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REVIEW STUDY ON COMPARISION OF SAFETY AND EFFICACY OF EDARAVONE A NEUROPROTECTIVE DRUG IN INDIAN POPULATION STROKE PATIENTS

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ABSTRACT

Edaravone a free radical scavenger is the only neuroprotective agent effective for both Amyloid lateral sclerosis and Acute ischemic stroke treatment. Free radicals play a crucial role in brain ischemic injury by exacerbating membrane damage through peroxidation of unsaturated fatty acids of cell membrane leading to neuronal death and brain edema. Hence use of a free radical scavenger is very much essential in such conditions. Oxidative stress is a viable target in stroke therapy which can be reduced by the use of edaravone. The studies we mentioned aims at the safety and efficacy of Edaravone in a group of Indian population of acute ischemic stroke patients. Study 1 was an open label prospective study which was conducted in the Department of Neurology, CSM Medical University, Lucknow, a tertiary health care centre in North India. The study was carried out between January and July 2008. Study 2 was a prospective open labeled, randomized controlled study conducted in the Department of Neurology, Chatrapathi Shahuji Medical University, Luck now, and a tertiary health care centre in North India. The study was conducted between May 2009 and May 2010. All the patients received 30mg of Edaravone dissolved in 100ml of normal saline infusion over 60 minutes twice for 14 days. The outcome assessment was done by using the Modified Rankin Scale (MRS) and the Barthel Index (BI). MRS score ≤ 2 at 90 days was considered to be favorable outcome. In study 1 and the mean MRS score decreased at day 7 to day 14 to day 30 to day 90($p<0.05$). The mean Barthes index increased at day 7($p<0.05$) from baseline, to day 14 to day 30 to day 90($p<0.05$). In study 2 the mean MRS decreased from baseline at 90

days in Edaravone group. The difference in mean MRS was not significant between two groups (P=0.0590). The mean BI increased from 41.20±32.70 at baseline to 82.40±18.32 at day 90 in the edaravone group as compared with 68.20±21.30 at 90 days in the placebo group. Both the studies concluded that there was safe and effective outcomes of Evaradone among the stroke patients and did not experience any major side effects.

KEYWORDS: Edaravone, neuroprotective drug, free radical scavenger, both ALS and AIS treatment.

INTRODUCTION

Edaravone is an antioxidant free radical scavenger which was the first drug for amyotropic lateral sclerosis (ALS) and acute ischemic stroke(AIS) approved by the U.S. Food and Drug Administration (FDA) in the year may 2017.[1] Acute ischemic stroke occurs when blood flow through brain artery is blocked by a clot and Amyloid lateral sclerosis is a progressive skeletal disorder which affects the skeletal muscles leading to death within 2-4 hours of onset.[1] The neuroprotective agent may block reperfusion injury and helps in decreasing neuronal damage. The term of two parts "amyotrophy" meaning atrophy of the muscles and "lateral sclerosis" meaning hardening of lateral region of spinal cord.[1] Neuroprotective agents for acute ischemic stroke have been investigated for decades now and edaravone is currently only agent approved for clinical settings.[1] Oxidative stress is involved in the pathway of ALS and AIS[1] and previously Riluzole is the only choice of drug but its efficacy was identifies to be moderate. The free radical scavenger Edaravone which was initially developed for the treatment of acute ischemic stroke has also been used for the treatment of ALS and AIS.[1] People with ALS and AIS have high oxidative stress Edaravone works by relieving the oxidative stress, which is related to the death of neurons. Keeping motor neurons healthy may help to preserve muscle function.[2] Edaravone prevents vascular endothelial injury in transient cerebral ischemia, inhibits the lipogenase pathway activation in the arachnoidic acid cascade and peroxidation of phosphotidyl choline liposomal membrane.[2] In patients with ALS and AIS the brain loses the ability to control muscle movements begin to die slowly, resulting in the complete [paralysis in the later stages of the disease. Early symptoms of the disease include muscle twitching's, weakness, cramping, stiffness, slurring of speech, difficulty in chewing and swallowing. Also includes psychological and cognitive difficulties such as involuntary crying, depression, nonadaptive social behavior. The average age of onset is between 55-65 years in Indian population. The

average life expectancy is between 2-5 years from the time of diagnosis, later it may worsen leading to death of the patient.[2] Edaravone first drug to be approved by the U.S. FDA has maximum efficacy for the treatment of ALS and AIS has both activities of a radical scavenger as well as an anti-inflammatory effects by reducing the induction of nitric acid synthase.[2] Beneficial effects of Edaravone can be identified when given in combination with the tissue plasminogen activators in acute ischemic stroke, it immediately reduces the oxidative stress and prevents further complications.[2] Edaravone sold under brand name Radicava is much safer to use in patients when compared to Riluzole. It is administered through intravenous infusions.[2] This drug was approved by FDA not only because of extended survival of the patients, it can also decrease the symptoms more quickly when compared with Riluzole.[2] Although ALS effects all races of people it is more prevalent among Caucasians.[2]

