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Clinical Outcome and Safety of Edaravone in ALS Patients in Tertiary Care Hospital

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Abstract

Introduction: Amyotrophic lateral sclerosis (ALS) is a progressive, fatal disease characterized by chronic degeneration of upper and lower motor neurons. We present the effect of edaravone on ALS patients.

Materials and Methods: We took 80 patients which were subjected to 12 week pre observation period. A total of 6 cycles of edaravone (60 mg iv infusion over a period of 1 hour) was given over a period of 6 months, each cycle per month. First cycle for 14 days and 10 of the first 14 days during cycles 2 to 6.

Results: Majority of patients i.e. 29 (36.25%) in our study were in their 4th to 6th decade of lifeWe observed that Mean of ALS-FRS score in minimal to mild category was, Pre-treatment score- 42.61111, Post treatment score- 42.55556, difference (0.055), P value of 0.7168 (insignificant).

Mean of ALS-FRS score in mild to moderate category was Pre-treatment score - 34.83721, Post treatment score- 34.97674.difference (-0.139), P value of 0.5423(insignificant).

After the 24 weeks treatment period there was no statistically significant benefit for the function, on the ALS-FRS score with edaravone treatment. As our study was an observational study and not placebo based and all studies which have been done in the past were randomised controlled studies, we compared the effect of drug pre and post treatment with their respective study design.

Conclusion: Edaravone can be given in patients who fall in minimal to mild and mild to moderate groups of revised ALS-FRS scoring system.

Keywords: ALS, Edaravone, ALSFRS score.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal disease characterized by chronic degeneration of upper and lower motor neurons. Amyotrophic lateral sclerosis (ALS) leads to progressive muscle wasting and weakness of the upper and lower extremities, bulbar palsy, and finally death within 3–5 years due to respiratory failure. Various mechanisms including the deposition of intranuclear and cytosolic protein and RNA aggregates, disturbances of protein degradative mechanisms, mitochondrial dysfunction, endoplasmic reticulum stress, defective nucleocytoplasmic trafficking, altered neuronal excitability, altered axonal transport, and excessive oxidative stress have been implicated as involved in the pathogenesis of ALS.

Oxidative stress biomarkers (3-nitrotyrosine, coenzyme Q10, 8-hydroxydeoxyguanosine, and 4-hydroxy-2,3-nonenal) are higher in people with ALS than in people without ALS. Edaravone (also known as MCI-186), a free-radical scavenger of peroxyl radicals and peroxynitrite, has been shown to inhibit motor neuron death in animal models by reducing oxidative stress. Edaravone has been given to 1·7 million patients with acute ischemic stroke in Japan since 2001 for improvement of neurological symptoms, disruption of daily activities, and functional impairment associated with acute ischemic stroke.

There are different scales for clinical assessment of patients degree of functional impairment and subjective health status of ALS patients like Modified Norris Scale, ALS AQ-40, ALS-FRS Rating Scale and Japanese ALS Severity Classification.

In the new case report form (CRF) the ALS-FRS has been revised and is now called the ALS-FRS-R. The ALS-FRS-R includes 12 questions. Each task is rated on a five-point scale from 0=cannot do, to 4=normal ability. Individual item scores are summed to produce a reported score of between 0=worst and 48=best.

Severity of disease of ALS patients can be assessed by ALS-FRS severity and Japanese ALS severity classification.

ALS-FRS Severity is classified as minimal to mild (score >40), mild to moderate (score 39-30), moderate to severe (score <29) and advanced disease (score <20).

Diagnosis of ALS is done by revised El-Escorial criteria and Awaji-Shima consensus. Revised El-Escorial criteria is defined as:

- Definite ALS → LMN + UMN signs in 3 regions.
- Probable ALS → LMN + UMN signs in 2 regions
- Probable Lab.supported-ALS → LMN + UMN in 1 region or UMN ≥1 region + EMG acute denervation ≥2 limbs.
- Possible ALS → LMN + UMN in 1 region.

Awaji-Shima consensus is defined as:

- Definite ALS
- Probable ALS
- Possible ALS

As per the safety profile of edaravone, there are various side effects which have been observed in the studies in the past. They are gait disturbance, headache, eczema, nasopharyangitis, muscular weakness, hypoxia, respiratory distress and glycosuria.

Aims and objectives

To assess the clinical outcome and safety of edaravone in Amyotrophic lateral sclerosis (ALS) patients.

