Effect of Intravenous Injection of Erythropoietin on Hospitalization Period in Patients with Acute Spinal Cord Trauma

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Abstract

Background & Aim: Spinal cord injury (SCI) has a very long history, and its cases form a large proportion of patients admitted to trauma centers in Iran. Studies show that repair after spinal cord injury can be done. In fact, many pharmaceutical agents, such as erythropoietin (EPO), are applied to reduce secondary injury following the initial disorder and to maintain the nerve tissue.

Methods & Materials/Patients: In this clinical trial, 60 patients with acute spinal cord injury classified as A to C according to Frankel classification grading system were selected and matched with regard to the Frankel classes, the cervical and dorsal levels and then divided into two groups A and B (each containing 30 patients). Group A, in addition to receive conventional treatment, took EPO and was evaluated in terms of hospitalization period outcomes (mean length of stay, lower extremity thrombosis, intubation, bedsores) and was compared with group B (receiving conventional medicines, such as methylprednisolone).

Results: Of the 60 patients, 15 patients were female and 45 were male, with the age range of 19-72 years. The mean length of stay in the case and control group was 10.6±6.52 and 13.8±10.37 days, respectively. Six patients died during hospitalization, including three patients in the case group and three patients in the control group. 12 patients were intubated during this period, including five patients in the case group and seven patients in the control group. Of the 29 patients with bedsores, 14 patients were in the case group and 15 patients were in the control group. None of the patients had lower extremity venous thrombosis during hospitalization.

Conclusion: No significant difference was found between the case and control group in the hospital stay length, intubation, bedsores and lower extremities venous thrombosis.

Keywords: Erythropoietin; Acute Spinal Cord Injury; Hospitalization Period

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Introduction

Acute spinal cord injury is among the most common disorders in the field of neurosurgery, and it accounts for referring of a large proportion of patients admitted to trauma centers in Iran (1). Scientists' researches have shown that repair after spinal cord injury can be done (2). Patients are classically put under two types of treatment: conservative and surgery, if necessary (3). Now, methylprednisolone treatment is the only remedial protocol that is associated with partial therapeutic benefits but dangerous side effects. Recently, neuroprotective therapies such as treatment with EPO, minocycline, progesterone and other medicines have made a lot of attractions for those involved in the approach to these patients (1, 4). In fact, many of these pharmaceutical agents are used to reduce secondary injury after the initial disorder and to maintain the nerve tissue (5). EPO increases cell survival through inhibition of apoptosis. In addition to the direct impact on reducing inflammatory and anti-apoptotic properties, EPO can also improve vascular perfusion, medullary excitability and neural stem

cells proliferation (6,7). EPO important role in the central nervous system (CNS) was also understood through the study of mice lacking EPO-R (8). A study on rat spinal cord trauma conducted in the department of biochemistry of Tabriz - Iran in 2010 showed that EPO has antioxidant and reducing lipid peroxidation properties (9). Therefore, the exogenous EPO was used in order to reduce the number of apoptotic cells in the early stages of spinal cord injuries (10). The severity of spinal cord injuries according to Frankel classification grading system are divided into five grades A to E:

• Grade A: No motor or sensory function
• Grade B: No motor function, but sensory function remains low
• Grade C: Sensory function is normal, but some motor functions are detected low
• Grade D: Sensory function is normal, and useful motor function is low
• Grade E: Sensory and motor functions are normal.

The aim of this study was to evaluate the effect of the medicine on sensory and motor function (according to the Frankel classification grading system) in patients with acute spinal cord injury (SCI) and hospitalization period outcomes (mean length of stay, lower extremity thrombosis, intubation, bedsores).

