

Citicoline in Patients with Traumatic Brain Injuries

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Abstract

Introduction: The present study aims to examine the pharmacotherapy effects of citicoline in patients suffering traumatic brain injury with DAI and GCS less than or equal to 8 diagnosis. The treatment efficacy of citicoline was assessed by the malondialdehyde (MDA) levels in plasma as a marker of oxidative stress and GCS clinical assessment of patients. Furthermore, because of the relation between MDA and lipid peroxidation, the lipid profile of patients was examined.

Methods: After obtaining a medical TESTIMONIAL, the patients divided randomizely into 2 groups (case and control). Peripheral venous blood samples (10 cc) were obtained from all patients in the first, sixth and twelfth days after admission to assess the levels of lipid profile and malondialdehyde. After obtaining the first sample, the patient of case group received injections of citicoline (500 mg q 6h) for 15 days. During this period, the GCS score of the patients was determined and recorded by one researcher.

Results: The MDA levels in different times of blood sampling were significantly different (P equal to 0.05), whereas control group showed no difference. In evaluation of lipid profile there was no significant difference at different times of blood sampling. The observed difference in the average plasma level of cholesterol had statistical significance between the two groups (P equal to 0.001), but no significant difference was found in other parameters of lipid profile (TG, HDL) as well as MDA. The GCS scores were significantly different at different times of post-admission (P equal to 0.001) in which the 15th day showed highest score, while, there was no statistical significant difference between GCS of two groups.

Conclusion: The results of this study suggest that citicoline is an effective neuroprotective agent and can reduce MDA levels.

Keywords: Citicoline; Diffuse Axonal Injury; Glasgow coma scale; Malondialdehyde; Lipid profile

Introduction

Nowadays, trauma is one of the most important causes of mortality and morbidity around the world and especially in the countries like Iran. Among the different types of trauma, "head trauma" can have the main role of morbidity and mortality of victims. In the United States of America (USA) the annual number of victims of Traumatic Brain Injury (TBI) may be more than 1 400 000 which 50 000 of them die.

Totally, there are two different types of TBI including regional and diffuse. Diffuse cerebral injury is the most common type of head trauma with expanded clinical subtypes from a concussion to Diffuse Axonal Injury (DAI). In the trauma of central nervous system, neuronal injury happens in two forms of primary and secondary. Primary injury is due to post-traumatic cell walls injury because of pressure and tension and is very rare. The main injuries usually happen because of the post-traumatic secondary injuries. Immediately after trauma, chemical and biochemical reactions have destructive effects on tissues [2-4].

These reactions begin with the neutrophilic proliferation and release of free radicals. These radicals induce lipid peroxidation which has final products including more fatty acids and free radicals [2]. The free radicals are unstable hydroxyl atoms or oxygen which has lost

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their one or two electrons and cause tissue injuries [5-7]. Because of the irreversible effects of nervous injuries, new therapeutic projects have focus on the free radicals [4].

It is especially important in patients with severe and critical TBI and DAI with GCS < 8 because the therapeutic plans of them are based on conservative and supportive methods to reduce the results of secondary injuries.

In this study, "citicoline" as a neuroprotective and fundamental item of phospholipid biosynthesis of cell walls is used. Because of unstable identities of free radicals, it is important to evaluate them directly. As a result, indirect methods such as study of their effects on products like MDA in plasma can be used [10-13]. This level is one of the most important biomarkers of lipid peroxidation [14]. There are different methods to evaluate the plasma level of MDA which one of the most sensitive of them is spectrometric method based on the reaction of MDA and thiobarbituric acid (TBA) [13,14]. Citicoline can be used in oral and injectional ways and has two peaks of plasma level:

One hour and 24 hours after administration [15].

Its metabolism is hepatic [15] and it have been used as a neuroprotective factor in different disorders like acute ischemic stroke, dementia, cognitional disorders, Alzheimer's disease and parkinsonism [18-24].

Because of the relationship between MDA & lipid peroxidation, in this study, lipid profile in the patients with DAI & GCS < 8 have been studied.