Inclusion criteria

1. Age 21-100 years
2. A diagnosis of ALS patients as per Awaji-Shima consensus (definite, probable and possible ALS).

Exclusion criteria

- Complications that may substantially influence evaluation of drug efficacy, such as Parkinson's disease, schizophrenia and dementia;
- Complications that require hospitalization, including liver, cardiac and renal diseases;
- Infections that require antibiotic therapy;
- Renal dysfunction with creatinine clearance of 50 ml/min or below within 28 days before treatment
- Patients on cancer treatment.

Methodology

The present study was conducted in the Postgraduate Department of Medicine, Government Medical College, Srinagar after obtaining the ethical clearance from the Institutional Ethical Committee. The study

was an observational study and was conducted over a period of one and a half year.

After obtaining the informed consent all the eligible patients were investigated for secondary causes as and when required as mentioned in proforma and assigned to receive edaravone.The study period consisted of 12 week pre observation period before the start of ist cycle followed by 24 week treatment period.

A total of 6 cycles of edaravone (60 mg iv infusion over a period of 1 hour) was given over a period of 6 months, each cycle per month. First cycle for 14 days and 10 of the first 14 days during cycles 2 to 6.

Clinical Outcome Evaluation

Clinical outcome was assessed by comparing revised ALS-FRScale pre and post treatment (after 6 months of treatment).

The evaluation was carried out at the following times:

- Before pre observation period
- Before the start of first treatment cycle
- At the end of 6th cycle

Safety Evaluation

Safety was assessed by following side effects:

- Gait disturbance
- Headache
- Muscular weakness
- Nasopharyngitis
- Eczema
- Respiratory distress
- Insomnia
- Hypoxia
- Glycosuria

Statistical Analysis

Data obtained was entered into Microsoft Excel. Categorical variables were summarized as frequency and percentage. Continuous variables were summarized as mean and standard deviation. Differences between before and after ALS-FRS-R scores was analyzed using paired sample 't' test. Two-sided p values was reported and a p value of < 0.05 was considered as statistically significant.

Results

Table 1: Distribution of patients as per age		
Age (Years)	Frequency	Percent
21-30	3	3.75
31-40	10	12.50
41-50	21	26.25
51-60	29	36.25
61-70	12	15.00
71-80	3	3.75
81-90	1	1.25
91-100	1	1.25
Total	80	100.00
Mean age	54.18±12.83	

Table 1(b): Age at symptoms onset		
Age at onset (Years)	Frequency	Percent
15-24	2	2.50
25-34	3	3.75
35-44	13	16.25
45-54	29	36.25
55-64	20	25.00
65-74	11	13.75
85-94	1	1.25
95-104	1	1.25
Total	80	100.00
Mean age at onset	52.75±13.08	

Table 2: Distribution of patients as per gender		
Gender	Frequency	Percent
Female	28	35.00
Male	52	65.00
Total	80	100.00

Table 3: Distribution of patients as per Area		
Area	Frequency	Percentage
Rural	53	66.25
Urban	27	33.75
Total	80	100.00

Table 4 : Distribution of patients as per their occupation		
Occupation	Frequency	Percent
Farmer	27	33.75
Govt. Employee	12	15.00
Housewife	11	13.75
Labourer	8	10.00
Shopkeeper	6	7.50
Teacher	5	6.25
Driver	2	2.50
Private employee	2	2.50
Tailor	2	2.50
Bank employee	1	1.25
Business	1	1.25
Butcher	1	1.25
Engineer	1	1.25
Weaver	1	1.25
Total	80	100.00

Table 5: Distribution as per Employment		
	Frequency	Percent
Employed	23	28.75
Unemployed	57	71.25
Total	80	100.00

Table 6: Educational status		
Education	Frequency	Percent
Illiterate	39	48.75
Up to Middle school	14	17.50
10^{th} class	5	6.25
12^{th} class	12	15.00
Graduate	6	7.50
Postgraduate	4	5.00
Total	80	100.00

Table 7: Mode of Onset		
Mode of onset	Frequency	Percent
Bulbar	29	36.25
Limb	51	63.75
Total	80	100.00

Table 8: Pattern of onset of motor neuron disease		
Pattern of onset of MND	Frequency	Percent
Bulbar	29	36.25
Upper to lower limb	35	43.75
Lower to upper limb	11	13.75
Upper limb (confined)	4	5.00
Lower limb (confined)	1	1.25
Total	80	100.00

