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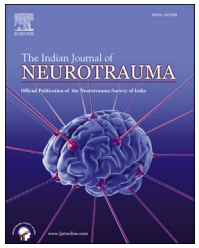

Original Article

Edaravon: Caution for use in traumatic brain injury. Experience in 127 patients

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ABSTRACT

Introduction: Edaravon, being a potential neuro-protective and neuro-tropic agent, was suggested for use in traumatic brain injury. During its use in 94 patients, a higher incidence of hypoalbuminemia was noted in a subset of trauma patients with severe brain injury.
Material and method: 94 patients were evaluated after administration of edaravon for the outcome of therapy in terms of Glasgow outcome score and the incidence of hypoalbuminemia. This was compared with 33 non-parallel patients of head injury who were not administered the medicine.
Result: The incidence of hypoalbuminemia and associated morbidity was found to be significant to reconsider the use of this medicine for severe traumatic brain injury. The outcome of patients treated with the medicine when compared with a non-parallel control group suggested that there was no significant benefit in administering edaravon in traumatic brain injury.
Conclusion: In spite of its limitations, this study emphasizes the need for further randomized placebo controlled studies before edaravon is considered for use in neuro-trauma.

1. Background

Edaravon [MCI-186, 3-methyl-1-phenyl-2-pyrazoline-5-one, MW 174.20] was introduced in clinical medicine in the year 2001.[1] It was initially advocated as a neuro-protective factor for stroke and later studies revealed the potential benefit in stem cell research. It was then advocated as a neuro-tropic agent. Experiments on rats revealed potential benefit in traumatic brain injury and spinal cord injury. This was then extended to humans. DCGI gave permission for the drug in the year 2010 [164-2010-DCGI] for the management of stroke. Until 2010, there was no available method for the analytical estimation of edaravon in blood.[2] After a period of use in brain injured patients, in the present study, however, no significant beneficial effect was observed. On the contrary a certain subset of patient developed hypoalbuminemia without significant hepatitis. The outcome of the present study has emphasized that the use of edaravon in brain injury should be deferred until its efficacy is established by further multicentric randomized studies.

2. Introduction

Traumatic brain injury continues to be a major concern for the neurosurgical community. The concern is especially with regard to the well known delayed lesions and the peri-contusion edema and neural damage. Hence, any medical option for post

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injury neuro-tropic effect will be welcome. With this hope, neurosurgeons are always on the lookout for drugs which will help quick recovery of the injured tissue. Stroke being the closest neighborhood, any drug used safely in stroke gets attention for use in traumatic brain injury. Such is a drug edaravon, which, after its suggested beneficial effect in stroke, was administered in animal experiments involving brain and spinal cord injury with evidence of benefit. It was then suggested for use in humans with traumatic brain injury. This study is an observation of a certain unexpected effect of edaravon which may be detrimental to the final outcome of brain trauma patients. The data of 94 patients were stratified retrospectively to identify the outcome of this drug in patients with traumatic brain injury. This findings were then compared with patients with similar injuries who were not administered the medicine. An unexpected increase in the incidence of hypoalbuminemia which resulted in adverse outcome in recovery was observed in some of these patients (Fig. 1).

3. Material and method

This is a study of 127 patients of severe head injuries, 94 of whom were administered 30 mg of injection edaravon for a period of 7 days two times a day as a slow infusion during the period 2008–2012 March and followed for 3 months. The rest 33 patients, from March 2012 to August 2012 with presenting score of 8/15 or less were included in the study and not administered the medicine. Patients with Glasgow coma score (GCS) 8 or less at the time of admission and age greater than 18 years were considered and all patients were managed with all other standard management protocol for the management of severe head injury. All patients were subjected to routine hematology and biochemistry tests as is necessary for the management for neuro-trauma patients. Patients with compromised liver function test and/or renal function test were not administered this drug. The 33 patients who were not administered edaravon were managed and followed in the same manner as the earlier group prospectively with first record at 1st week and second between 10 and 12 weeks for outcome assessment. Since the study was triggered by the observation of significant hypoalbuminemia in a subset of the patients treated, the end points chosen were serum Albumin levels at day 7 to day 9 and Glasgow outcome score (GOS) between 10 and 12 weeks.

