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Original Research Article

Comparative analysis of edaravone add-on versus riluzole alone in amyotrophic lateral sclerosis

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ABSTRACT

Background: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative progressive disorder affecting the motor neurons with a prevalence of 5 per 100000 population in India. Riluzole, a presynaptic glutamate receptor blocker, was the only treatment available for last 20 yrs. Recently Edaravone, a free radical scavenger, was approved in 2017 by FDA for its neuroprotective behaviour in ALS and is being used as an add-on drug. This study was undertaken to analyse the add-on beneficial effects of Edaravone with Riluzole in ALS patients and compare it with patients on Riluzole alone.

Methods: A prospective, analytical, hospital-based study of 2 years in duration was conducted in the Department of Pharmacology and Neurology, S.C.B. MCH, Cuttack. All adult patients diagnosed with ALS (based on neurogenic pattern with spontaneous activity in EMG) were included in the study. One study group received Riluzole orally alone while the other group received Edaravone IV infusion along with Riluzole. Efficacy was assessed using ALSFRS-R score, evaluated at baseline and at the end of each month till 6 months. Causality assessment was done by using the WHO-UMC Causality assessment scale and severity assessment was done using Modified Hartwig and Seigel severity scale. Cost effective analysis was done by calculating ICER (Incremental cost effective ratio).

Results: Each group had 70 study subjects with similar baseline characters. There was no significant difference observed studying the baseline characteristics. The ALSFRS-R scores were assessed for 6 months which showed deterioration. Mean ALSFRS-R score significantly decreased by – 5.12 and – 8.87 in Gr A and B respectively at the end of 6 months. A total of 80 ADRs were recorded in the study subjects which were of mild severity.

Conclusions: Edaravone add-on significantly improved functions in ALS patients in comparison to Riluzole alone therefore, it may be prescribed to ALS patients to reduce the disease progression.

Keywords: ALS, ALSFRS-R score, Edaravone, Riluzole, ICER

INTRODUCTION

Amyotrophic Lateral Sclerosis also known as Lou Gehrig's disease is a neurodegenerative, progressive disorder affecting the motor neurons. A substantial amount of motor neurons (upper and lower) is lost mainly from the spinal cord and brainstem. The worldwide incidence of

ALS is observed to be 0.8 to 1.5 per 100,000 while the prevalence is 2 to 7 per 100,000.¹ Likewise, in India the incidence and prevalence is 1.5 to 2.7 and 3 to 5 per 100,000 respectively.²

ALS has two major symptoms; muscular atrophy and reduced muscle strength and death occurs due to

respiratory paralysis.³ The average life expectancy in ALS is 2-5 years from the time of diagnosis. Most common onset is typically from the limbs and few as bulbar involvement. Most cases of ALS are sporadic but a small percentage of ALS cases (5-10%) have familial origin which is inherited as autosomal dominant mutation.⁴

ALS as a neurodegenerative disease lacks an effective treatment and for the past 20 years Riluzole was the only approved drug available for ALS. Riluzole as a neuroprotective drug blocks the glutaminergic neurotransmission in the CNS preventing neuronal death.⁵ In 2017 Edaravone was approved for ALS apart from its use for acute cerebral infraction. It acts as a free radical scavenger which prevents the oxidation of lipids that damages the cell membranes of neurons. Along with the antioxidant activity it also causes enhancement of prostacyclin production, hydroxyl radical trapping, quenching of active oxygen that provides neuroprotection against oxidative stress in motor neurons.⁶

Riluzole has a short survival benefit of 2 to 3 months which equates to a 9% increase in 1 year survival; therefore, a new therapeutic option may be required to slow down the disease progression in ALS.¹ As Riluzole has limited survival benefit, Edaravone add-on might slow down the disease progression and deterioration of daily functional activities. Hence this study was undertaken with the aim to compare and analyse the efficacy, safety and cost effectiveness of Edaravone add-on versus Riluzole alone in Amyotrophic Lateral Sclerosis.

METHODS

Current study is a prospective, analytical study conducted in the Department of Pharmacology in collaboration with the Department of Neurology at SCB Medical College, Cuttack for a period of 2 years from September 2017 to September 2019. Patients diagnosed with ALS by the treating physician attending neurology OPD and IPD were taken in this study after fulfilling the inclusion and exclusion criteria. The study was carried out after the approval from the IEC (ICE/IRB No: 866) and written informed consent was taken from all the study subjects before including them in the study.