Table 9: Duration of disease in years		
Duration of disease in years	Frequency	Percent
0.6	1	1.25
0.10	1	1.25
0.11	2	2.50
0.1	1	1.25
0.2	11	13.75
0.3	2	2.50
0.8	2	2.50
0.8	1	1.25
0.9	1	1.25
1	9	11.25
1.2	2	2.50
1.4	1	1.25
1.5	6	7.50
1.6	4	5.00
1.8	2	2.50
1.9	1	1.25
2.3	1	1.25
2.5	3	3.75
2.6	2	2.50
2.7	1	1.25
2.8	2	2.50
3	12	15.00
3.2	1	1.25
3.5	4	5.00
3.6	3	3.75
4.5	1	1.25
6	1	1.25
6.5	1	1.25
9	1	1.25
Total	80	100.00

Table 10: Duration of MND as per Pattern of Onset						
Duration (years)	Bulbar		Limb		Total	
	No.	%	No.	%	No.	%
<2	18	38.29	29	61.70	47	58.75
>2	11	33.33	22	66.66	33	41.25
Total	29	36.25	51	63.75	80	100.00

Table 10 (A) : Outcome		
Outcome	Frequency	Percent
Alive	56	70.00
Expire	24	30.00
Total	80	100.00

Table 10 (b): Expired patients as per pattern of onset of MND		
Pattern of onset of MND	Frequency	Percent
Bulbar	12	50.00
Limb	12	50.00
Total	24	100.00

Table 10(c): Treatment cycle of Edaravone		
Treatment cycle of Edaravone	No. of expired	Percent
After 1 cycle	00	00.00
After 2 cycle	03	12.50
After 3 cycle	02	08.33
After 4 cycle	00	00.00
After 5 cycle	00	00.00
After 6 cycle	19	79.16
Total	24	100.00

Table 11: Lost to follow up		
Lost to follow-up	Frequency	Percent
Lost follow up	9	11.25
No	71	88.75
Total	80	100.00

Table 12: Side Effects of Edaravone		
Side Effect	Frequency	Percent
Respiratory distress	3	33.33
Shivering	1	11.11

Table 13: Comparison of ALS-FRS severity scale pre and post treatment in all patients					
Variable	No.	Mean	Std. Dev.	Std. Err.	P value
Score at 0 month	71	35.05	6.76	0.80	0.4181
Score at 6 month	71	35.19	6.80	0.80	
Difference	71	-0.14	1.45	0.17	

Table 14: Pre and Post Treatment comparison score as per Gender Distribution					
Gender	No.	Mean	Std. Dev.	Std. Err.	P value
Female	26	-0.34	1.49	0.29	0.3705
Male	45	-0.02	1.43	0.21	
Combined	71	-0.14	1.45	0.17	
Difference		-0.32		0.35	

Table 15: Pre and Post Treatment score as per pattern of onset of MND					
Pattern of onset MND	No.	Mean	Std. Dev.	Std. Err.	P value
Bulbar	25	-0.48	1.44	0.28	0.1495
Limb	46	0.04	1.44	0.21	
Combined	71	-0.14	1.45	0.17	
Difference		-0.52		0.35	

Table 16(a): No.of patients in Disease severity classification as per revised ALS-FRS scale		
Disease severity (score)	No. of patients	Percentage
Advanced disease (<20)	04	5.63
Moderate to severe (<29)	06	8.45
Mild to moderate (39-30)	43	60.56
Minimal to mild (>40)	18	25.35
Total	71	100

Table 16(b): Pre-and Post Score difference as per Disease severity					
Disease severity (score)		Obs	Mean	SD	p value
Advanced disease (<20)	0 month	4	17.75	1.89	0.39
	6 month	4	17.5	1.73	
	Difference		0.25	0.5	
Moderate to severe (<29)	0 month	6	25.5	3.27	0.43
	6 month	6	26.5	3.83	
	Difference		-1.0	2.89	
Mild to moderate (39-30)	0 month	43	34.83	2.70	0.54
	6 month	43	34.97	3.09	
	Difference		-0.13	1.48	
Minimal to mild (>40)	0 month	18	42.61	1.85	0.71
	6 month	18	42.55	2.12	
	Difference		0.05	0.63	

Table 16(c): patients with increased score				
		Obs	Mean	P value
Patients with increased score	0 month	16	33.81	0.00
	6 month	16	35.99	
	Difference		-2.18	

