Erythropoietin plus Methylprednisolone or Methylprednisolone in the Treatment of Acute Spinal Cord Injury: a Preliminary Report

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Abstract- Recent studies in animal models indicate that recombinant human erythropoietin (rhEPO) is very effective in enhancing neurological recovery after spinal cord injury (SCI). We aimed to evaluate the effect of rhEPO plus methylprednisolone sodium succinate (MPSS) compared to MPSS alone to improve neurological function of patients after SCI in a randomized clinical trial. During a 15-month period 30 patients presenting to emergency departments of two university affiliated hospitals within less than 6 hours after acute SCI were randomized to two groups. Both groups received MPSS 30 mg/kg initially and 5.4 mg/kg every hour till 23 hours if admitted within 3 hours and till 47 hours if recruited within 3-6 hours after injury. Group EPO also received 500unit/kg rhEPO on admission and another 500 unit/kg 24 hours later instead of placebo in group MPSS. Neurologic evaluation was performed on admission, 24, 48, 72 hours and one and 6 months later. Range of patients' age was 18-65 years. There was no significant difference between patients receiving two types of treatment in neurological exam on admission (P=0.125), 24 hours after admission (P=0.108) and 48 hours after admission (P=0.085). However, one week (P=0.046), one month (P=0.021) and six months (P=0.018) after admission these differences were significant. MPSS plus rhEPO started within 6 hours after acute spinal injury may be more effective than MPSS plus placebo in improvement of neurologic dysfunction. More studies with larger sample sizes are warranted.

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Keywords: Pinal cord; Erythropoietin; Methylprednisolone sodium succinate; Trauma

Introduction

Acute spinal cord injury (ASCI) occurs in various countries across the world with an annual incidence of 15-40 cases per million (1). Although not common, it has a major functional, medical and financial effect on the injured person, as well as, significant burden to the society by requiring long-term care expenditures.

Although methylprednisolone sodium succinate (MPSS) has shown modest benefits in the National Acute Spinal Cord Injury Study II (NASCIS II) trial and continues to be used in many countries as a standard of care (2) this treatment remains controversial and has dropped to an optional choice of treatment by some expert committees (3). Erythropoietin (EPO) has recently been shown to have direct neuroprotective effects in cell culture models and after application in the brain (4). Expression of EPO and its receptors in the nervous system as well as its anti-apoptotic, anti-oxidant and anti-inflammatory effects have been reported extensively (5).

In this pilot study we evaluated the efficacy of EPO plus MPSS compared to MPSS plus placebo for improving neurological function of patients assessed by American Spinal Injury Association (ASIA) scale after ASCI, in a small randomized double-blind prospective study.

Materials and Methods

This study was a randomized controlled double-blind clinical trial, approval by the institutional ethics

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committee and all the enrolled patients completed a written informed consent. Eligible patients were those who had an acute spinal cord injury, presenting to emergency wards of two university affiliated hospitals within less than 6 hours after the trauma (based on previous models of induced SCI in animals). Any loss of sensation or motor function below the spinal lesion was considered indicative of spinal cord injury.

Ineligible patients were those with involvement of nerve root or cauda equina only, penetrating wounds, multiple trauma, those who needed surgical intervention, those with fracture-dislocation, receiving steroids, age under 18 years, and hematocrite level higher than normal. Randomization was done by drawing of cards with pre- written numbers. Patients with odd numbers were assigned to control group (MPSS+ placebo; group M) and even numbers to intervention group (MPSS+ erythropoietin; Epo group). Neurologic function was assessed on admission to each center, after 24, 48 and 72 hours, one week, one month and 6 months later. Each patient was assessed using American Spinal Injury Association (ASIA) impairment scale (modified from the Frankel classifications) using the following categories (6,7):

A- Complete: No sensory or motor function is preserved in sacral segments S4-S5.

B- Incomplete: Motor function is preserved below the neurologic level and extends through sacral segments S4-S5.

C- Incomplete: Motor function is preserved below the neurologic level, and most key muscles below the neurologic level have muscle grade less than 3.

D- Incomplete: Motor function is preserved below the neurologic level and most key muscles below the neurologic level have muscle grade greater than or equal to 3.

E- Normal: Sensory and motor functions are normal.

Neurologic examinations were performed only by an approved and blinded physician unaware of the patients' group assignment. Rectal and urinary sphincter function was evaluated on admission and one month later. All patients were also asked about sexual dysfunction 6 months later.

Methylprednisolone was provided in 500 milligram vials and prepared with normal saline as diluents at a concentration of 3 mg per ml. The patients in both groups received MPSS 30 mg/kg initially intravenously during 15 minutes and 5.4 mg/ kg every hour till 23 hours if admitted within 3 hours after injury. The MPSS was continued for 47 hours with the same dose if the patients were presented to emergency ward during 3-6 hours after trauma.