In some previous studies, the effects of this drug on animal models [16] or effects on the amount of cerebral edema [17] or relationship between MDA and oxidative stress had been shown [25].

As a result, we designed this study to provide a standardized pharmacotherapeutic protocol based on quantitative and exact laboratory criteria.

Objectives:

1. Primary Objectives: To study the effects of citicoline on the consciousness and plasma level of MDA and lipid profile in the victims of TBI with DAI & GCS < 8;
2. Secondary objectives:
 - A. To compare the plasma level of MDA between the patients of TBI and the diagnosis of DAI & GCS < 8 treated with citicoline and group of controls;
 - B. To compare the plasma level of lipid profile between the patients of TBI and the diagnosis of DAI & GCS < 8 treated with citicoline and group of controls;
 - C. To compare the GCS between the patients of TBI and the diagnosis of DAI & GCS < 8 treated with citicoline and group of controls;

Methods and materials

The bases of this study are scientific theories of different articles. As a result, the frame of this project is planned.

In 1991, Levin has been studied the effects of citicoline in the treatment of post injury manifestations and cognitive disorders after mild to moderate closed head injuries. In this study, there were 14 patients classified in two similar groups. Compared with placebo, citicoline was effective on the reduction of post traumatic symptoms. Moreover, the psychological findings showed improved level of cognitive memory in the users of citicoline. The results of that study proposed the effectiveness of citicoline in the mild to moderate head trauma.

In 1999, in a study of a clinical research center of Massachusetts Institute of Technology, the results of citicoline administration in the victims of TBI broadcasted [26].

One of the first reports of neuroprotective characteristics of citicoline, published in 2000 showing the positive dose-dependent effects of citicoline on injured cortex and hippocampus [30].

Another research in 2000 showed the results of intraperitoneal injection of citicoline in the reduction of brain edema of rats [17].

In 2002, oxidative markers such as MDA and superoxide dismutase (SOD) evaluated in patients of TBI and focused on the relationship between them and GCS [27].

In 2006, the effects of citicoline on the level of MDA, nitric oxide and also trauma size ratio have been examined [16].

And finally another study in 2009 showed the positive effects of citicoline on the functional outcomes of victims of TBI.

Type of Study: Double blind randomized clinical trial;

Target Population: the victims of trauma with diagnosis of DAI & GCS < 8 hospitalized in the ward of trauma of "imam reza" hospital in Tabriz;

Sampling Methods: randomized parallel group design based on random allocate project to randomize 40 patients in two groups of cases = A (treated with citicoline) and controls = B (treated without citicoline) as shown here:

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Inclusion Criteria:

1. Age between 18 & 65 years old
2. Informed consent
3. Without major traumatic lesions of thorax, abdomen and extremities
4. Without cardiovascular disorders
5. Without hyperlipidemia, hyperglycemia or hypertension

Exclusion Criteria:

1. Admitted during the 1st 24 hours after trauma
2. Past medical history of cardiovascular disorders
3. Past history of malignancy
4. Major trauma of thorax, abdomen and extremities
5. Patients with focal cerebral injuries such as cerebral contusion or hematoma and other indications of surgical interventions
6. Drug history of antihypertensive, antihyperlipidemic and antihyperglycemic agents
7. Unstable hemodynamics
8. Pregnancy
9. Surgical interventions during the 1st 24 hours after trauma
10. Cardiopulmonary resuscitation during the 1st 24 hours after trauma
11. Death during study or discharge before the end of study

After the obtaining informed consent and based on inclusion criteria, we examined the patients and classified them into two groups of cases & controls.

The duration of study included 15 days and blood samplings were obtained in the 1st, 10th & 12th day of admission to evaluated the lipid profile and plasma level of MDA.

We administrated citicoline intravenously and slowly with dosage of 500 mg/6h. One examiner evaluated GCS and plasma level of MDA and lipid profile was documented on data sheets and at last data were analyzed by a consultant of biostatistics.