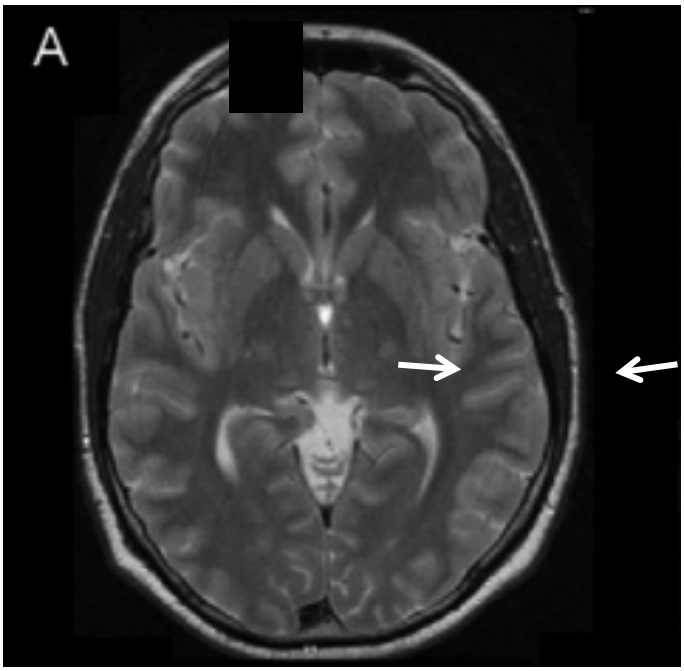


Figure 1: T2 Hyperintensities in Corticospinal Tracts

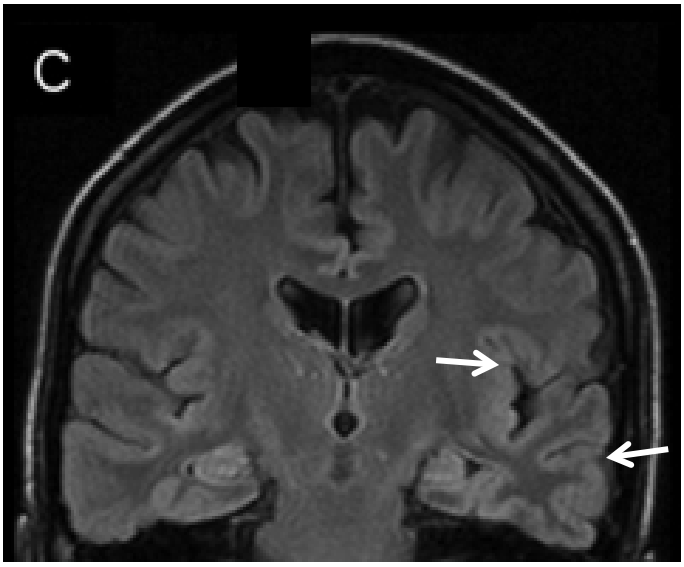


Figure 2: Flair Hyperintensities in Corticospinal Tracts

Images of Patients with Secondary Causes of MND

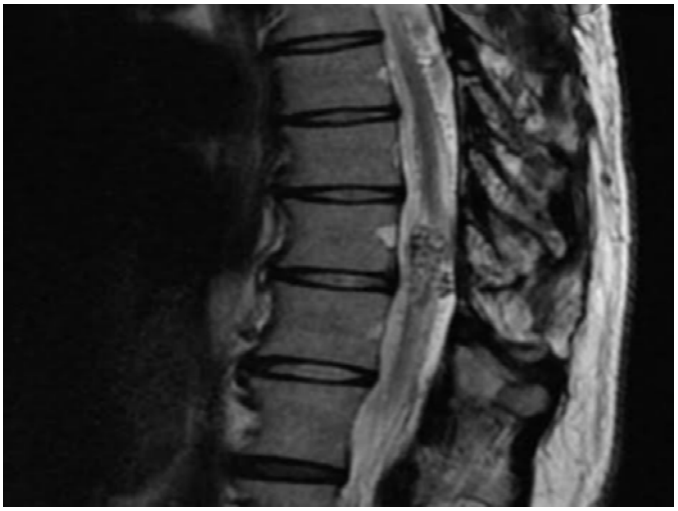


Figure 3: Spinal Av Malformation