4. Results

A total of 94 patients from 2008 to 2012 March were considered for the review (Table 1). All patients were scored GCS 8/15 or less with no other major systemic injury other than maxillofacial injuries noted in 27 (28.7%) patients. 43 of 94 (45.7%) patients were alcohol abusers. 23 of the 94 [24.4%] patients underwent cranial surgical procedures within 48 h of trauma. 14 [14.8%] patients were transfused with blood following surgery. 4 of 94 patients died due a primary cause that could be attributed to the brain injury. Another 19 of the 94 patients died due to sepsis and hemodynamic failure. Severe peripheral pitting edema was noted in all the 19 patients between 5th to 7th day post therapy. Of the 94 patients who were administered edaravon, 68 (72.3%) patients developed mild to moderate grade of hypoalbuminemia [mild hypoalbuminemia – 2.5 gm% to 3 gm%, moderate hypoalbuminemia – 1.5 gm% to 2.5 gm% and severe hypoalbuminemia – less than 1.5 gm%]. Corrective albumin transfusions were possible in 14 patients.

After the above cohort, the administration of the medicine was stopped in the following 33 patients till August 2012. All patients were with GCS below 8/15 at admission. 4 (12.1%) had maxillofacial or mandibular fractures. 15 of 33 (45.4%) patients were alcohol abusers. 7 of the 33 (21.2%) patients underwent cranial surgical procedures within 48 h of trauma. 2 [6%] patients required blood transfusion. 23 patients of the 94 [24.4%] succumbed to the injury within 15 days of injury. Of the 33 patients who did not receive edaravon, 2 (6%) developed hypoalbuminemia. 4 [12%] patients succumbed to the brain injury in this group with cause being attributed to the primary brain trauma.

Glasgow coma score (GCS) of 30 patients from the edaravon group who did not develop clinically significant hypoalbuminemia were compared with 30 patients in the non-edaravon group for a period of 3 weeks [4 patients from the edaravon group were lost to followup] (Table 2). No significant difference was noted with regard to Glasgow outcome score or neurological recovery. At 10–12 weeks 4 patients were lost to followup in the edaravon administered group. In this group of the remaining 26 patients, 15.3% improved to grade 4, 50% improved to grade 3 and 34.6% remained at grade 2 recovery. In the 30 patients not administered edaravon 23.3% patients improved to grade 4, 53.3% patient improved to grade 3 and 23.3% remained at grade 2 on the Glasgow outcome scale.

No patient had allergic reaction to the drug. Coagulation disorder with prolongation of INR between 2 and 2.5 occurred in the edaravon group but could not be attributed to the drug. Thrombocytopenia was not observed in any patients though transient drop of platelet counts were noted in 26 of 94 (27.6%) patients in the edaravon group and 9 of 33 (27.3%) patients in the no edaravon group and neither could this effect be attributed to the drug. No patient developed renal function dysfunction that could be attributed to the use of edaravon. Leukocytopenia and leukocytosis being often associated with trauma of this severity, though observed were not investigated in further detail with regard to primary etiology like myelosuppression.

It was observed that the incidence of hypoalbuminemia following administration of edaravon was significantly high compared to the group in which edaravon was not given. Hypoalbuminemia resulted in volume depletion into the third space thereby adversely affecting the hemodynamic status of patients and hence in recovery from severe head injury. Use of edaravon was not associated with any significant improvement in the neurological outcome of patient in both the groups.

5. Statistical evaluation

From a drug to hypoalbuminemia crosstabulation and application of chi square test, hypoalbuminemia was found to be