EPO was provided in 4000 unit vials. The patients in EPO group (based on previous models of induced SCI in animals) received α-recombinant human erythropoietin (PDpoetin, Pooyesh Darou, Tehran, Iran) 500 unit/kg initially and another 500 unit/kg intravenously after 24 hours of first dose in 500 ml normal saline during 30 minutes. The patients in M group received the same infusion of normal saline without EPO. The primary end point was a change in neurologic function according to ASIA score between baseline and follow-up examinations. Plain antero posterior, lateral films and MRI of the spine were obtained for all patients. Spinal computed tomography (CT) was obtained as needed.

The aim of the study was to recruit thirty patients as it was a pilot study and eligible patients were relatively rare. Data was analyzed using SPSS software (version 16) by Fisher's exact test. $P<0.05$ was considered to be significant.

Result

During a 15-month period, 30 patients including 23 males and 7 females were included. Motor vehicle accident was the cause of injury in 22 (66%) of patients. The range of the patients age was 18-65 years and cervical spine was the site of injury in 18 and thoracic spine in 12 patients. The demographics of the patients are presented in table 1. The two groups had no significant differences with respect to age, sex, weight, site of spinal injury, time of drug administration after the injury and mean of ASIA score on admission.

Frequency and proportion of subjects with different ASIA score by type of treatment is shown in table 2. In addition, as we have two variables, type of intervention and the outcome which is ASIA score and both are categorical, type of intervention has two categories and ASIA score has 5 categories the proper test is Fisher exact test. The frequency of subjects who were in different categories of ASIA score based on the type of intervention at six times of the measurement were compared by this test and their significance level are also presented by table 2.

There was no significant difference between patients receiving two types of treatment in neurological exam on admission (P=0.125), 24 hours after admission (P=0.108) and 48 hours after admission (P=0.085). However, one week, one month and six months after admission these differences were significant. As it is shown in table 2, 20% of subjects of Epo group are in category E of ASIA score but none of the patients from

M group are in the Category E of ASIA score (P=0.046). One month and six months after admission 6 patients of Epo group were in the category E, however 1 patient of M group was in the category E (P=0.021 after 1 month, P=0.018 after 6 months). Table 3 shows the number of subjects, based on the type of treatment, in different categories of ASIA score on admission and six months thereafter. The difference in incidence of sexual dysfunction was not statistically significant between two groups at presentation and 6 months after follow up; 7 patients in group E and 9 patients in group M. No significant side effect was noted during the study period.

Table 1. patients' demographics in group M (Methylprednisolone) and group E (Erythropoietin)

	Group M	Group E	*P*-value
Patients (n)	15	15	--
Age (Mean ± SD)(years)	28.1 ± 11.3	34.5±12.6	0.15
Sex (Male / Female)	13/2	10/5	0.39
Weight (kg)	66.3±3.9	65.4±6.8	0.67
Site of injury (cervical / thoracic)	10/5	8/7	0.71
Cause of injury (traffic accident / fall)	11/4	11/4	--
Time of drug administration (first 3 hours / 3-6 hours after the trauma	5/10	6/9	--
Mean of ASIA* score on admission (range)	2(1-4)	2.07(1-4)	--

*ASIA: American Spinal Injury Association

Table 2. ASIA scores at admission and 5 follow up examinations after the injury in group M (Methylprednisolone) and group E (Erythropoietin)

	A Number (%)	B Number (%)	C Numbe (%)	D Number(%)	E Number(%)	Group	*P*-value
On admission	7 (46.67)	2 (13.33)	5 (33.33)	1 (6.67)	0 (00.00)	M	0.125
	8 (53.33)	0 (00.00)	5 (33.33)	2 (13.33)	0 (00.00)	Epo	
After 24 hours	7 (46.67)	2 (13.33)	5 (33.33)	1 (6.67)	0 (00.00)	M	0.108
	8 (53.33)	0 (00.00)	3 (20.00)	4 (26.67)	0 (00.00)	Epo	
After 48 hours	7 (46.67)	2 (13.33)	3 (20.00)	3 (20.00)	0 (00.00)	M	0.085
	7 (46.67)	0 (00.00)	3 (20.00)	4 (26.67)	1 (6.67)	Epo	
After one week	7 (46.67)	2 (13.33)	3 (20.00)	3 (20.00)	0 (00.00)	M	0.046
	7 (46.67)	0 (00.00)	3 (20.00)	2 (13.33)	3 (20.00)	Epo	
After one month	5 (33.33)	3 (20.00)	3 (20.00)	3 (20.00)	1 (6.67)	M	0.021
	2 (13.33)	3 (20.00)	1 (6.67)	3 (20.00)	6 (40.00)	Epo	
After six months	4 (26.67)	3 (20.00)	2 (13.33)	5 (33.33)	1 (6.67)	M	0.018
	2 (13.33)	0 (00.00)	4 (26.67)	3 (20.00)	6 (40.00)	Epo	