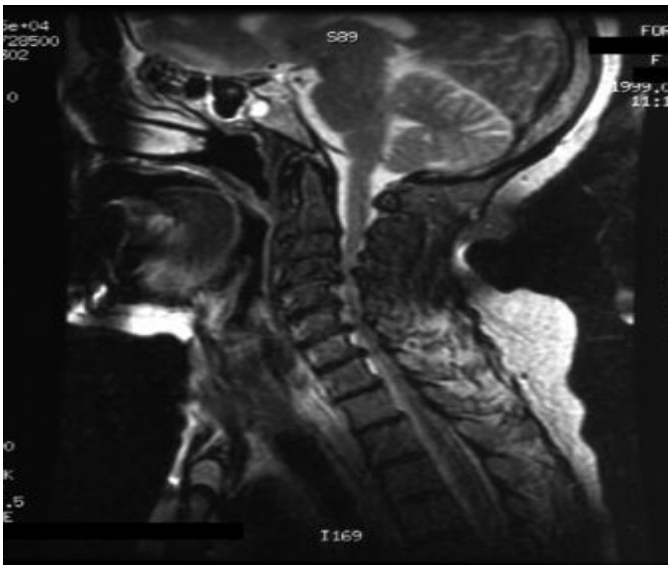


Figure 4: Spinal Av Malformation

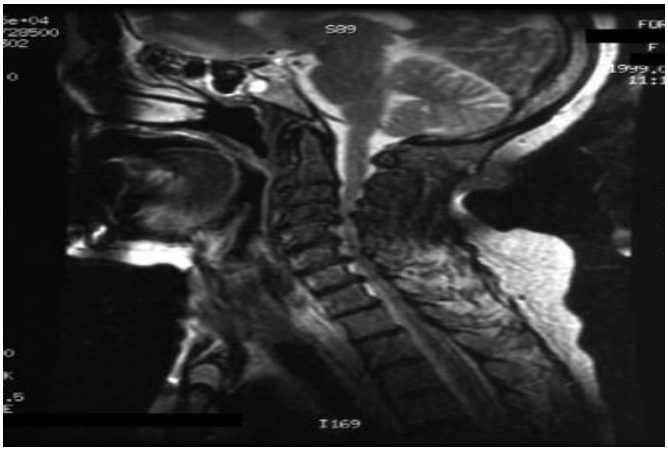


Figure 5: Cervical Spondylosis

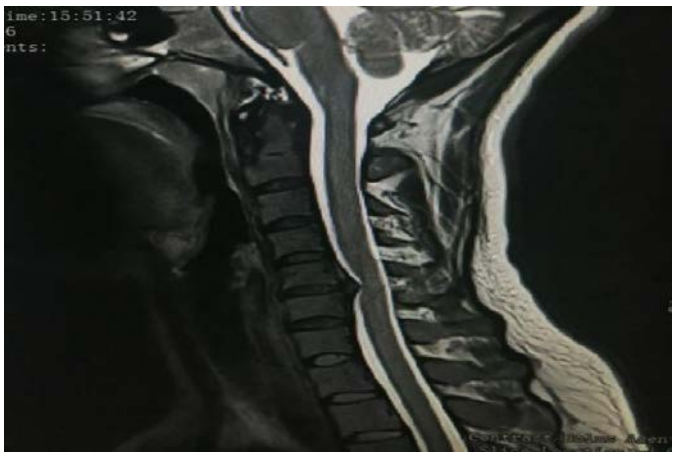


Figure 6: Spinal Cord Impingement (Cervical Spondylosis).

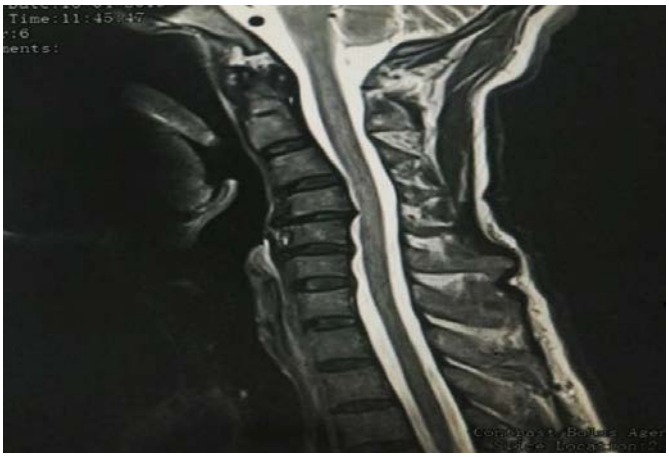


Figure 7: Cord Impingement With signal Change (Cervical Spondylosis).