Methods and Materials/Patients

In this clinical trial, 60 patients with acute spinal cord injury classified as A to C according to Frankel classification grading system were matched with regard to the Frankel classes, the cervical and dorsal levels and then divided into two group A and B (each containing 30 patients). Group A, in addition to receive conventional treatment, took EPO and was evaluated in terms of hospitalization period outcomes (mean length of stay, lower extremity thrombosis, intubation, bedsores) and it was compared with group B (receiving conventional medicines, such as methylprednisolone). The inclusion criteria in our study were as follows: acute spinal cord injury with the Frankel grading A to C, hospital referring within the first eight hours of trauma incidence, a written informed consent completed by patient to participate in the study and spinal vertebral fractures (C1-T12). The exclusion criteria were uncontrolled high blood pressure, hypersensitivity to human albumin, pregnancy and lactation, erythroid leukemia, history of thromboembolic events, Severe diseases of coronary, peripheral, carotid or cerebral arteries and brain injury with low GCS due to lack of accurate determination of sensory-motor function of patient. The sensory-motor function in all patients with traumatic spinal cord injury, spinal cord (cervical-thoracic) and nerve injury (complete or partial) were evaluated according to the Frankel classification grading system in the admission time. Then, the treatment protocols were performed for all patients according to the guidelines of neurosurgery literatures as follows (11): all patients referring to hospital within the first 8 hours of spinal trauma were prescribed methylprednisolone bolus IV infusion of 33mg/kg within a fifteen minutes, and after 45 minutes, methylprednisolone infusion of 5.4 mg/kg continued within 23-47 hours. Subsequently, the patients were divided into two groups. The first group (the case group) following completing informed consent form received 500 unit/kg of EPO IV infusion for three days in three divided doses and methylprednisolone (12). (Recombinant human EPO alfa vial, produced by recombinant DNA technology, has 165 amino acids and a molecular weight of 34,000 Daltons. Each vial, made by Exir Pharmaceutical company in Iran, contains 2000 units.) The second group (control) only received methylprednisolone. During hospitalization, complications resulted from spinal cord injury, such as the need for intubation, lower extremity deep vein thrombosis [diagnosed by daily measurement of the tibia and femur circumference in patients and Doppler ultrasonography of lower extremity vessels in suspected cases] and bedsores were evaluated. The length of hospital stay was registered. This study was registered by Iranian Registry Clinical Trial (IRCT) under the number of IRCT2014041417272N1. All patients completed written informed consent form before starting the study. The patients could leave the study at any time. The obtained data were analyzed by descriptive statistics (Mean ± SE), frequency, percentage and T- test for quantitative variables in independent groups and chi square test for qualitative variables. The statistical analyses were performed by SPSS software Ver.16. In this study, the P value less than 0.05 was considered statistically significant.

Results

In this study, of the 60 patients, 54 patients (90%) completed the study, and 6 patients (10%) died. Of the 60 patients, 45 patients (75%) were male and 15 patients (25%) were female. Of the 30 patients in the case group, 20 patients (66%) and 10 patients (34%) were male and female, respectively. In the control group, 25 patients (83%) were male and 5 patients (17%) were female. Statistical analysis showed no statistically significant difference between the two groups in sex at P=0.116. The mean age of all patients was 41.6 ± 15.1 years (Min=19 years, Max=72 years). The mean age in the case group was 40.7±15.8 (Min = 20, Max =65) years, and in the control group was 42.4±13.7 years (Min =19, Max=72). There was no statistically significant difference in the mean age between the two groups at P=0.25. The mean length of stay in the case and control group was 10.6±6.52 and 13.8±10.37 days, respectively. There was no statistically significant difference between the two groups (P=0.85). Of the 60 patients, trauma was caused in 19 patients (32%) due to the fall and 41 patients (68%) by a vehicle crash. In the case group, trauma accounted for fall in 8 patients (26%) and crash in 22 patients (74%), while in the control group, fall in 11 patients (36%) and crash in 19 patients (64%) caused trauma event. Of the 60 patients, 29 patients (48%) and 31 patients (52%) suffered from cervical spinal cord trauma and thoracic spinal cord trauma, respectively. In the case group, 14 patients (47%) had cervical spinal cord trauma and 16 patients (53%) thoracic spinal cord

