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Research Article

DOES EDARAVONE IMPROVE NEUROLOGICAL RECOVERY IN ACUTE SPINAL CORD INJURY? - A PILOT RANDOMIZED CONTROL TRIAL

Rajeshwar Nath Srivastava., Amar Chandra Sharma and Saloni Raj

Dept. of Orthopaedic Surgery, King George's Medical University, Lucknow, U.P., India

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ABSTRACT

Objective: Does Edaravone improve neurological recovery in acute spinal cord injury?
Methods: Twenty eight (28) thoracolumbar injury cases, admitted within 72 hrs after injury, participated in this prospective study. Subjects with polytrauma and head injuries were excluded from the study. Study subjects were randomized in two treatment groups -Group1 (n=14) subjects received placebo (saline) (controls) and Group 2 (n=14) subjects received 30mg Edaravone intravenously twice a day for 14 days (cases). The subjects were followed for 12 weeks and their neurological status recorded at baseline, at 4th and 12th week. Neurological recovery was assessed by AIS neurological grading, motor and sensory scores.
Results: The recovery observed in motor and sensory scores in group 2 subjects was statistically significant as compared to group 1 subjects at week 4 (motor- p=0.00, sensory- p=0.02) and 12 (motor- p=0.000, sensory- p=0.03).
Conclusions: Intravenous use of Edaravone may act to prevent the secondary damage and/or restoration of neurological function in SCI. Consequently, it may prove to be an effective strategy for therapeutic intervention in SCI.

INTRODUCTION

Free radicals and reactive oxygen species (ROS) are constantly formed in the organism as part of normal and essential biological processes.[1] Free radical generation and lipid peroxidation have been shown to be early events subsequent to spinal cord injury (SCI). During SCI, the cells are vulnerable to free radicals induced damage, abundant lipid content formation and relative paucity of antioxidant enzymes.[2] This sustained flux of free radicals results in an imbalance of the intracellular redox state regulated by Superoxide Dismutases (SOD) and Catalases (CAT). Thus, this altered redox status can be reverted through antioxidant treatment and may be an effective way of repairing the SCI.[3] Aksenova *et al*.[4] suggested that protein oxidation increases after experimental injury in rat spinal cord tissue with increased protein carbonyl formation in damaged spinal cord tissue. This was associated with changes in activity and expression of an oxidative sensitive enzyme, creatine kinase BB, which plays an important role in the maintenance of Adenosine triphosphate (ATP) level in the Central nervous system (CNS) tissue. Damage to Creatine Kinase (CK) function in the CNS may severely aggravate the impairment of energy metabolism.[4]

SCI triggers several secondary effects; one of these is oxidative stress, which is a hallmark of SCI. Thus, alleviating oxidative stress may be an effective way of therapeutic intervention of SCI. Extensive research over the past several decades has identified numerous bioactive compounds that have antioxidative stress benefits in animal models of SCI. These continued studies on bioactive compounds with ROS-scavenging capacity may lead to the development of effective antioxidant based modalities for treating SCI in human subject also.[5] Some agents such as glucocorticoid steroid methylprednisolone and non-glucocorticoid 21-aminosteroid tirilazad have been shown to possess significant antioxidant properties and improve recovery of SCI patients in clinical trials.[6, 7]

Use of steroids as an anti-inflammatory and antioxidative agent has long been propagated. The well known NASCIS trials I, II and III failed to provide convincing evidence in favour of steroids in SCI. Methylprednisolone (MP) was routinely employed in the clinical treatment of SCI as far back as 1960 based on their ability to decrease cerebral edema. It is a lipophilic steroid having anti-inflammatory and anti-oxidant properties.[8,9] A RCT of MP in the treatment of SCI reported significant neurologic recovery in patients treated within eight

Corresponding author:* **Rajeshwar Nath Srivastava
Dept. of Orthopaedic Surgery, King George's Medical University, Lucknow, U.P., India

hours of injury.[10] New guidelines on the use of MP developed under the guidance of AOSpine North America, AOSpine International, and the American Association and Congress of Neurological Surgeons (AACNS) suggested that that a 24-hour infusion of high-dose methylprednisolone can be offered to adult patients who present within 8 hours of acute SCI.[11]