EPIDEMOLOGY

ALS and AIS has an incidence of 1.5 to 2.7/100000/year and a prevalence of 3 to 5/100000. The average age of onset is above 55 years in western studies which was also found similar in Indian population. There is a male predominance ratio of approximately 5:1. An increased risk of occurance of AIS and ALS is predominantly found in rural population because of more exposure to chemicals and pesticides and development of neuronal injury.[3]

A study conducted about the pattern of neuron disease in institute of neurology, Calcutta. A total of 110 patients were included, amyloid sclerosis and stroke constituted of about 43.6%. Disease was more common in males compared to females and average duration was about 12 months.[3]

A hospital based prospective study was conducted in was carried out in Indira Gandhi medical college, Shimla. 32 patients were enrolled for a period of one year. Maximum number of patients were between 40-69. Males were more affected than females. Maximum numbers of cases were from a rural background.[4]

A cross sectional study was performed among 30 patients in national quaternary referral care centre for neurological disorders in southern India. All patients were diagnosed with definite AIS. The mean age of onset was above 50 years. Males were more affected when compared to females.[4]

METHODOLOGY

Study 1 was an open label prospective study which was conducted in the Department of Neurology, CSM Medical University, Lucknow, a tertiary health care centre in North India. The study was carried out between January and July 2008. The study was approves by Institutional Ethical Committee. The study included patients with ischemic stroke who were hospitalized between 6 and 72 hours of onset of stroke. Patients, less than 18 years of age, those who received any thrombolytic therapy, patients with severe renal dysfunction, pregnant ladies, lactation, hepatic disease patients were excluded from the study. A detailed history, general physical and neurological examinations were done for all the patients. All diagnostic tests were done for the patients. Diagnosis of ischemic stroke was done according to World Health Organization. The stroke subtypes were classified as per the Trial of ORG 10172 in acute stroke treatment (TOAST) study criteria.[5]

All the patients received 30mg of Edaravone dissolved in 100ml of normal saline infusion over 60 minutes twice for 14 days. Some patients also received oral aspirin and 20% mannitol infusion depending on the type of stroke whenever required. Samples for all routine laboratory tests were obtained and analyzed at enrollment, at day 7 and day 14. Patients meeting criteria (an increase in the NHSS score of 4 points) or a new stroke during first week also went further follow-up imaging.[5]

The patients were assessed at enrollment and at 7,14,30,90 days. The severity of stroke was assessed by the National Institute of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS). Assessment during follow-up was done by using the Modified Rankin Scale (MRS) and the Barthel Index (BI). MRS score ≤ 2 at 90 days was considered to be favorable outcome. The results were expressed as mean ± standard deviation. We compared clinical outcome (MRS and BI) at days 7,14,30,90 using paired t-test. The level of significance was set at $p<0.05$.[5]

Study 2 was a prospective open labeled, randomized controlled study conducted in the Department of Neurology, Chatrapathi Shahuji Medical University, Lucknow, and a tertiary health care centre in North India. The study was conducted between May 2009 and May 2010. The study was approved by Institutional Ethical Committee, India. The study included patients with AIS who were hospitalized between 6 to 72 hours of onset of stroke. Patients, less than 18 years of age, those who received any thrombolytic therapy, patients with severe renal dysfunction, pregnant ladies, lactation, hepatic disease patients were excluded from the