The numbers are absolute number of the patients in each group.
*ASIA: American Spinal Injury Association

Table 3. Number of subjects, based on the type of treatment, in different categories of ASIA score on admission and six months thereafter

		6 months after admission					
		A	**B**	**C**	**D**	**E**	**Total**
M group On admission	**A**	4	3	0	0	0	7
	B	0	0	2	0	0	2
	C	0	0	0	5	0	5
	D	0	0	0	0	1	1
	E	0	0	0	0	0	0
	Total	4	3	2	5	1	15
Epo group On admission	**A**	2	0	4	2	0	8
	B	0	0	0	0	0	0
	C	0	0	0	1	4	5
	D	0	0	0	0	2	2
	E	0	0	0	0	0	0
	Total	2	0	4	3	6	15

Discussion

During the last decade intensive research has been done to bring a number of promising therapies to clinic to treat patients with SCI but unfortunately none of them demonstrated sufficient efficacy to be widely accepted. The complexity of the pathophysiologic mechanisms involved in SCI explains the diversity of experimental pharmaceutical approaches to this disorder. Injury of the nervous system provokes a complex cascade of pre inflammatory cytokines and other molecules that ultimately result in apoptosis and necrosis of neurons, oligodendrocytes and endothelial cells (8).At present, it is widely accepted that two major pathophysiological events account for the neurological deficits associated with SCI: primary and secondary injurious events(9). Primary mechanisms, including forces of compression, contusion, shear, distraction and dislocation are not amenable to therapy however, with the onset of delayed secondary processes, a therapeutic window exists for intervention. This intervention is ideally achieved by medications with anti-inflammatory, anti-apoptotic and anti excitatory and regenerative potentials. One of the most promising candidates is EPO, a hematopoietic growth factor produced mainly by kidney and fetal liver (10).

Recent studies in animal models indicate that EPO is very effective in enhancing neurological recovery after experimental SCI (11-14) Also a recent clinical trial reported substantial improvement in outcome of stroke patients with ischemic infarcts treated with recombinant human EPO (rhEPO) (15).

The results of our small randomized clinical trial demonstrate a neurological benefit in ASIA score of patients with SCI associated with the systemic administration of MPSS with and without rhEPO 5000 unit per kg presented to emergency department within 6 hours after trauma. This improvement in ASIA scale was significantly more profound in group Epo (Table 3). This is in accordance with many animal studies in experimental models of SCI (8,11,12,16,17). In agreement with NASCIS II and III and Japan MPSS studies, we also observed a gradual improvement of ASIA scale in methylprednisolone group (9). This is interesting because ASIA impairment scale has been developed and recommended as a standard measure of SCI evaluation and improvement after these studies (18). This finding may explain why MPSS is still considered as an acceptable therapeutic option in SCI in many countries. Only patients with a normal state of consciousness were included in the study to avoid potential underestimation of the initial ASIA scores related to patient‘s inability to cooperate. Consequently the validity of the observed improvement after 6 months is a reliable finding.

Although a modest improvement in sphincter function was observed in both groups after one month, the difference of improvement was not statistically significant between the two groups. This finding may be due to different mechanisms of injury and healing between autonomic neuronal cells and other sensory and motor neurons. This rationalization may also explain not significant difference between two groups regarding sexual dysfunction after 6 months of cord injury. Although a marked beneficial effect of EPO in SCI has been observed, more needs to be learnt about the therapeutic window, optimal site of administration and dose-ranging characteristics. Results of studies in animal models indicated the effectiveness of treatment with rhEPO in SCI (11-14,19) however, the time of rhEPO administration seems to be correlated with the necessary number of doses. When rhEPO was used shortly after the injury one dose was enough to improve neurological outcome but multiple doses were more effective when the treatment was delayed (20). We included patients with less than 6 hour from the injury so we used two doses of rhEPO with 24 hours interval.

A major concern of clinicians is that besides tissue protective effects, EPO has also hematopoietic activity, with associated risk of thrombosis however, we didn’t encountered any clinically significant thromboembolic phenomenon in the group Epo. The substantial safety profile of rhEPO in treatment of anemia along with its neuroprotective effects in animal models will encourage the design of more and larger clinical trials to confirm the efficacy of this drug in SCI.

Conclusion: This study may be considered as the first step to confirm the efficacy of EPO in medical treatment of traumatic cord injury. The promising result of this clinical trial will hopefully encourage more studies in the role of rhEPO in SCI.

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