Other promising botanical compounds, their molecular targets and mechanisms of action with regard to potential protection against SCI have also been described. These include carotenoids and phenolic compounds.[6] Riluzole, a benzothiazole drug, having neuroprotective properties based on sodium channel blockade and mitigation of glutamatergic toxicity, has been found to be associated with improved functional outcomes and increased neural tissue preservation. It is supposed to attenuate certain aspects of the secondary injury cascade leading to diminished neurological tissue destruction in animal spinal cord injury (SCI) models.[12] A phase III trial is currently undergoing to establish its role in SCI and the results are awaited.[13]

Edaravone, a phenolic compound, is another known neuroprotective antioxidant and may strongly scavenge free radicals, protecting against oxidative stress and neuronal apoptosis. It is already being used in animal models for protection from secondary damage in SCI and brain damage caused by ischemia/reperfusion and subsequent cerebral infarction.[14,15] Few studies have also reported its beneficial effects on traumatic brain injury (TBI) in humans. Since the pathophysiology of Traumatic brain injury (TBI) and SCI is similar, we hypothesized that since spinal cord and brain together form CNS, the response of Edaravone on SCI should be alike. On this basis, the present study was designed to determine the effect of Edaravone in the neurological recovery in SCI patients.

METHODS

This RCT is registered under Clinical Trail Registry of India (CTRI) and the registration number is CTRI/2017/02/007957. Twenty eight (28) unstable thoracolumbar injury cases were participated in the study (classified according to thoracolumbar injury severity scale and score (TLISS). The inclusion criteria of subjects were Age-16-65 years, either gender, Vertebral fracture T8-L1, Neurological involvement (Association Impairment Scale (AIS-B-D) and duration of Injury < 72 hours. Associated injuries such as limb fractures, thoraco-abdominal injuries, head injuries and pre-existing central or peripheral neurologic diseases (such as previous stroke, radiculopathy or polyneuropathy) needing intervention were excluded.

All the subjects were managed non- operatively by conservative methods. A pillow under the lumbar spine to maintain normal lordosis for "postural reduction" and bed rest for 12 weeks was ensured in all. Off-loading of bony prominences and pressure sensitive areas to prevent pressure injuries by regular changes of position in bed every two to three hours was ensured throughout day and night. The joints of the lower limbs were passively moved through the full range each day to prevent stiffness and contractures. Foot drop and equinus contracture were prevented by placing a vertical pillow between the foot of the bed and the soles of the feet.

The subjects were randomized in two treatment groups as cases and controls using computer generated random number table. Group 1 patients did not receive Edaravone and considered as controls whereas Group 2 patients were considered as cases and receive 30 mg Edaravone (intravenously) twice a day for 14 days. The subjects were followed for 12 weeks by the corresponding author throughout the study period. Neurological status of each patient was recorded at baseline, 4th and 12th week by using AIS neurological grading. The primary outcome of this study was to find out the effect of Edaravone on the neurological recovery in SCI.

We would like to certify that all applicable Institutional and Governmental regulations concerning the ethical use of human volunteers/animals were followed during the course of this research.

Statistics: Demographics and mode of injury are represented as frequency and percentage. Differences between AIS grade were tested by Chi-square test. Differences in motor and sensory scores between the two groups were calculated using unpaired student t-test.

RESULTS

Age and gender were found statistically insignificant between two groups (Table 1). In our study the most common mode of injury was fall from height (11patient) followed by road traffic accidents (8 patient) followed by fall of weight over them (5 patient) and the least common was from hit by animals (4 patient). (Table 2)