study. A detailed history taking general, physical, neurological examinations were done and recorded on a predesigned proforma. Patients were assessed at enrollment and at 90 days by an experienced physiotherapist, who was blinded for the treatment given, using Modified Rankin Stroke Scale (MRS) and the Barthel Index (BI). The stroke severity was assessed by the National Institute of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS). Diagnosis of ischemic stroke was done according to World Health Organization. The stroke subtypes were classified as per the Trial of ORG 10172 in acute stroke treatment (TOAST) study criteria. After inclusion the patients were randomly divided into two groups according to computer generated random sequences. The study group received 30mg of Edaravone dissolved in 100ml of normal saline infusion over 60 minutes twice for 14 days. The control group received normal saline infusion as placebo. Both the groups standard therapy for ischemic stroke and other symptomatic treatment. While patients receiving infusions, vital signs and adverse effects were recorded regularly. Samples for all routine laboratory tests were obtained and analyzed at enrollment, at day 7 and day 14. We compared clinical outcomes (MRS and BI) at 90 days between two groups. MRS score ≤2 at 90 days was considered as a favorable outcome. The numbers of patients with favorable outcomes (MRS≤2) were compared between the two groups by using Chi square test. For BI, the results were expressed as mean± standard deviation and the mean were comparing between two groups by independent t-test. The final analysis were based on an "an intention to treat" approach that included all randomized patients received at least one dose of study medication. The level of significance was set at $P<0.05$.[6]

RESULTS

STUDY 1: Twenty eight patients meeting inclusion criteria were admitted during the study period, out of which 22 patients were enrolled into the study. The reasons for exclusion of 6 patients was refusal to give informed consent(2 patients), unclear time of onset(2 patients), hepatic dysfunction(1 patient), and suspected malignancy(1 patient).[5]

Table 1: Baseline Characterstics of Patients In Study 1.

Patient Characteristics	Baseline
Mean age (years)	64.15 ±13.72
Male sex – number (٪)	15/22
Mean time from onset of stroke to treatment (hours)	26.5 ±21.27
Baseline NIHSS >8	10/22
Hypertension	13/22
Previous stroke	2/22

Previous TIA	1/22
Ischemic heart disease	1/22
Atrial fibrillation	2/22
Diabetes mellitus	3/22
Stroke subtype Large-artery atherosclerosis Small-artery atherosclerosis Cardioembolic stroke	 17/22 3/22 2/22

Table 2: Modified Rankin Scale At Various Days of Follow Up In Study 1.

15 patients (68%) had favorable outcomes at 90 days

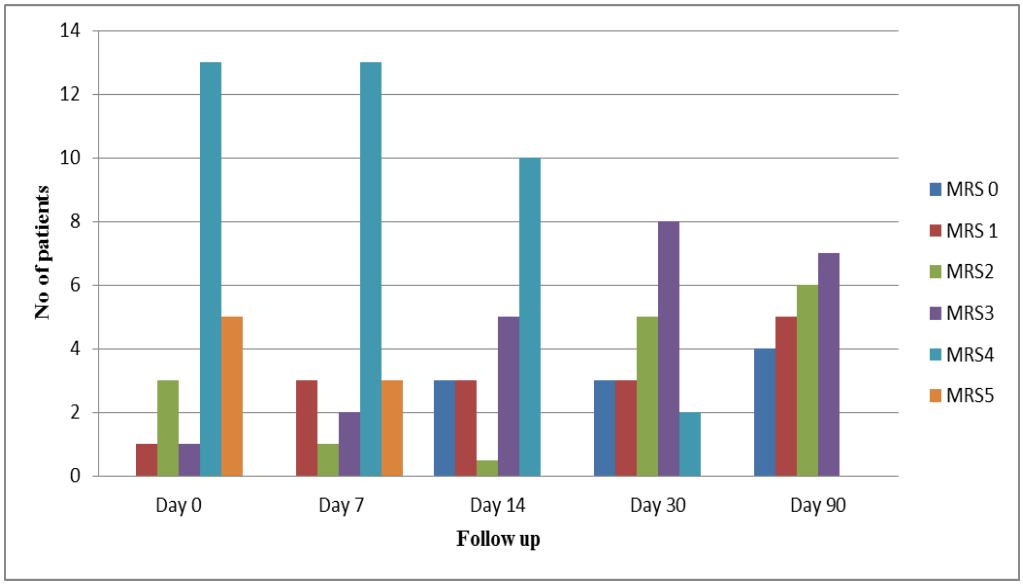


Table 3: Clinical Outcomes of Patients in Study 1.

