



Original Article

Effect of Intravenous Injection of Erythropoietin on the Peroxidation Metabolites in Patients with Acute Spinal Cord Injury

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Abstract

Objective: Acute spinal cord injury (ASCI) is among the most common and important disorders in the field of neurosurgery and causes sensory, motor, urinary tract impairment or combination of them. Many pharmacological agents, like Erythropoietin, are used to reduce secondary damage after the primary insult and try to preserve nerve tissue.

Materials and Methods: In the present clinical trial, 60 patients with ASCI in the Frankel classification, the category A to C, and the selection of matched Frankel class into two groups A and B (each group consisted of 30 patients) were participated. Group A underwent the conventional treatment received methylprednisolone and erythropoietin. In the first day of hospitalization and 4 day after admission the amount of Malondialdehyde (MDA) and Total Antioxidant Capacity (TAC) evaluated and compared to group B (that received conventional treatment such as methylprednisolone).

Results: In the first day of hospitalization the average amount of MDA was 5.37 nmol/ml in the case group and 4.76 nmol/ml in the control. Four days after admission average MDA decreased to 3.83 nmol/ml in case group and 3.98 nmol/ml in the control. TAC in the first day of hospitalization was 1.37 nmol/ml in the case group and 1.25 nmol/ml in the control group. In day 4 after admission the average TAC in case group decreased to 1.08 nmol/ml and 1.14 nmol/ml in the control.

Conclusion: There is a significant correlation between the reduction of oxidation metabolites in the case and control group. This indicates that Erythropoietin and pro-inflammatory cytokines by reducing metabolites and inflammation can consequently reduce spinal cord injury.

Keywords: Erythropoietin, Acute spinal cord injury, Malondialdehyde, Total antioxidant capacity Neuroprotective, Methylprednisolone

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Received: 2015-10-09

Accepted: 2016-05-09

DOI: [10.13183/jecns.v3i1.40](https://doi.org/10.13183/jecns.v3i1.40)

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Introduction

Acute Spinal cord injury (ASCI) is among the most common and important disorders in the field of neurosurgery and causes sensory, motor, urinary tract impairment or a combination. In Iran there are many patients who refer trauma centers [1]. Achieved progress of care providing systems in terms of repairing spinal cord injuries is continuously happens from ancient times to the present [2]. Researchers have shown that there is a possibility of recovery after acute spinal cord injury [2]. Two traditional types management for these patients are: Conservative and surgical treatment, if necessary [3].

Here, methylprednisolone is the only protocol treatment with part of the therapeutic benefit and associated dangerous side effects.

Recently Neuroprotective therapies such as erythropoietin, minocycline, progesterone and etc. have attracted a lot of staffs to approach the patients [1-4]. Many pharmacological agents in fact, in this field, are used to reduce secondary damage after the primary insult and tried to preserve nerve tissue [5]. Inflammation plays an important role in spinal cord injury. Although the use of anti-inflammatory such as prednisone has the beneficial effect but the use of methylprednisolone is shown to have moderate beneficial effects. For serious complications of spinal cord injury,

the use of erythropoietin is beneficial to reduce inflammation and limit the neuronal apoptosis. The aim of this study was to investigate the effect of Erythropoietin on sensory and motor status of patients with acute spinal cord injury.

Materials and Methods

In this clinical trial, 60 patients with ASCI in the Frankel classification, the category A to C, and the selection of matched Frankel class into two groups A and B (each group consisted of 30 patients) were participated. Group A underwent conventional treatment received methylprednisolone, and erythropoietin. In the first day of hospitalization and 4 days after admission the amount of the peroxidation metabolites pathway such as Malondialdehyde (MDA) and Total antioxidant capacity (TAC) evaluated and compared to group B (that received conventional treatment such as methylprednisolone).

In all patients with traumatic spinal cord injury, spinal (thoracic-cervical) and damage neurological (complete or incomplete), in the admission stage of sensory - motor patients were classified according to Frankel, and blood samples for the study of MDA and TAC levels were taken. The protocol of treatment for all patients in the guideline of neurosurgery was performed as follows [6].