Table 1 Demographic and mode of Injury

Gender	Number of subjects					
	Total (n=28)		Interventional (Case) (n=14)		Conventional (Control) (n=14)	
	No.	%	No.	%	No.	%
Male	19	67.86	9	64.28	10	71.42
Female	9	32.14	5	35.71	4	28.57
Age Group (years)						
18-30	7	25.00	3	21.42	4	28.57
31-45	12	42.86	5	35.71	7	50.00
46-60	9	32.14	6	42.85	3	21.43
Mode of Injury						
Fall from height	11	39.29	7	50.00	4	28.57
Road Traffic Accident	8	28.57	2	14.29	6	42.86
Hit by animal	4	14.29	1	07.14	3	21.43
Others	5	17.86	4	28.57	1	07.14
Time since injury at the time(hours) of admission						
<24 hrs	5	17.86	2	14.29	3	21.43
<48 hrs	14	50.00	7	50.00	7	50.00
<72 hrs	9	32.14	5	35.71	4	28.57
Level of vertebral injury						
T8 to T12	15	53.57	7	50.00	8	57.14
L1 to L2	13	46.43	7	50.00	6	42.86
Neurological level (sensory level was same as motor level)						
T8 to T12	10	35.71	4	28.57	6	42.46
L1 to L2	18	64.29	10	71.43	8	57.14

Values are represented as frequency and percentage (%)

Statistically significant recovery was observed in group 2 patients than in controls (group 1) in terms of AIS[6] score after 4th week which was continued till 12th weak. (Table 3)

Table 2 Comparison of AIS grade between two groups at different period

Clinical score	Case (B/C/D)	Control (B/C/D)	χ^2 (95% CI)	P value
AIS at admission	6/7/1	12/2/0	5.78 (0.1 to 0.8)	0.05
At 4th week	0/10/4	10/4/0	16.57 (1.0 to 1.03)	0.000
At 12th week	0/2/12	2/8/4	9.6 (0.3 to 0.8)	0.008

Values are given as frequency.

Differences were tested by Chi-square test. (*, p value <0.05 considered statistically significant)

Table 3 Comparison of motor score between two groups at different period

Clinical score	Case	Control	95% CI	P value
Motor at admission	59.71±10.43	52.42±6.75	1.009to1.28	0.03*
Motor at 4th week	71.57±9. 74	57.14±9.85	1.112to1.416	0.001*
Motor at 12th week	86.42±5.55	70.14±13.0	1.111to1.379	0.000*

Data were represented as mean± SD (SD: Standard Deviation)

*Difference between groups was calculated using unpaired student t-test (p- value considered satisfactory significant).

In this study we evaluated the neurological recovery in both groups in terms of motor score.[16] We found that the recovery was maximum in interventional group (Group 2) in comparison to control group at after 4th week and after 12th weak which was found to be statistically significant. (Table 4)

Table 4 Comparison of sensory score between two groups at different follow-up

	Case	Control	95% CI	P value
Sensory at admission	181±26.39	164±23.48	0.99 to 1.23	0.07*
Sensory at 4th week	191±19.61	171±25.95	1.01 to 1.23	0.02*
Sensory at 12th week	200±18.97	179±28.65	1.01 to 1.24	0.03*

Data were represented as mean± SD (SD: Standard Deviation)

*Difference between groups was calculated using unpaired student t-test (p- value considered satisfactory significant).

In this study we also evaluated the neurological recovery between two groups in terms of sensory score.[16] We found that the significant recovery was maximum in group 2 in comparison to control group (group 1) at after 4th week which was found to be statistically significant.

DISCUSSION

This pilot RCT was done to determine the efficacy of Edaravone in the treatment of acute spinal cord injury subjects in humans and to determine its role in neurological recovery in comparison to placebo. We found a significant difference in neurological recovery at 4 weeks and at 12 weeks in subjects treated with Edaravone within 72 hours of injury. The free radicals generated as a consequence of secondary inflammatory cascade following primary insult to the spinal cord results into lipid peroxidation leading to neural tissue damage and disruption of neurological function distal to the site of injury. Edaravone is known to exert great free radical scavenging activity. [14, 15] The protective effects of Edaravone have been reported in studies on SCI in rats[17] and on TBI in humans[18], and as on date, is the only known antioxidant that has been approved for blocking this peroxidation.[18] Since the pathophysiology of brain and spinal cord injury is quite similar, we hypothesized that Edaravone could be beneficial for treatment in SCI patients also.