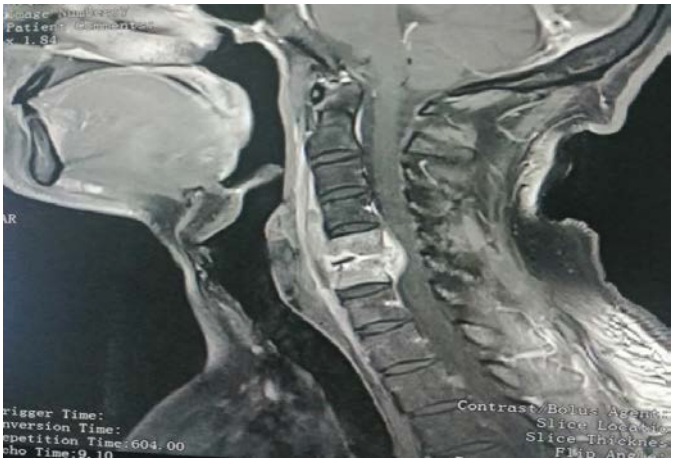


Figure 8: Tuberculosis with Epidural Collection

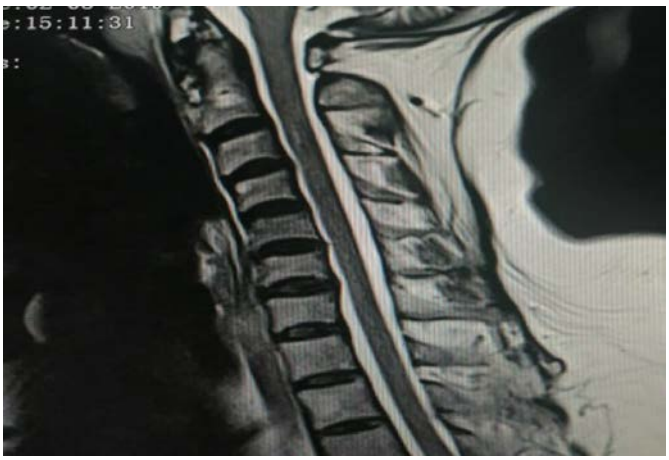


Figure 9: Tiny Syrinx

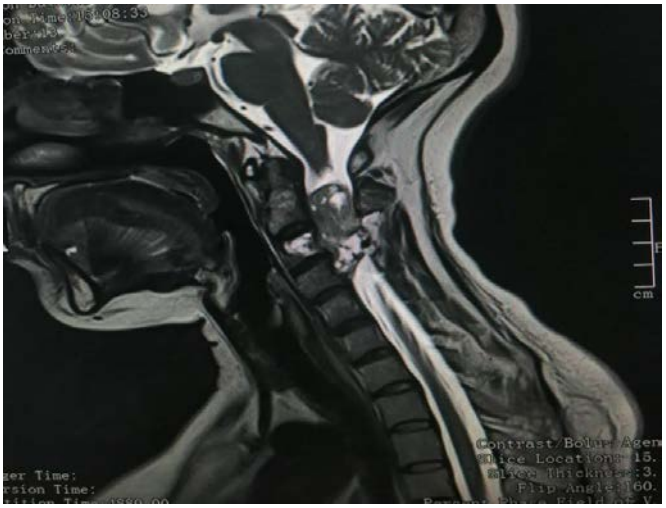
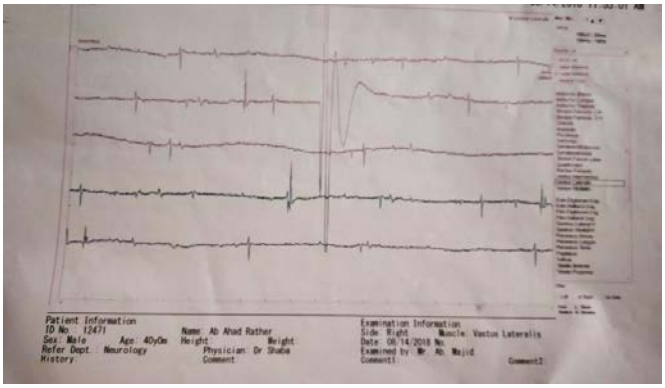
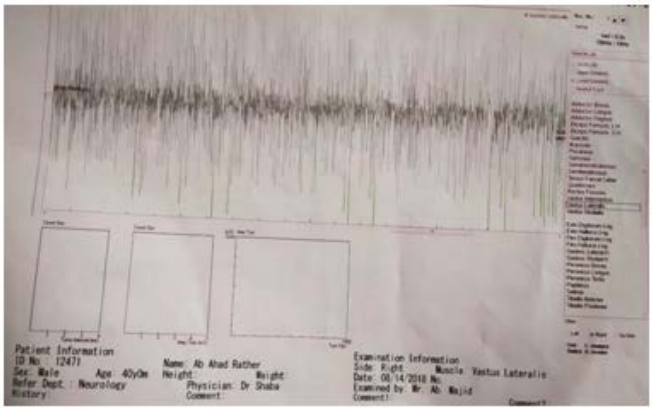