A total of 140 subjects were included. Patients with either sex within an age group of 25 to 65 years showing the typical neurogenic pattern with spontaneous activity such as fasciculations and fibrillations in the EMG, patients at grade 1, 2 and 3 according to the Japan ALS severity

classification, subjects who were categorised as definite ALS or Probable ALS according to the El Escorial revised Airlie House diagnostic criteria and subjects having the disease duration of less than 2 years were included.⁷

Patients with signs of dementia, ALS associated with life threatening disease, patients with tracheostomy and showing signs of conduction blocks having any hepatic or renal dysfunction and pregnant females were excluded.

70 patients were randomly assigned to each treatment arm by the treating physician. Group A received edaravone along with riluzole whereas group B received riluzole. Edaravone was given in a dose of 60 mg IV mixed with normal saline that was infused over 1 hour once daily. Riluzole 50 mg was taken per oral twice daily. Edaravone was given for 6 cycles. In the 1st cycle Edaravone was given once daily for 14 days followed by a drug holiday of 14 days whereas, from 2nd to 6th cycle Edaravone was given for 10 days daily with a drug holiday of 18 days.

Follow up was done at the end of each cycle till 6 months. After the study subjects were enrolled the efficacy parameter was measured by using the ALSFRS-R scores. The parameters in the ALSFRS-R score were categorized as bulbar, motor and respiratory functions for the convenience of this study. At the end of each month the ALSFRS-R scores were calculated. EMG was done at the time of diagnosis and was repeated at the end of 3rd and 6th month respectively. Any ADR reported during the study period was recorded in the suspected ADR Reporting form. Causality assessment and severity assessment was done using the WHO-UMC causality assessment system and Modified Hartwig and Seigel severity scale respectively. Cost effective analysis was done by calculating ICER (Incremental cost-effective ratio).

The data were analysed using Statistical Package for Social Sciences software (SPSS version 20.0, IBM SPSS inc., Chicago, IL). Data were published as mean and standard deviation. Categorical data were analysed using chi-square test. Continuous dataset was analysed by using the appropriate statistical tests.

RESULTS

There were 70 study subjects in each group. The baseline characteristics of the study participants are given on (Table 1). There was no significant difference observed in these parameters between the two study groups.

Table 1: Baseline Parameters (n=140).

Baseline characteristics		Group-A	Group-B	p value
Mean age (Mean±SD)		45.5±10.3	44.5±9.12	0.54
Gender	Male	44 (64%)	48 (69%)	0.47
	Female	26 (36%)	22 (31%)	
Duration of illness	Mean±SD	12.77±4.8	11.97±4.78	-
	<6 months	10 (14%)	9 (13%)	0.36

Continued.

Baseline characteristics		Group-A	Group-B	p value
	6-12 months	21 (30%)	29 (41%)	
	12-24 months	39 (56%)	32 (36%)	
	25-36 months	10 (14%)	19 (23%)	
Onset of disease	Limb onset	44 (63%)	51 (73%)	0.2
	Bulbar onset	26 (37%)	19 (27%)	
ALS severity grade	Grade 1	5 (7.1%)	7 (10%)	0.47
	Grade 2	20 (28.5%)	25 (35.7%)	
	Grade 3	45 (64.2%)	38 (54.2%)	

Efficacy assessment

The ALSFRS-R scores showed significant deterioration in bulbar functions from the 4th month in Gr-A and from the 1st month itself in Gr-B. The difference was found to be significant from the 3rd month onwards between both the groups (Figure 1A). The ALSFRS-R scores showed

significant deterioration in motor functions from the 4th month in Gr-A and from the 1st month itself in Gr-B. The difference was found to be significant from the 2nd month onwards between both the groups (Figure 1B). The ALSFRS-R scores showed significant deterioration in respiratory functions from the 1st month in Gr-A and in Gr-B. The difference was found to be significant from the 2nd month onwards between both the groups (Figure 1C).