On literature review, we came across several important observations which led us to hypothesize and design this study such as in SCI, the most dreadful consequence is generation of free radicals causing extensive neuronal loss; great radical scavenging activity of Edaravone; and that the tissue saving strategies utilizing anti-inflammatory treatments may be more useful in traumatic SCI than in TBI.[19] We will now try to explain each of these individually to understand the purpose and finally the outcome of this study.

Together, the brain and spinal cord form the central nervous system having many similarities in their development and hence their physiological behaviour. Similarly, the pathophysiology of TBI and SCI is quite similar in their secondary injury following the primary mechanical insult; the loss of ionic homeostasis, glutamate excitotoxicity, mitochondrial dysfunction and microvascular disruption. These complex and integrated secondary injury cascades lead into pathways that yield free radical formation inducing oxidative damage which is a pathophysiological hallmark of central nervous system (CNS) injury. These uncontrolled reactive oxygen chain reactions triggered by secondary injury cascades can feed back into the secondary injury response creating an endless pool of ROS and the ultimate consequence is massive neuronal death.[20]

Edaravone, a phenolic compound, has great radical scavenging activity. [14,15] The protective effects of Edaravone in patients of extracerebral diseases like carotid endarterectomy[21] and acute myocardial infarction has already been observed.[22] A study on TBI patients conducted by Kenji Dohi *et al.*[18] proved that administration of 30 mg Edaravone scavenges alkoxyl radical (OR-) and significantly reduces levels of these radicals. However P. Chaudhuri found no significant benefit in administering Edaravone in TBI patients and mentioned that the use of Edaravone should be reconsidered due to incidence of hypoalbuminemia and associated morbidity in these patients.[23] They emphasized on a need to conduct randomized placebo controlled studies to ensure the use of Edaravone in neuro- traumatic conditions. Therefore, we decided to plan this pilot randomized controlled trial to determine the efficacy of Edaravone in SCI.

Finally, we came across a report by Batchelor PE *et al*[19] comparing inflammation in the rat brain and spinal cord following mechanical injury. They found inflammation in the CNS predominantly involved microglia and macrophages, and believed it to be a significant cause of secondary injury following trauma and this was significantly greater in the spinal cord compared to the brain. Since a greater degree of inflammation in the spinal cord is likely to result in more extensive secondary damage, tissue saving strategies utilizing anti-inflammatory treatments may therefore be more useful in traumatic spinal cord than brain injury.[19] This observation led us to hypothesize that Edaravone if beneficial in TBI may have a similar or better role in SCI.

It is a known fact that primary SCI is irreversible and resistant to any intervention. Recently several authors have reported the potential of stem cells in improving neurological functions following ASCI. Autologous bone marrow derived MNC's have been reported to be safe and cost effective and an algorithm to obtain these has aslo been published.[24-27] The present study focused on secondary inflammatory cascade and the consequent neurologic changes which can be prevented and reversed, if taken care of in early stages. We feel that the

improvements in neurologic function presumably will reflect biologic changes in the spinal cord. We therefore, further studied the role of Edaravone in neurological recovery in comparison to placebo and found a significant improvement in functional outcome, sensory, motor scores and in AIS grades in group-2 indicating the usefulness of Edaravone as a neuroprotective agent in SCI.

Minor adverse effects in group-2 like nausea, headache and itching were noted in some participants but resolved on their own without requiring any specific attention or intervention. To the best of our knowledge, this is the first study using Edaravone in acute SCI patients with positive outcomes. Being a pilot study, a well designed double blind RCT with a follow up of at least 1 year, consequently, may prove it to be an effective strategy for therapeutic intervention in SCI.

CONCLUSION

We found that intravenous use of Edaravone may reduce the secondary injury after acute SCI. Improving basic knowledge of antioxidant therapy in the treatment of SCI may help clinicians and researchers to identify and proactively intervene in an effort to minimize secondary damage in acute SCI. In future this may become a milestone in the management of acute SCI. In future, a larger study may have to be undertaken to provide further evidence of the efficacy and cost-effectiveness of Edaravone in the management of SCI.

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