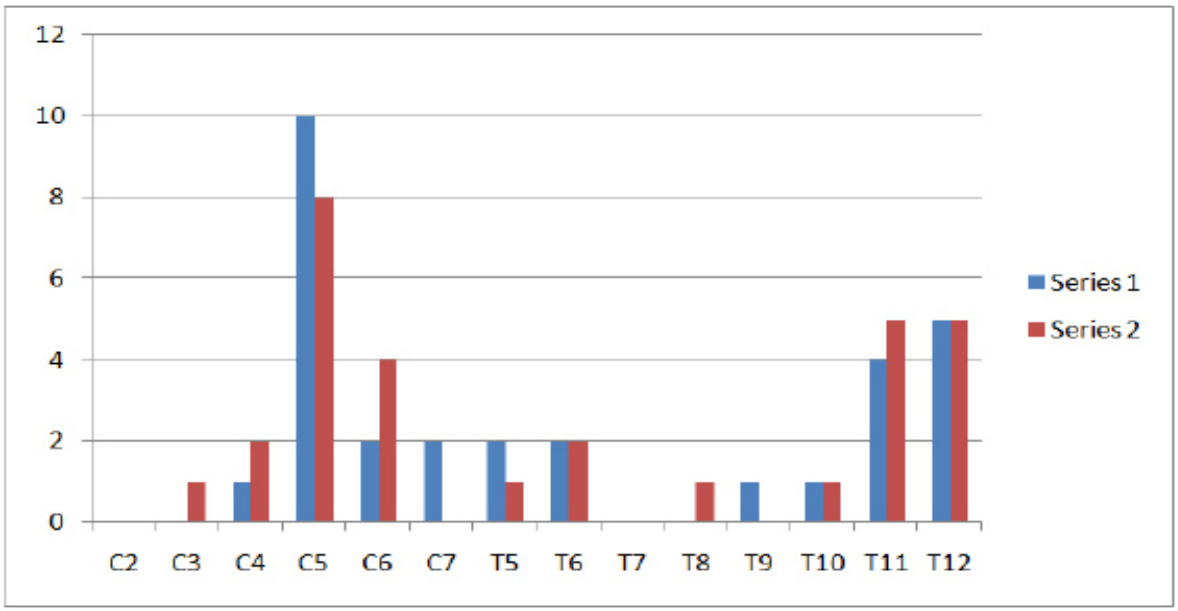

Figure 1. The Patients' Frequency in terms of Spinal Cord Injury Site in the Two Groups

trauma. In the control group, 15 patients (50%) had cervical spinal cord trauma and 15 patients (50%) thoracic spinal cord trauma (Figure 1).

Of a total of 60 patients, six patients (three patients in each group) died during hospitalization (10%). All 6 patients suffered from traumatic cervical Fx c5 injury, led to death due to respiratory complications. No statistically significant relationship was found between the two groups in mortality (P=0.66). The mean hemoglobin of the patients on the first day of admission was 11.21±1.86. This mean was 12.3±1.91 and 11.90±1.81 in the case and control group, respectively. On the fourth day of admission, the mean hemoglobin dropped to 11.51±1.7. The case and control group had the mean hemoglobin of 11.61±1.92 and 11.42±1.46, respectively. On the discharge day, the mean hemoglobin was 11.68±2.006. This mean in the case and control group was 12±1.68 and 11.38±2.25, respectively (Figure 2). There is no statistical significant difference between the two groups in EPO taking and Hb increase (P=0.33), and there is not seen a statistically significant relationship between the hemoglobin increase and lower extremity thrombosis.

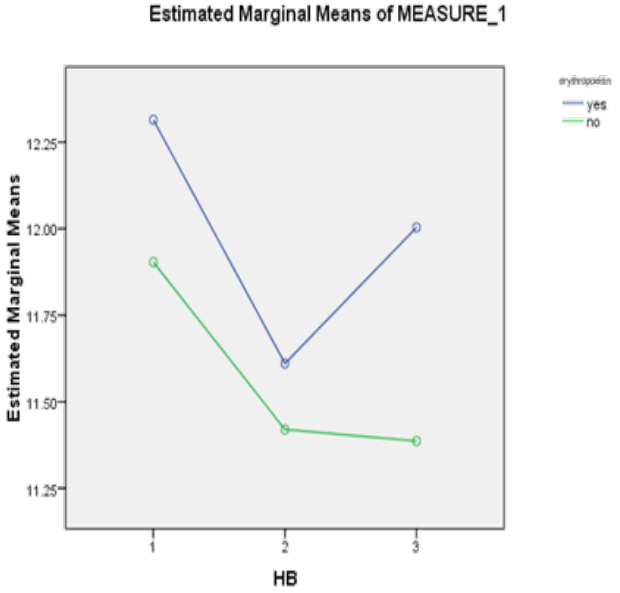

Figure 2. Hemoglobin Graph in the Two Groups

During hospitalization period, of 60 patients, 12 patients (20%) were intubated, including 5 patients (41%) and 7 patients (59%) in the case and control group, respectively. No significant relationship was found between the two groups in intubation (P=0.37).

During the hospitalization, of 60 patients, no patient with lower extremity venous thrombosis was found. During this period, 29 patients suffered from bedsores (ranged from erythematous skin to deep wounds), including 14 patients (48%) in the case group and 15 patients (52%) in the control group. No significant relationship was found between the two groups in bedsores (P=0.50).

Discussion

Spinal cord injury is the most important disease following trauma that could lead to cripple a person for a lifetime, poor quality of life, the high cost of care for the patient and eventually short life. Therefore, conducting remedial measures for the early recovery of patients and improving their quality of life are very important (7, 13, 14). One of the treatment measures that was considered in this study was the neuroprotection effect of EPO medicine on patients with acute spinal injury. EPO hormone is a 165 amino acid glycoprotein belonging to type I cytokine family. It was formerly believed that only role of EPO is regulating erythropoiesis. This role is resulted from EPO ability to inhibit apoptosis in erythroid cells, which is a consequence of the maturation of erythroid cells (12). Researches over the past decade have shown that EPO and its receptor are expressed in tissues unrelated to the erythropoiesis, including brain, lung, spleen and heart. As a result, a new protective effect of the cells was recorded to EPO in some organs. For example, EPO reduced injury and dysfunction after ischemia reperfusion in mice kidney. Also, EPO showed a protective effect in models of myocardial ischemia (15, 16). Furthermore, EPO has leading role in neuroprotection, neurogenesis and neurotrophic activity in the central nervous system. These actions caused EPO to be