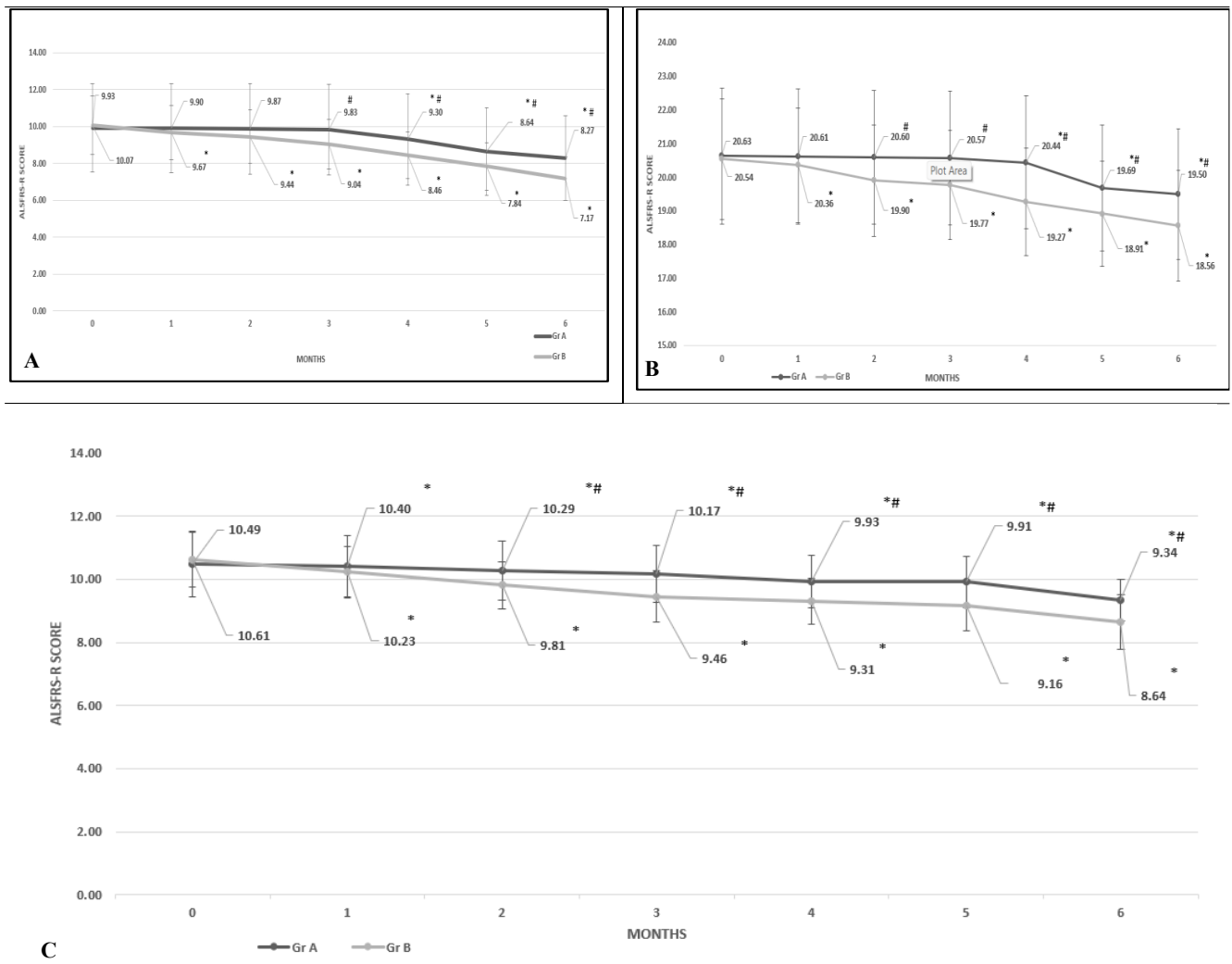


Figure 1: ALSFRS-R scores showing the bulbar, motor and respiratory functions between both groups (n=140). (A) Mean ALSFRS-R score showing Bulbar functions. (B) Mean ALSFRS-R score showing the Motor functions. (C) Mean ALSFRS-R score showing Respiratory functions.

(* p < 0.05; paired t test, within groups and # p < 0.05; unpaired t test, between groups)

The EMG pattern recorded at baseline was neurogenic and there was no change observed at the completion of our study period in both the groups. The total ALSFRS-R score of group A showed significant difference in disease

progression from third month onwards in comparison with group B (Table 2). The disease progression was slowed with Edravone add-on therapy.in comparison to use of Riluzole alone.

Table 2: Comparing the total ALSFRS-R scores between both groups (n=140).

Time frame	Gr-A (E+R)	Gr-B (R alone)	P value
Baseline	30.92±5.3	31.11±6.2	-
1 st month	30.61±5.1	29.98±6.3	-
2 nd month	29.78±5.1	28.05±6.1	-
3 rd month	28.75±5.0	26.71±5.9	0.03 [#]
4 th month	28.24±5.0	25.37±6.0	0.0029 [#]
5 th month	27.15±5.0	23.98±6.1	0.0013 [#]
6 th month	25.80±5.05	22.24±6.22	0.00029 [#]

Unpaired t test #P<0.001, significant decline in the total ALSFRS-R scores when compared between both groups.