All patients who were taken to hospital with ASCI during the first 8 hours, received methylprednisolone 33mg/kg as a bolus intravenously within fifteen minutes infusion. After 45 minutes, 5.4 mg/kg methylprednisolone infusion within 23-47 hours was given. Then patients divided into two groups, the first group (cases), after obtaining the consent of the patient, in addition to methylprednisolone, 500 unit/kg body weight of erythropoietin (Exir Pharmaceuticals, Iran) through intravenous infusion in 3 divided doses was given within 3 days [7].

In second group (control) an additional treatment other than methylprednisolone was not added. In both group the amount of Peroxidation Metabolites was checked.

Before the initiation of trial we explained to all patients about the written consent. Patients were free to leave the study and did not participate in the study at any time of the study.

The method was based on measurement of serum MDA reaction with thiobarbituric acid (TBA), normal butanol extraction, was measured by absorption spectrophotometry and compared with a standard curve which was obtained from a commercial company MERK. TAC was measured as the method that the company was prepared RANDOX.

Data were obtained by using descriptive statistics (Mean ± SD and Frequency-Percentage). Independent samples t-test and repeated measurement analysis of variance (ANOVA) for quantitative variables and chi-square test for qualitative variables and statistical software 16SPSS™ review and statistical analysis was performed. P value less than 0.05 were considered to be statistically significant.

Results

At the end, 54 patients completed the study and 6 patients died. In both group factors like gender-age-intensity lesion

(according to Frankl) the level of injury and trauma were matched. The mean amount of MDA was 5.25 nmol/ml that in the interventional group the mean 5.38 nmol/ml and in the control group and 4.76 nmol/ml, respectively. The 4 day after admission amount of MDA was 3.91 nmol/ml that in interventional group 3.83nmol/ml, and in the control group 3.98 nmol/ml reduced. P<0.001 statistically significant correlation between MDA decreased on the first and fourth admission between the two groups (Figure 1).

Mean TAC in the first day of hospitalization 1.31nmol/ml was that in the interventional group was 1.37 nmol/ml and in the control group 1.25 nmol/ml, respectively. 4 days after admission the amount of TAC was 1.11 nmol/ml that in case group it was 1.08 nmol/ml and in the control group 1.14 nmol/ml which was reduced. P<0.001 was statistically significant correlation between TAC that decreased on the first and fourth admission between the two groups (Figure 2).

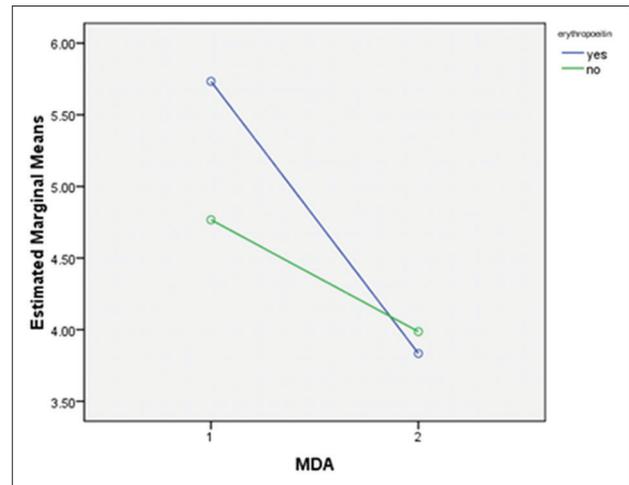


Figure 1. MDA changes pre (1) & post (2) treatment phases in two groups.