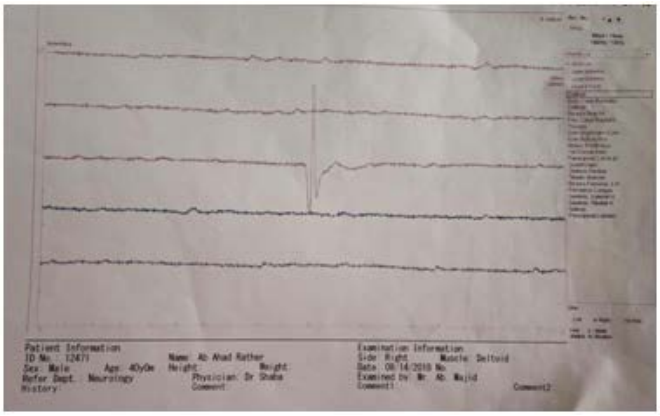
Figure 10: Spinal Tumour

Extramedullary

Neurogenic EMG showing fibs, fasciculation delayed interference pattern and long duration muaps suggesting denervation renervation changes







Discussion

In this study we have used Revised Amyotrophic Lateral Sclerosis (ALS) – Functional Rating Scale (FRS).

The present study has assessed the clinical outcome and safety of edaravone in ALS patients by comparing revised ALS-FRS score pre and post treatment.

In our study, out of 80 studied patients, majority i.e. 29 (36.25%) were aged 51-60 years followed by 21 (26.25%) patients aged 41-50 years.

There were 12 (15.0%) patients aged 61-70 years, 10 (12.5%) were aged 31-40 years. There were 3 (3.75%) patients belonging to age group of 21-30 years and and 3 patients from age group 71-80 years and 1 (1.25%) patient from age group of 81-90 years and 1 patient from 91-100 years.

Majority of patients i.e. 29 (36.25%) in our study were in their 4^{th} to 6^{th} decade of life when they observed symptoms at onset of the disease, followed by 20 (25%) patients who were 55-64 years of their life. 13 (16.25%) patients were 35-44 years, 11 (13.75%) patients were 65-74 years old at onset of symptoms. 2 of our patients observed the onset of symptoms when they were aged 15-24 years with one patients (1.25%) each aging 85-94 and 95-104 years. Mean age at onset of symptoms was 52.75±13.08 years.

In our study, males surpassed females with 52 (65%) versus 28 (35%).

In our study, out of 80 studied patients, majority i.e. 53 (66.25%) were from rural areas and 27 (33.75 %) were from urban areas.

Farmers, government employee and housewives constituted the bulk of sample in our study with 27 (33.75%), 12 (15.0%) and11 (13.75%) respectively. There were 8 (10%) labourers, 6 (7.5%) shopkeepers, 2 (2.5%) each driver, private employee and tailors. Bank employee, businessmen, butcher, engineer and weaver were one (1.25%) each.

In our study, 57 (71.25%) patients were non-employed and 23 (28.75%) patients were employed.

In our study out of 80 studied patients, 39 (48.75%) were illiterates, 14 (17.5%) were upto middle school, 12 15.0%) were in 12^{th} class, 6 (7.5%) were graduates, 5 (6.25%) were 10^{th} class and 4 (5%) were postgraduates.

Mode of onset was bulbar in 29 (36.25%) and limb in 51 (63.75%).

As per onset of motor neuron disease, 35 (43.75%) had upper to lower limb, 29 (36.25%) had bulbar, 11 (13.75%) had lower to upper limb, 4 (5%) had upper limb (confined) while as 1 (1.25%) had lower limb (confined).

Duration of disease was upto 2 years in more than half of the patients studied i.e. 47 (58.75%) were followed by 2-4 years in 29 (36.25%).

Out of 47 patients of disease duration of less than two years, 18 patients were of bulbar onset, and 29 patients were of limb onset and out of 33 patients of more than two years of disease duration, 11 patients were of bulbar onset and 22 patients were of limb onset.

Out of 80 patients, 24 (30%) expired while 57 (70%) were alive.

Out of 24 expired patients, 12 (50.00%) patients were of limb onset pattern and 12(50.00%) patients were of bulbar onset pattern.

Out of total 24 expired patients, 19 patients died after receiving complete 6 cycles of edaravone, and 5 patients during treatment course (3 patients after receiving 2 cycles, 3 patients after completion of 3 cycles), and all of these were died due to natural course of disease, none due to side effect.

In our study, only 9 (11.25%) of the 80 patients were lost to follow up. Among 9 patients who lost to follow up, 5 (55.55%) expired before completion of cycle due to natural course of disease and 4 patients had side effect.