Safety assessment

A total of 80 ADRs (41, 58.5% in Group A; 39, 56% in Group B) were recorded in the study subjects. The most common ADR was headache in both the groups. Other ADRs observed were diarrhoea, nausea and vomiting, dyspnoea, drowsiness, dizziness, weakness and loss of appetite. Fever and itching were seen only in Group A subjects and constipation was seen only in Group B subjects (Figure 2). Out of a total of 80 ADRs, 15 from Group A were probably due to the study drug. Likewise, 8 and 11 ADRs were assessed as possible and 18 and 28 as unlikely in Group A and Group B respectively (Table 3). All the ADRs were assessed to have mild severity according to modified Hartwig and Siegel scale.

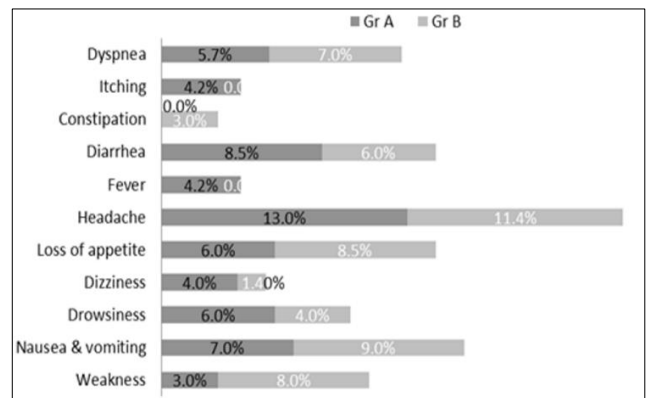


Figure 2: Individual ADRs seen in both the groups (n=140).

Table 3: Causality assessment of ADRs.

Causality assessment	No. of patients (%)	
	Group A(E+R)	Group B (R alone)
Probable	15 (36.5%)	0
Possible	8 (19.5%)	11 (28.2%)
Unlikely	18 (43.9%)	28 (71.7%)
Total	41 (58.5%)	39 (55.7%)

Cost effective analysis

The cost of treatments and the mean ALSFRS-R scores at the end of six months treatments in both the groups were

depicted in (Table 4). ICER was found to be 557.02. About extra 557.02 rupees would be spend to slowdown unit deterioration in the ALSFRS-R scores in ALS patients in Edravone add-on group.

Table 4: ICER (Edravone add-on and Riluzole alone group).

Drug	Group- A(E+R)	Group – B (R)	Incremental cost-effective ratio (ICER)
Cost per patient	Rs 2712 a	Rs 612 b	ICER = $\Delta C / \Delta E$ = Cost Difference/ Mean difference in ALSFRS-R scores (a-b) / (c-d)

Continued.

Drug	Group- A(E+R)	Group – B (R)	Incremental cost-effective ratio (ICER)
Mean Difference in ALSFRS-R scores in both groups	5.1 c	8.87 d	(2712-612)/(5.1 -8.87) = 2100/3.77 = 557.02

To have unit increase in efficacy extra amount of Rs557.02 had to be spent.

DISCUSSION

In ALS both upper motor neurons and lower motor neurons degenerate leading to gradual weakening of muscle and most patients die from respiratory failure within 3-5 years from the appearance of first symptoms. Riluzole has been the sole treatment option for these cases delaying the disease process for the last 20 years. On 2017, Edaravone was approved for these cases due to its promising study result. In this study it was taken as an add-on treatment with Riluzole in one treatment arm to see its advantages over the use of Riluzole alone.

The mean age of the study subjects was 45.5±10.3 and 49.5±9.1 in Group A and Group B respectively. This finding differs from the studies conducted by Masamitsu okada et al, Sachin sondhi et al where patients were mostly in their 6th decade.^{8,9} Out of 140 patients 64% in Group A and 69% in Group B were males which is similar to studies by Sachin sondhi et al, Sanjay pandey et al, Masamitsu et al.^{9,2,8}

Maximum cases presented as limb onset (68%) and this clinical presentation corroborates with other studies like Sanjay pandey et al, Akio kimura et al.^{2,10} The mean duration of illness in Group A was 12.77±4.8 months and in Group B was 11.97±4.78 months which is similar to S.S kaushal et al.⁹ Out of 140 patients 59% were in grade 3, followed by 32% in grade 2 and 9% in grade 1. This finding was different from the study by masamitsu et al where maximum participants belonged to ALS grade 2.⁸