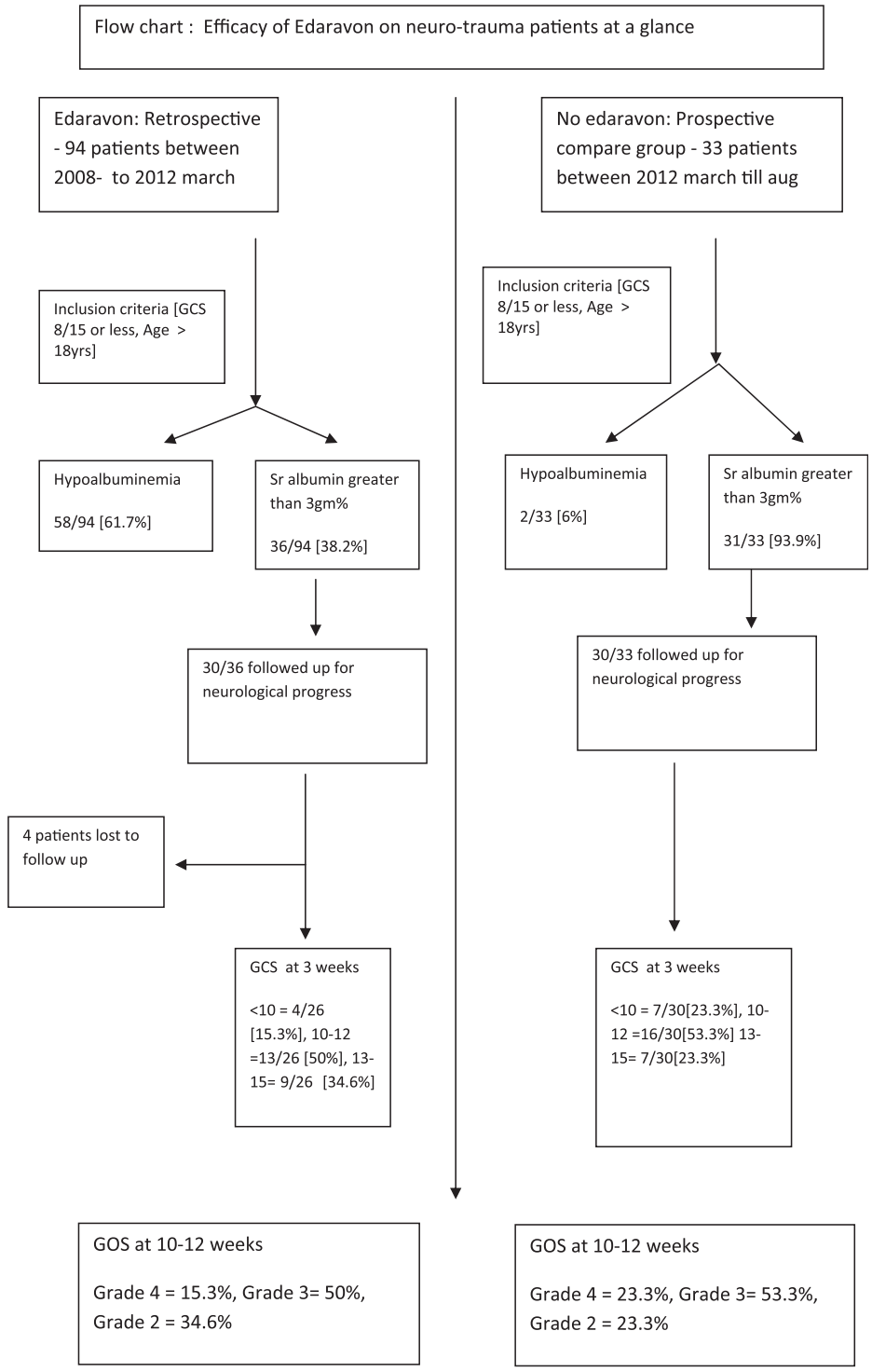

Fig. 1

significantly more common in the edaravon group [chi sq test value 30.34, df = 1, $p < 0.001$] (Table 3). The Glasgow outcome score GOS was compared between the edaravon administered group who did not develop hypoalbuminemia to the patients not administered edaravon to assess the benefit of the drug. Chi square test was applied and was found to have no significant difference [chi sq test value 1.098, df = 1, $p < 0.577$] (Table 4).

6. Discussion

With introduction of the molecule edaravon into clinical practice, having its primary application in stroke, its use was extended to management in brain trauma without much evidence in its favor. Though the manufacturer mentions the hepatotoxic adverse effect, it was remarked as the possibility

Table 1 – Patient profile and significant outcome in the two groups.

	Edaravon group (94 patients)	No edaravon (33 patients)
Maxillofacial injury	28.7% (27/94)	12.1% (4/33)
Alcohol abusers	45.7% (43/94)	45.4% (15/33)
Cranial surgery	24.4% (23/94)	21.2% (7/33)
Blood transfusion	14.8% (14/94)	6% (2/33)
Hypoalbuminemia	72.3% (68/94)	6% (2/33)
Death	24.4% (23/94)	12% (4/33)

Table 3 – Statistical analysis of the observed incidence of hypoalbunemia.