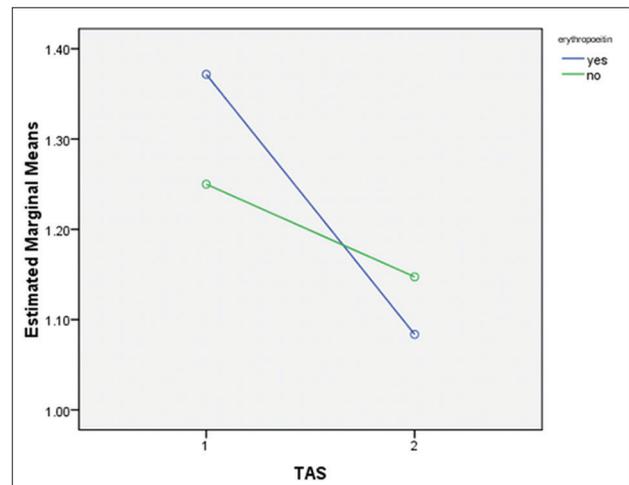


Figure 2. TAC changes pre (1) & post (2) treatment phases in two groups.

Discussion

Spinal trauma disease is one of the most significant injuries that can cripple a person for a lifetime, and causes low quality of life, cost of care and the short life. Early treatment is important factor to improve the quality of life of patients [8-10]. Therefore, in this study the effect of the neuroprotection of erythropoietin in ASCI patients with severe sensory and motor dysfunction were studied.

Erythropoietin hormone is a 165 amino acid glycoprotein which belongs to the type I cytokine family. Initially it was thought that only plays the role of erythropoietin erythropoiesis regulation of erythropoietin ability to inhibit apoptosis in erythroid cells, which is a result of the maturation of erythroid cells [11].

Erythropoietin acts as a neurotropic factor in the central nervous system. The function of erythropoietin for the treatment of diseases associated with neuronal [12].

In a study that was conducted in 2010 on rat spinal cord injury, it was observed that erythropoietin had antioxidant properties and reduced lipid peroxidation and decreased in serum levels of MDA as a marker of lipid peroxidation [13]. In Yazihan et al. (2008) study, erythropoietin administration in spinal cord injury in rats reduced peroxidation metabolites [14].

Another investigation by Hanged et al. studied the effect of erythropoietin in ASCI in rats. They showed the protective effect of erythropoietin with reduced lipid peroxidation metabolites [15].

In our study MDA levels in patients in case group was 5.73 nmol/ml and in control group 4.76 nmol/ml, respectively. Four days after the onset of the study, the level of MDA in case group it was 3.83 nmol/ml and in control group it was 3.98 nmol/ml that was significantly different and we observed reduction in MDA.

Also, in our research, TAC levels in patients in case group was 1.37nmol/ml and in control group 1.25 nmol/ml. Four days after the study began the level of TAC in case group was 1.08nmol/ml and control group 1.14nmol/ml. That was significantly different and we observed reduction in TAC.

Qian et al. in a study showed that erythropoietin has Neuroprotective activity in several models of excitotoxic neuronal injury, focal or global cerebral ischemia model and a model of spinal cord injury [16]. This was also confirmed by Arishima et al [17].

Inflammatory processes play an important role in the pathogenesis of ischemia that erythropoietin can be helpful in reducing the inflammation. Inflammation leads to the removal of leukocytes from the blood [18]. These cells produce inflammatory mediators and cytokines leading to damage and blockage of the small vessels [19,20]. Erythropoietin may reduce endothelial cells lining the passage of leukocytes as well as increased resistance to endothelial cells against ischemia [18].

Erythropoietin express have been seen in neurons and astrocytes. A strong response to erythropoietin seen with endothelial vascular cells [21,22]. Erythropoietin could increases cell survival by inhibiting apoptosis [23]. In addition to the direct effects, its neuronal protective effect may be due to enhanced vessel growth [24]. In addition angiogenesis effects, it has role in

regulation of vascular permeability and protection of endothelial cells [25,26].

Conclusion

Reduced metabolites of lipid peroxidation such as MDA and TAC showed significant difference in both groups (experimental and control).

This indicates that erythropoietin and pro-inflammatory cytokines by respectively reducing metabolites and inflammation can reduce the apoptotic pathway and ultimately reduce spinal cord injury.

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