The decline in the ALSFRS-R scores was seen to be more profound in Group B than Group A. These findings corroborated with the findings of Hide Yoshino et al and Makoto Akimoto and colleagues.^{10,11}

The bulbar and motor functions, found that a significant deterioration from the baseline after the 4th month in Group A and after the 1st month in Group B and was similar to the findings by Kimura et al, Itoyama Y et al and Brooks BR et al.^{10,12,13} Difference between two groups was significant from the 3rd month onwards in bulbar function and from the 2nd month onwards in motor function. Respiratory function did not show much improvement in both the treatment arms but inter group difference was significant from 2nd month onwards.

Headache, nausea and vomiting, loss of appetite and diarrhoea were the commonly occurring ADRs in both the study groups.

After getting treated with Edaravone, 9% of patients developed diarrhoea which corroborated with the findings in a study conducted by Hide Yoshino et al 13% had headache, 5% had fever and itching, 6% had dyspnoea similarly, 8% had nausea and vomiting and 3% had weakness.¹⁰ The serious adverse reactions reported with Edaravone in their study were hypersensitivity and allergic reactions, followed by headache, dermatitis, eczema.

A study conducted in the US by Carlyne Jackson et al showed dyspnea, fatigue, nausea and vomiting along with adverse effects like gait disturbances, asthenia, respiratory failure, pulmonary embolism, deep venous thrombosis, which were clearly not found in our study.¹⁴ Similarly, a study conducted by Satoshi Yamashita et al reported ADRs like vein inflammation, worsening of pneumonia, difficulty in vascular access, renal dysfunction which were not seen in our study.¹⁵ A phase 3 trial conducted in Japan by Hideyuki Sawada et al reported nasopharyngitis and dysphagia to be the most common side effect which were not reported in our study.¹⁶ A study by Satoshi Yamashita, Y maeda et al showed renal dysfunction in ALS patients in long term use of Edaravone.¹⁵

After taking Riluzole 13% of the study subjects developed headache, 9% had loss of appetite, 8% had weakness and dyspnoea, 3% had constipation and 6% had diarrhoea, drowsiness was seen in 3% of patients, 1% had dizziness. Gastrointestinal Side effects were very common. The GI side effects were similar to a study conducted by Roch Torreilles, Camu W et al.¹⁷ All the side effects occurring in our study were seen to be reported by a study conducted by Alessandro Introna et al.¹⁸ There were some few other side effects like limb paresthesias, cramps, increase in liver enzymes, dysgeusia which were reported in a very few patients in their study. Such ADRs were not found in our study. Loss of appetite and dizziness were reported by Aya inone shibui et al.¹⁹ Their study also reported ADRs like elevated liver enzymes, urinary urgency, interstitial pneumonia which was not seen involving any study participant in our study. As no serious Adverse Drug Reactions were found in our study, in both groups, therefore Edaravone and Riluzole are quite safe.

The cost was compared between both the groups. This study compared the cost of usage of adding Edaravone with Riluzole than using Riluzole alone for ALS. Adding Edaravone to Riluzole was costing Rs 189840 for 6 months (24 weeks) while that for using Riluzole alone was Rs 42840. The per patient cost was Rs 2712 in Edaravone Add-on group and it was Rs 612 in Riluzole alone group. Incremental cost-effective ratio (ICER) was 557.02. There

was a higher cost involved but the effectiveness on adding Edaravone to Riluzole was also significantly higher as compared in using Riluzole alone in ALS to delay the disease progression.

The pharmacoeconomic review report by mitshubishi pharma cooperation reported that Edaravone was not cost effective compared with the standard care of treatment ICER ratio of \$1957200 per quality life adjusted life year gained.²⁰ Canadian Drug Expert Committee found out the cost per patient using Edaravone was \$1424 while annually the cost of Edaravone was \$185,182 which was not cost effective as compared with the standard care.²¹

Briana santaniello published that the total cost associated with ALS in the US per patient may be substantially higher which is \$182,125 as the total annual cost to be estimated.²² Edaravone due to its higher cost policies generally has a restricted use in patients.

CONCLUSION

Edaravone being a new class of drug has provided a new hope in strolling the disease progression in ALS. The adverse effect profile and the cost of the treatment are also manageable. Further studies in this direction can lead to improved outcome in ALS patients.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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