diffuse cerebral injury is the most common type of head trauma with expanded clinical subtypes from concussion to diffuse axonal injury (DAI). Neuronal injury happens in two forms of primary and secondary. The main injuries usually happen because of post-traumatic secondary injuries. Chemical and biochemical reactions triggered by trauma release free radicals (2-4). These reactions begin with the neutrophilic proliferation which in turn releases free radicals inducing lipid peroxidation and its final products including more fatty acids and free radicals (2). Free radicals are unstable hydroxyl or oxygen atoms which have lost their one or two electrons and have the ability to cause tissue injuries (5-7).

Due to the irreversible nature of neuronal injuries, new therapeutic projects have been focused on the free radicals (4). This would be of great importance especially in patients with severe and critical TBI and DAI with Glasgow Coma Score (GCS) <8, as the therapeutic plans in these conditions are mostly based on conservative and supportive methods to reduce the results of secondary injuries. Due to the unstable identities of free radicals, indirect methods such as study of their effect on products such as malondialdehyde (MDA) in plasma are usually used to evaluate the free radicals (10-13). MDA is one of the most important biomarkers of lipid peroxidation and oxidative stress (14).

Citicoline is a neuroprotective agent and fundamental item of phospholipid biosynthesis in cell walls (8,9). Neuroprotective characteristics of citicoline have been confirmed in different diseases including acute ischemic stroke, dementia, cognitional disorders, Alzheimer's disease, and Parkinsonism (15-20). The effect of citicoline has been evaluated on animal models in some studies (15) and examined based on qualitative criteria such as amount of cerebral edema (16) or the relationship between MDA and oxidative stress. Therefore, we aimed at evaluating the plasma levels of MDA in patients having received citicoline to assess the efficacy of this medicine on the secondary injury in patients with TBI.

2. Methods

In a double-blind randomized clinical trial, patients suffering from traumatic brain injury with GCS≤8 and DAI diagnosis who had been hospitalized in the trauma ward of Imam Reza Hospital, Tabriz, Iran were studied. After obtaining informed consent from the guardians of the patients and based on the inclusion criteria, we examined the patients and classified them into two groups of cases and control. Inclusion criteria were age between 18 and 65 years old, absence of major traumatic lesions in thorax, abdomen or extremities, absence of cardiovascular disorders, and absence of hyperlipidemia, hyperglycemia or hypertension. Exclusion criteria included admission during the first 24 hours after trauma, past medical history of cardiovascular disorders, prior history of malignancy, major trauma of thorax, abdomen or extremities, patients with focal cerebral injuries such as cerebral contusion or hematoma and other indications of surgical interventions, drug history of antihypertensive, antihyperlipidemic or antihyperglycemic agents, unstable hemodynamics, pregnancy, surgical interventions during the first 24 hours after trauma, cardiopulmonary resuscitation during the first 24 hours after trauma, and death during the study or discharge before the end of study. The study was approved by the local Ethics Committee.

Forty patients were randomly divided into two groups of cases (group A, treated with citicoline) and controls (group B, treated without citicoline). The duration of study was 15 days and blood samplings were performed on the 1st, 10th and12th days of admission to evaluate the plasma levels of MDA. Citicoline was administered intravenously and slowly with

dosage of 500mg/6h. One examiner who was blinded to the study measured the plasma levels of MDA.

Statistical analysis was performed with SPSS for Windows version 15.0 using analysis of variance (ANOVA) or Independent Samples T test, wherever appropriate. A *P* value less than 0.05 was considered to be statistically significant.

3. Results

In the control group, the mean plasma levels of MDA were 2.54±0.83, 2.43±0.79 and 2.39±0.97 ng/dL in first, second, and third blood samplings, respectively (*P*=0.85). In the case group, the mean plasma levels of MDA were 2.46±1.08, 1.99± 0.81 and 1.60±0.6 ng/dL in first, second and third blood samplings, respectively (*P*=0.01). The mean total plasma levels of MDA were comparable in the case (2.64±1.08 ng/dL) and control groups (2.54±0.83 ng/dL) (*P*=0.78).

4. Discussion

In some previous studies, the effects of citicoline have been evaluated in animal models (15) and examined based on qualitative criteria such as amount of cerebral edema (16). In other studies, the relationship between MDA and oxidative stress has been evaluated. To the best of our knowledge, the present study is the first to evaluate the neuroprotective effects of citicoline in TBI and DAI patients. Throughout the study, analysis of data showed that the administration of citicoline in the TBI patients could be effective on the reduction of MDA plasma levels as an oxidative stress marker. As a result, the primary hypothesis of the authors suggesting that citicoline could possess neuroprotective characteristics in the secondary cerebral injury in human models is approved to some extent. As mentioned above, our study was the first study to be based on quantitative criteria involving the human models compared with past qualitative and animal studies. The most important finding of our study was that plasma levels of MDA in the citicoline group was significantly less compared with the control group at all three stages of the blood sampling.

Based on this study, citicoline, as a neuroprotective drug and necessary substance of biosynthesis of cell wall phospholipids, can lead to reduced levels of MDA which is a biomarker of lipid peroxidation in the patients with head trauma. Therefore, it is suggested to add patients with traumatic brain injury to the list of citicoline administration indications.

Conflicts of interest

The authors declare that they have no conflict of interest.

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