a suitable alternative for the treatment of diseases associated with neuronal death. Fang Xiang – qian et al. showed in a study that EPO has a neuroprotective activity in several models of excitotoxic neuronal injury, including focal or global cerebral ischemia and spinal cord injury model (17). This was also confirmed by Arishima et al (18). In addition, it was shown that neurons make EPO, both in-vitro and in-vivo (19). All previous studies were conducted on animals, and the effects of EPO in human acute spinal cord trauma have recently been studied. Although the use of EPO improve sensory and muscular power according to Frankel classification grading system and it is expected that it decreases hospitalization period outcomes such as hospital stay length, intubation, bedsores caused by immobility of organs and hospital long stay, statistical difference was not observed between the case and control group in hospital stay length, intubation, and bedsores. Thus, further studies should be done. The present study also suggests the following: 1. The sample size of the patients was 60. Considering the study type and follow-up duration, it is recommended that the study is conducted with larger sample size to achieve right result. It will lead to evaluate the effects of EPO therapy on the functional recovery of patients more accurately and with higher statistical value. 2. It is suggested that patients are followed-up for a longer period of time and evaluated for vascular events in future studies. 3. The EPO dose used in the study was 500 units per kg of patient. It is recommended that lower doses of the medicine be used and the results compared in future studies aimed at achieving a treatment program at a lower cost.

Conclusion

No significant difference was found between the case and control group in the length of stay in hospital, intubation and bedsores. The use of EPO increases the amount of hemoglobin in patients that it is not statistically significant. Also, none of the 60 patients had lower extremity venous thrombosis during hospitalization.

Funding

None.

Conflicts of Interest

The authors have no conflicts of interest.

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Comments

The study of Meshkini et al. (1) adds very little to the literature on spinal cord injuries (SCI). The authors performed a clinical trial on 60 SCI patients, focusing on C1 to T12. The authors divided patients into two groups, each consisting of 30 patients. In group A, they injected erythropoietin 500 unit/kg intravenous infusion for three days in three divided doses in addition to methylprednisolone. The control group of SCI patients was treated in the standard way including methylprednisolone. The authors evaluated the duration of hospital stay and associated complications: deep vein thrombosis, bed sores, and death. There was no significant difference between the outcomes measures of the two groups. Three patients in each group (10%) died. We have some important concerns about this study.

First, the authors mention that they divided patients into two groups. Although the study was a prospective study, it was not a randomized clinical trial (RCT). They did not use the word random in the report of their study.

Second, because all spinal cord levels from C1 to T12 were included, the authors had a heterogeneous group and there is some evidence that cervical SCI has a different outcome than the thoracolumbar area (2). At our institution, we prefer to perform homogeneous studies and separate all spinal injuries into three groups: cervical, thoracic, and conus medullaries—or at least cervical vs thoracolumbar—to achieve more accurate results, even in a descriptive way without analysis.

The authors did not mention primary versus secondary outcome

measures. They just evaluated duration of hospital stay. Although we use duration of hospital stay as a secondary outcome measure at our institution, length of hospitalization is not an important factor for development of complications. Even in western countries where cost is an important issue, duration of hospital stay is never more than a secondary or minor outcome measure. We also prefer to use the American Spinal Injury Association impairment score for measurement of the outcomes of SCI patients, not the scale of Frankel, which is outdated.

Third, the authors wrote, "29 patients (48.3%) suffered from bedsores (ranging from erythematous skin to deep wounds)." We appreciate the authors' honest and accurate registration of pressure sores. The mean hospitalization stay was less than two weeks, however, and pressure sores in almost half of the patients in this short period show care below the standard level. We know the center in this study is among the good centers of the country. Therefore, we also expect a similar high percentage of pressure sores in other urban university centers of the country. For further studies, we recommend recording in detail the grade of pressure sore from I to IV, the site of the sore, when the sore developed, and how sores were treated. The Spinal Cord Injury Rehabilitation Evidence Project (3) and the World Health Organization have standard questionnaires for pressure sores.

Fourth, the authors suggest, "The EPO dose used in the study was 500 units per kg of patient. It is recommended that lower doses of the medicine be used and the results compared in future studies aimed at achieving a treatment program at a lower cost." When there is no effect with a drug with a higher dose, how we can expect a therapeutic effect with a lower dose?

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