Scale	Baseline	7 days	14 days	30 days	90 days
Mean NIHSS score	10.62±8.86	6.62±7.48*	5.12±6.13*	4.12±4.64*	3.12±4.71^{+}
Mean GCS	13.87±2.01	14.12±1.64$^{:}$	14.5±1.06$^{:}$	14.5±1.34$^{:}$	14.5±1.34$^{:}$
Mean MRS score	4.01±0.92	3.62±1.18*	2.87±1.55*	2.25±1.28^{+}	1.86±1.07^{+}
Mean Barthel index	40.00±30.11	53.12±3.79*	63.75±0.59*	69.12±25.07^{+}	75.62±22.86+

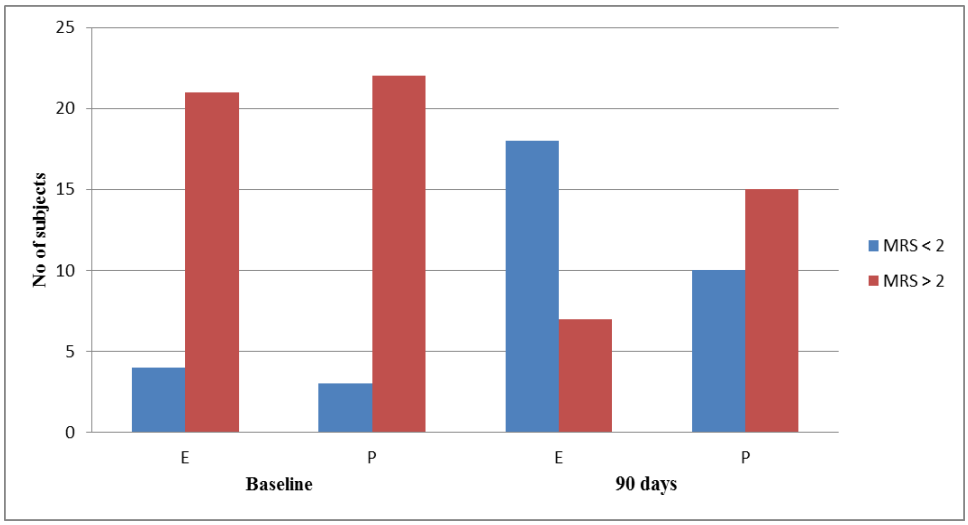
It was observed that the mean NHS score decreased from 10.62±8.86 at baseline to 6.62±7.48 at day 7($p<0.05$), to 5.12±6.03 at day 14($p<0.05$), to 4.12±4.64 at day 30($p<0.05$) and to 3.12±4.17 at day 90($p<0.05$). The mean GCS increased from 13.87±2.01 at baseline to 14.12±1.64 at day 7(p=NS). The clinical outcome also improved favorably and the mean MRS score decreased from 4.01±0.92 at baseline to 3.62±1.18 at day 7 ($p<0.05$), t 2.87±1.55 at day 14($p<0.05$), to 2.25±1.28 at day 30($p<0.05$), to 1.86±1.07 at day 90($p<0.05$). The mean Barthel index increased from 40.00±30.11 at baseline to 53.12±3.79 at day 7($p<0.05$),to 63.75±0.59 at day 14($p<0.05$), to 69.12±25.07 at day 30($p<0.05$)and 75.62±22.86 at day 90($p<0.05$).

Table 4: Baseline Characteristics of Patients in Study 2.

Characteristics	Edaravone group(n=25)	Placebo group (n=25)	Statistics
Sex (M/F)	16/9	15/10	χ^2 : P = 0.771
Age (years)*	58.12 ± 10.79	56.0 ± 8.15	χ^2 : P = 0.437
Time in hours (onset)*	30.08 ±18.87	25.48 ± 13.59	t : P = 0.328
Modified Rankin Scale median	4	4	W : P = 0.647
Modified Rankin Scale*	3.84 ± 1.17	4.0 ± 1.08	t : P = 0.619 Fischer exact; P=1
Modified Rankin Scale≤2	4	3	t : P = 0.767
NIHSS*	10.56 ± 5.74	10.08 ± 5.66	t : P = 0.767
NIHSS (>8)	14	14	χ^2 : P = 1
Barthel index	41.2 ± 32.70	44.20 ± 22.76	t : P = 0.708
Glasgow coma scale*	13.48 ± 2.69	13.40 ± 2.78	t : P = 0.918
Diabetes mellitus	6	5	χ^2 : P = 0.733
Hypertension	14	12	χ^2 : P = 0.571
Smoking	10	7	χ^2 : P = 0.370
Coronary artery	6	5	χ^2 : P = 0.733

STUDY 2: A total of 72 patients having clinical diagnosis of AIS 6 to 72 hours duration were admitted, in which 58 patients were included in the study. Out of excluded patients 18 had previous history of stroke, 3 patients had renal dysfunction, and 1 patient had hepatic malignancy. Among these 50 patients 25 patients received Edaravone infusion, while remaining received normal saline as placebo.[6] Among Edaravone group, 18 patients had large artery atherosclerosis, 5 patients had small artery occlusion, and 2 patients had cardio embolic stroke. Where as in the placebo group, 16 patients had large artery stenosis, 6 patients had small artery occlusion, 3 patients had cardio embolic stroke.