Drug * Hypoalbuminamia crosstabulation

	Hypoalbuminemia	Normal	Total
No edaravon	2	31	33
Edaravon	58	36	94
Total	60	67	127

Test applied – chi-square: test value 30.34, df = 1, $p < 0.001$. Hypoalbuminaemia was significantly more common in the edaravon group. *Edaravon.

of hepatic dysfunction which is rare in the dosage of 30 mg infusion given twice a day. Much more significant than clinical drug induced hepatitis is the hepatic hypofunction – typically expressed in the synthetic function of the liver – that can play a spoiler game in the hard work of a neurosurgeon. Edaravon (3 methyl-1-phenyl-2-pyrazolin-5-one) has been described as a strong free radical scavenger and most studies have been done in Japan.[3–7] Since 2001 the beneficial effects of edaravon on the ischemic brain both in animal and humans have been studied.[3,8–10] Adhering to the same view of free radical mediated injury to the penumbra zone of the contused brain, a neuro-protective and recently a neuro-tropic effect has been sighted as a rationale for the use of the medicine in traumatized brain. Its indication for use in situations where free radical injury is anticipated has yielded good results.[10] These studies, which are limited in various aspects, have been predominantly conducted on laboratory animals.[3,11–14] The neuro-protective effect of edaravon in brain trauma has been reported by several groups though none of them were done on human subjects. The beneficial effect of the drug noted as objective signs of recovery in neuropathology studies, may not have significant correlation in the clinical outcome following severe head injury. On the other hand any form of therapy predicted to give a better neurological recovery but resulting in adverse effect in general recovery should be considered as counter-productive. Sinha[7] studied the effect of edaravon on Indian population in ischemic stroke administered for 14 days and found no side effects. They have reported improvement in neurological scores in their followup. The Edaravon Acute brain Infarction Study (EABIS)[1] observed significant improvement in clinical outcome.

In the present study, the outcome was measured in terms of Glasgow outcome scale at 3 months. No significant difference was found in the outcome scales between the group administered edaravon and the group not administered edaravon. On the other hand the mortality was more in the edaravon group. The possible etiology from this investigation was the drug induced hepatic dysfunction resulting in persistently reduced serum albumin levels and thereby causing a decrease in the circulating volume. 34 patients could afford multiple 20% albumin transfusions. These patients showed transient improvement in the circulating volume status. However this effect did not sustain beyond 48 h. This may suggests the presence of more than one mechanism for the poor outcome of patients treated with edaravon. A review of the literature reveals great support to the mechanism of recovery of injury to the brain – ischemic or traumatic after administration of edaravon. Many of the studies have been done in Japan and mostly on mouse. Long term data particularly with regard to

Table 4 – Statistical GOS analysis.

Drug * followup GOS crosstabulation

	Grade 2	Grade 3	Grade 4	Total
No edaravon	7	16	7	30
Edaravon	9	13	4	26
Total	16	29	11	56

Test applied – chi square: test value 1.098, df = 2, p = 0.577. No significant difference observed in Glasgow outcome score [GOS] of patients in two groups (when patients administered edaravon and not administered edaravon, without hypoalbuminaemia were followed up). *Edaravon.

Table 2 – Glasgow outcome score in the two groups.

			Edaravon administered	Edaravon not administered
5	Good recovery	Resumption of normal life despite minor deficits	15.3% (4/26)	23.3% (7/30)
4	Moderate disability	Disabled but independent. Can work in sheltered setting	50% (13/26)	53.3% (16/30)
3	Severe disability	Conscious but disabled. Dependent for daily support	34.6% (9/26)	23.3% (7/30)
2	Persistent vegetative	Minimal responsiveness	–	–
1	Death	Non survival	–	–

Glasgow outcome score [courtesy: trauma.org].

clinical outcome in the critical patient with multi-system involvement, as in traumatic shock, is not available. To the best of knowledge, this is the first report of an adverse outcome of edaravon in severely injured patients. This study has certain limitations. It is partly retrospective and compared with a prospective group. It has been started following an observation of increased mortality in a subset of patients receiving the drug and conducted by a single investigator thereby subjecting the study to possible bias. Nonetheless, this study certainly raises caution as to the need for more controlled studies in severely traumatized patients before it is advocated as an adjunct therapy for brain trauma. The author has stopped the use of the medicine till further clinical data is available.

7. Conclusion

The need for effective neuro-protective and neuro-tropic medicines have given us several options which have mainly undergone stage IV clinical trials in a relatively restricted group. Often the benefits of the findings are extended to indications with pathologically similar lesions. However such extended indications need to be applied with caution. This study concludes that edaravon was not found to be safe in severe brain trauma patients. Edaravon did not appear to significantly change the disability outcome of these patients. This study is a single center, single investigator, non-randomized, retrospective observation study with non-parallel comparison group and may have significant bias error. The study, however, suggested an increase in mortality due to a possible drug induced adverse effect on hepatic function resulting in loss of homeostasis of the trauma patient. Hence, there is a need to conduct a multi-centric controlled randomized trial before it is recommended in neuro-trauma.

Conflicts of interest

The author has none to declare.

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