Analysis of Data: With the usage of SPSS and t-test, we analyzed our data ($P < 0.05$).

Results

Based on inclusion and exclusion criteria, we classified our patients in 4 groups:

1. 18-29 years old
2. 30-41 years old
3. 42-53 years old
4. 54-64 years old

In this classification, we had 24 patients (60%) in the 1st group, 14 patients (35%) in the 2nd one and 2 patients (5%) in the 3rd one. There wasn't any patient in the 4th group.

One of the findings is related to the comparison between the mean plasma level of MDA in two groups of cases and controls:

In the former ones, the mean level was 2.64 ± 1.08 (ng/ml) while in the later was 2.54 ± 0.83 (ng/ml). Analysis of variances showed that both of variances were equal. As a result, we used t with equal variance which resulted in $t = 0.27$ and $P = 0.78$ ($P > 0.05$) in the confidence interval of 95%. It means that there wasn't any significant difference between two means.

The second parts of our results were related to the comparison between the markers of lipid profile in two groups which can be seen in three tables:

Group	Number	Mean	F	P - value	t	df	P - value
Cases	20	162.45 ± 42.50	0.554	0.46	3.29	38	0.02
Controls	20	121.80 ± 35.12	0.554	0.46	3.29	38	0.02

Table 1-4: Mean plasma level of CHOL.

Group	Number	Mean	F	P - value	t	df	P - value
Cases	20	47.50 ± 6.64	6.82	0.01	1.02	38	0.31
Controls	20	44.20 ± 12.82	6.82	0.01	1.02	38	0.31

Table 2-4: Mean plasma level of HDL.

Group	Number	Mean	F	P - value	t	df	P - value
Cases	20	179 ± 218.79	1.60	0.21	1.09	38	0.28
Controls	20	125 ± 45.51	1.60	0.21	1.09	38	0.28

Table 3-4: Mean plasma level of TG.

And finally we compared the mean GCS in two groups. As you see in the table 4-4, there isn't any significant difference between them.

Group	Mean	F	P - value	t	df	P - value
Cases	8.25 ± 3.06	0.17	0.68	1.08	198	0.27
Controls	8.72 ± 3.05	0.17	0.68	1.08	198	0.27

Table 4-4: Mean GCS.

Discussion

In recent years, citicoline has been the object of remarkable interest as a possible neuroprotectant. Analysis of data of present study showed that the administration of citicoline could be effective on the reduction of MDA plasma level. As a result, this study presented citicoline as a neuroprotective drug in the secondary cerebral injury. Although the level of consciousness of patients was not affected with this drug and it may be due to multifactorial identity of consciousness. Our study was the 1st study based on quantitative criteria involving the human models compared with past qualitative and animal studies.

The most important findings of our study included:

1. The plasma level of MDA in the group of cases during the 3 stages of blood sampling was significantly different compared with the group of controls in the confidence interval of 95%.
2. The mean plasma level of cholesterol was more in the group of cases.
3. The mean GCS in the different days of admission, in the confidence level of 95%, was significantly different between these two groups and this difference in the 1st day was the most ($P < 0.001$), but totally there wasn't significantly difference in the level of consciousness and GCS between two groups.

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, as mentioned earlier, the present study is the first to evaluate neuroprotective effects in TBI and DAI patients. Throughout the study, analysis of data showed that administration of this drug could be effective on reduction of MDA plasma level as a marker of oxidative stress in patients with DAI. It means that the primary hypothesis of authors is approved to some extent. These data confirm that citicoline can efficiently exert a neuroprotective activity.

On the other hand, based on this study, citicoline as a neuroprotective drug and necessary substance of biosynthesis of phospholipids of cell walls can lead to reduced level of MDA as a biomarker of lipid peroxidation in the patients of head trauma.

Conclusion

Totally, we can conclude that the patients with severe TBI are new categories of indications of citicoline as a neuroprotective drug. We also suppose to design new studies with long term durations, more target population and with focus on the clinical manifestations, especially GCS, in the future.

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