Table 5: Number of Subjects (Mrs < 2 & > 2) In Edaravone (E) Group And Placebo (P) Group And 90 Days.



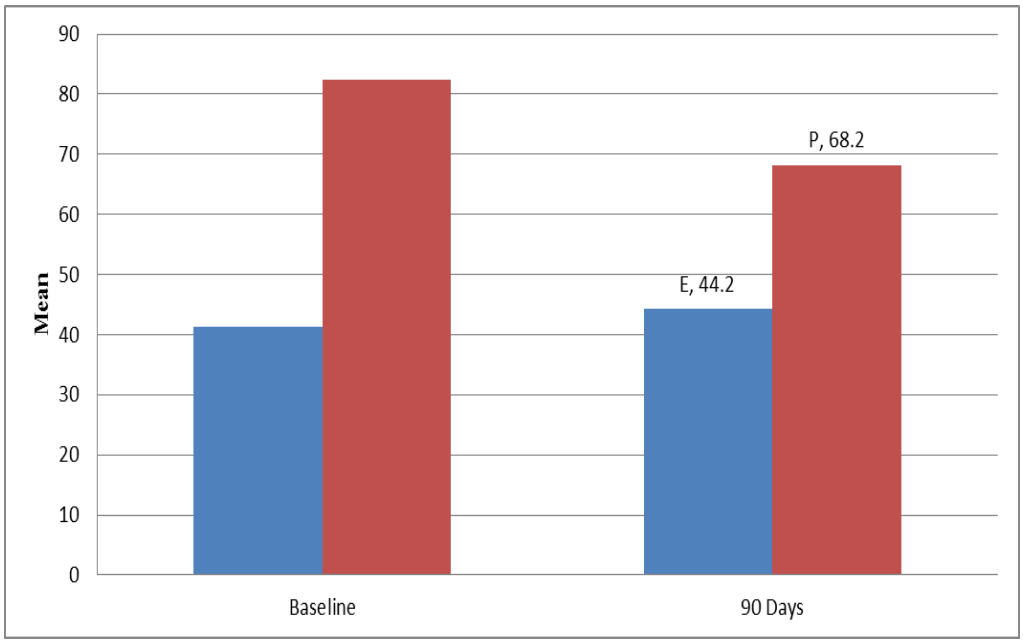
Only one patient developed an increase in NHS score by 4 points and an increase in infract size. Edaravone treatment was very well tolerated and none of patients experienced any adverse reactions.[5] One patient in each Edaravone and placebo group died at day 3 and day 5 respectively. 18 patients (72%) had positive outcomes (MRS≤2) at 90 days in Edaravone group, while 10 patients (40%) had favorable outcome in placebo group.

Table 6: Outcome At 90 Days In Edaravone and Placebo Groups.

Characteristics	Edaravone	Placebo	Statistics
Modified Rankin scale 2/> 2	18/7	10/15	χ^2 : P = 0.023*
Modified Rankin scale (Mean ± SD)	2.04 ± 1.30	2.72 ± 1.33	U: P = 0.059
Barthel index (Mean ± SD)	82.40 ± 18.32	68.20 ± 21.30	t: P = 0.015*

The mean MRS decreased from 3.84±1.17 at baseline to 2.04±1.30 at 90 days in Edaravone group. Whereas the mean MRS score is placebo group was 2.72±1.33 at 90 days. The difference in mean MRS was not significant between two groups (P=0.0590).

Table 7: Barthel Index In Edaravone (E) And Placebo (P) At Baseline and 90 Days.



The mean BI increased from 41.20±32.70 at baseline to 82.40±18.32 at day 90 in the Edaravone group as compared with 68.20±21.30 at 90 days in the placebo group.

Table 8: Frequency of Modified Rankin Scale in Edaravone and Placebo Groups At 90 Days.