There were 3 (33.33%) who had side effect as respiratory distress, required ventilator support and while as 1 (11.11%) had shivering with no associated symptoms (fever, hypotension etc.)

We classified our patients on the basis of severity according to ALS-FRS score. Out of 71 patients, 18 patients were in minimal to mild (score >40), 43 patients were in mild to moderate (score 39-30), 06 patients were in moderate to severe (score <29) and 04 patients were in advanced disease (score <20).

We observed that Mean of ALS-FRS score in minimal to mild category was, Pre-treatment score- 42.61111, Post treatment score- 42.55556, difference (0.055), P value of 0.7168 (insignificant).

Mean of ALS-FRS score in mild to moderate category was Pretreatment score - 34.83721, Post treatment score- 34.97674.difference (-0.139), P value of 0.5423(insignificant).

After the 24 weeks treatment period there was no statistically significant benefit for the function, on the ALS-FRS score with edaravone treatment. As our study was an observational study and not placebo based and all studies which have been done in the past were randomised controlled studies, we compared the effect of drug pre and post treatment with their respective study design and found similar observation as in study done by **Koji Abe K et al (2014)[30],** where they had conducted a 36 week confirmatory study, consisting of 12 week pre observation period followed by 24 week treatment. They found that changes in ALSFRS-R during 24 week treatment were -6.35±0.84 in placebo group and -5.70±0.85 in edaravone group with a difference of 0.65±0.78 (P=0.411).In conclusion reduction in ALSFRS-R was smaller in edaravone group, but efficacy of edaravone for treatment of ALS was not demonstrated. Another study which confirms our finding was done by the **Writing group on behalf of the edaravone (MCI-186) ALS 18 study group (2017)[47]**. They conducted a 24 week double blind randomised study in which they explored efficacy of edravone in ALS patients with Japan ALS severity classification of grade 3.They took 25 patients who met japan severity classification of grade 3. 13 patients recieved edaravone and 12 patients recieved placebo. The least squares mean change in ALSFRS-R score±standard error during 24 week treatment was -6.52±1.78 in edaravone group and -6.00±1.83 in placebo group; the difference of -0.52±2.46 was not statistically significant (p=0.835).

However, in our study a subgroup analysis showed slight improvement in the subjects with definite or

probable ALS at entry who had score of 2 or more on all items of ALS-FRS, a disease duration of two or less and independent living status. After 24 weeks period of treatment, there was improvement in the function on ALS-FRS score in 16 patients, out of which 12 patients were in minimal to mild score and 4 patients were in mild to moderate range. And of these 11 were males and 05 were females and 12 limb with onset and 04 with bulbar onset.

In this subgroup population, pretreatment mean of 33.8125, post treatment mean of 36.0000, difference of -2.1875, p value=0.0000 was observed.

Thirty nine patients remained in the static zone in which there was no further deterioration of function on the ALS-FRS score.

Similar observation was seen in **Sawada H Expert Opinion on Pharmacotherapy 2017 study** Phase III trial for subgroup patients of ALS (MCI186-19 trial) in which the eligibility criteria were more restrictive compared with MCI 186-16, and the criteria were determined by post-hoc analysis of MCI 186-16 results. In MCI 186-19, patients with a shorter disease duration and a larger vital capacity were enrolled. Under these conditions, edaravone was efficacious in ALS patients with milder symptoms and signs, as well as shorter disease duration. Moreover, the effect size of edaravone was relatively small. The change in ALSFRS-R scores was estimated to be approximately −5 points in the edaravone group over a 24-week period in both trials, and in the placebo group, the changes were −6.35 points and −7.5 points in the MCI 186-16 and MCI 186-19 trials, respectively.

This limited effect size of edaravone may have resulted in the difference not reaching statistical significance in the MCI 186-16 trial, whereas it was significant in MCI 186-19.The MCI 186-19 trial demonstrated that edaravone was safe and efficacious, according to scores on a functional scale of ALS over the course of 24 weeks.

Conclusion

Despite dozens of trials over the last 20 years, only 2 drugs have received Food and Drug Administration Approval, Riluzole and Edaravone, which have modest benefits on survival and disease progression.

After the 24 weeks treatment period there was no statistically significant benefit for the function, on the ALS-FRS score with edaravone treatment in patients with severe and advanced disease.

Edaravone can be given in patients who fall in minimal to mild and mild to moderate groups of revised ALS-FRS scoring system. The effect of edaravone on muscle strength and respiratory function is not clear.

Extended studies and long term follow up are needed to establish clinical efficacy and adverse effects of edaravone.

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