Modified Rakin Sale	Edaravone (Frequency ٪)	Placebo (Frequency ٪)
0	3 (12)	0 (0)
1	4 (16)	6 (24)
2	11 (44)	4 (16)
3	5 (20)	9 (36)
4	1(4)	4 (16)
5	0 (0)	1 (4)
6	1 (4)	1 (4)

The was a significant difference (P<0.005) between the groups in favor of Edaravone. Adverse reactions were observed in 3 patients (12.5%) in Edaravone group, and in 5 patients (20.8%) in placebo group. Such reactions consisted of skin rash in 1 patient, abnormal liver function in 1patient, abnormal renal function in 2 patients and fever and diarrhea in 2 patients. All of them recovered with treatment Edaravone treatment was well tolerated.[6]

DISCUSSSION

In the study 1: Out of 22 patients 15 patients had favorable outcomes (MRS≤2) at 90 days. This study is the first type of study which was conducted in India other than Japan on the effects and significance of Edaravone in the treatment of AIS. Acute brain infraction study group observed a significant improvement in the functional outcomes of Edaravone group as evaluated by the modified Rankin scale. Our study observed significant early improvement which persisted till the completion of the study period.[5]

In our study 1, the time to treatment after the onset of acute ischemic stroke was kept between 6 to 72 hours and the dose of Edaravone was 30 mg twice daily for 14 days. An early phase II study had indicated that the Edaravone was effective up to 72 hours of onset of stroke and improvement at 14 days was 52% for 20mg, 64% for 30mg and 64% for 60mg per day of Edaravone respectively. On the basis of this study the appropriate dose of Edaravone for the treatment of AIS was considered to be 30 mg twice daily for 14 days.[5]

The use of Edaravone was considered to be safe in acute ischemic stroke patients as there was no occurance of adverse reactions in any of our patients. Edaravone groups reported insignificant skin rashes, and abnormal liver functioning. There were few cases of renal failure and fulminant hepatitis and hence therefore carefully monitor the renal and liver functions while administering Edaravone.[5]

Finally the results of the study conclude that the use Edaravone treatment may be safe and effective in providing early and sustained neurological improvement in patients with acute ischemic stroke.[5]

In our study 2: The treatment of AIS is mainly dependent on antithrombotic agents, such as antiplatelet, thrombolytic and anticoagulants and neuroprotective agents such as free radical scavengers and antioxidants. The neuroprotective agents may block perfusion injury and help in decreasing the neuronal damage. In the present study, 18 out of 25 patients had favorable outcome (MRS≤2) at 90 days as compared with 10 patients in placebo group, and 3 patients became completely asymptomatic (MRS=0) in Edaravone group while none in placebo group [Table 3]. Our study observed significant improvement in the functional outcome in Edaravone group and also demonstrated the safety of its use in Indian population. The Edaravone Acute Brain Infraction Study also observed significant improvement in functional outcomes in Edaravone group as evaluated by the Modified Rankin Scale.[6]

According to the study the time limit for treatment after the onset of AIS was kept between 6 to 72 hours and the dose of Edaravone was kept at 30 mg twice daily for 14 days. An early phase II study had indicated that the Edaravone was effective up to 72 hours of onset of stroke and improvement at 14 days was 52% for 20mg, 64% for 30mg and 64% for 60mg per day of Edaravone respectively. On the basis of this study the appropriate dose of Edaravone for the treatment of AIS was considered to be 30 mg twice daily for 14 days.[6]

The major adverse reactions were skin rashes, abnormal liver functions and renal disfunctioning and they were more frequent in the placebo group studies. The safety of Edaravone was established in an Indian study also and also its usage is, more effective and safer than other medications. The use of Edaravone was considered to be safe in acute ischemic stroke patients as there was no occurance of adverse reactions in any of our patients. Edaravone groups reported insignificant skin rashes, and abnormal liver functioning. There were few cases of renal failure and fulminant hepatitis and hence therefore carefully monitor the renal and liver functions while administering Edaravone. We therefore conclude that Edaravone a novel free radical scavenger can provide safer and effective outcomes in the patients with AIS.[6]

LIMITATIONS

The limitations of study 1 and study 2 are similar

Small sample size was considered, a larger randomized case controlled studies may be even more beneficial.

No blinding of clinician was done.

CONCLUSION

The treatment of ALS and AIS is not well developed worldwide. Many patients die worldwide due to improper treatment. Edaravone is an antioxidant free radical scavenger which was the first drug for amyotropic lateral sclerosis (ALS) and acute ischemic stroke (AIS) approved by the U.S. Food and Drug Administration (FDA) in the year may 2017. All the studies concluded that Edaravone is safe and effective for the treatment of both ALS and AIS and is effective in providing early and sustained neurological improvement in patients with acute ischemic stroke.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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