Neurology Asia 2009; 14 : 7 – 10

Edaravone in acute ischemic stroke, An Indian experience

MK Sinha *MD*, Anuradha HK *MD*, R Juyal *MD*, R Shukla *DM*, RK Garg *DM*, AM Kar *DM*

Department of Neurology, Chhatrapati Shahuji Maharaj Medical University, Lucknow, India

Abstract

Background and Objective: This study aims to evaluate the safety and efficacy of edaravone, a novel free radical scavenger, in a group of Indian patients of acute ischemic stroke. *Methods:* Twenty two patients of acute ischemic stroke were given 30 mg of Edaravone twice daily for 14 days by infusion. The outcome assessment was by the Modified Rankin Scale (MRS) and Barthel Index (BI). MRS score ≤ 2 at 90 days was considered as a favorable outcome. *Results:* Fifteen patients (68%) had favorable outcome. The mean MRS score decreased from 4.01±0.92 at baseline to 1.86±1.07 at day 90 (p<0.005). The mean Barthel index increased from 40.00±30.11 at baseline to 75.62±22.86 at day 90 (p<0.005). The changes in the MRS and BI were observed from 7 days. None of the patients experienced any adverse effect.
Conclusion: Edaravone treatment was safe and effective in providing early and sustained neurological improvement in patients with acute ischemic stroke.

INTRODUCTION

Edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazoline-5-one), a novel free radical scavenger, prevents vascular endothelial injury, delays neuronal death in transient cerebral ischemia and ischemic brain edema, inhibits activation of lipoxygenase pathway in the arachidonic acid cascade and peroxidation of the phosphatidylcholine liposomal membrane in vitro.[1] A number of Japanese studies have shown it to be efficacious in patients with acute ischemic stroke.[2-6] However, there has been no data available on the effect of edaravone in patients with acute ischemic stroke in the Indian subcontinent. The aim of this study was to investigate the effects of edaravone in terms of functional outcome in patients with acute ischemic stroke in a group of Indian patients.

METHODS

This prospective open label, exploratory study was conducted in the Department of Neurology, CSM Medical University, Lucknow; a tertiary health care center in North India. The study was carried out between January and July 2008. A written informed consent was undertaken prior to inclusion in the study. The study was approved by the Institutional Ethics Committee.

The study included patients with acute ischemic stroke who were hospitalized between 6 and 72 hours of onset of stroke. Patients with age less than 18 years, unclear time of onset, those who received any thrombolytic therapy, those with severe hepatic disease, renal dysfunction, pregnancy or lactation were excluded from study. A detailed history, general physical and neurological examinations were done and recorded on a predesigned proforma. Routine hematological, biochemical tests, X-ray chest posteroanterior view, electrocardiogram and transthoracic echocardiography were performed in all the patients. On admission, all patients underwent computerized tomography (CT) using a Somatom Hiq CT scanner (Siemens) using 10 mm axial sections. Whenever possible, T2-weighted and diffusion weighted magnetic resonance (MR) along with MR angiography was performed with a Signa Excite 1.5 Tesla instrument (General Electric Medical Systems, Milwaukee, WI, USA). Diagnosis of ischemic stroke was made according to the World Health Organisation (WHO) definition.[7] The stroke subtypes were classified as per the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) study criteria.[8]

All patients received 30 mg of edaravone dissolved in 100 ml of normal saline by infusion over 60 minutes twice daily for 14 days.[3] Some

Address correspondence to: Dr. Rakesh Shukla, Professor, Department of Neurology, CSM Medical University, (Erstwhile King George's Medical University), Lucknow, India -226003. Phone no: 0522-2257090, Fax no: 0522-2257090, Email: rakeshshukla_rakesh@rediffmail.com

patients also received oral aspirin or warfarin depending on type of stroke and 20% mannitol infusion, whenever required. While patients were receiving infusions, vital signs and adverse events were recorded regularly. Samples for routine laboratory tests including hemoglobin, total and differential white blood cell count, platelet count, plasma glucose, urea, creatinine, electrolytes, liver function tests and prothrombin time were obtained and analyzed at enrollment, at day 7, and at day 14. Patients meeting the criteria for progressive stroke (an increase in the NIHSS score of 4 points) or a new stroke during the first week also underwent follow-up imaging.

The patients were assessed at enrollment and at 7, 14, 30 and 90 days. The stroke severity was assessed by the National Institute of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS). Assessment during follow up was done by an experienced physiotherapist, who was blinded for the outcomes, using the Modified Rankin Scale (MRS) and the Barthel index (BI).[9] MRS score ≤ 2 at 90 days was considered as favorable outcome. The results were expressed as mean ± standard deviation. We compared clinical outcome (MRS and BI) at days 7, 14, 30 and 90 using paired *t*-test. The level of significance was set at $p<0.05$.

RESULTS

Twenty eight patients meeting the inclusion criteria were admitted during the study period, out of which 22 patients were enrolled in the study. The reason 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).

The baseline clinical characteristics of the study subjects are shown in Table 1. Fifteen patients (68%) had favorable outcomes at 90 days, as shown in Figure 1. The mean NIHSS 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 ± 4.71 at day 90 ($p<0.005$). 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 ($p<0.05$), to 2.87 ± 1.55 at day 14 ($p<0.05$), to 2.25 ± 1.28 at day 30 ($p<0.05$) and to 1.86 ± 1.07 at day 90 ($p<0.005$). 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 to 75.62 ± 22.86 at day 90 ($p<0.005$) (Table 2). One patient developed progressive stroke (an increase in the NIHSS score of 4 points) and a repeat CT scan revealed increase in the infarct size. Edaravone treatment was well tolerated and none of the patients experienced any adverse effect.

Table 1: Baseline characteristics of patients

Patient characteristics	Baseline
Mean age (years)	64.15 ± 13.72
Male sex – number (%)	15/22 (68.18)
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	17/22
Small-artery occlusion	3/22
Cardioembolic stroke	2/22

DISCUSSION

In the present study, 15 out of 22 patients had favorable outcome (MRS ≤2) at 90 days. To our knowledge, this is the first Indian study and perhaps the first study outside Japan on effect of edaravone in acute ischemic stroke. The Edaravone Acute Brain Infarction Study (EABIS) Group observed significant improvement in functional outcome in the edaravone group as evaluated by the modified Rankin Scale.[9] Our study observed significant early improvement which persisted till the completion of study period.

In our study, 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, in agreement with EABIS researchers.[3] An early phase II study had indicated that edaravone was effective up to 72

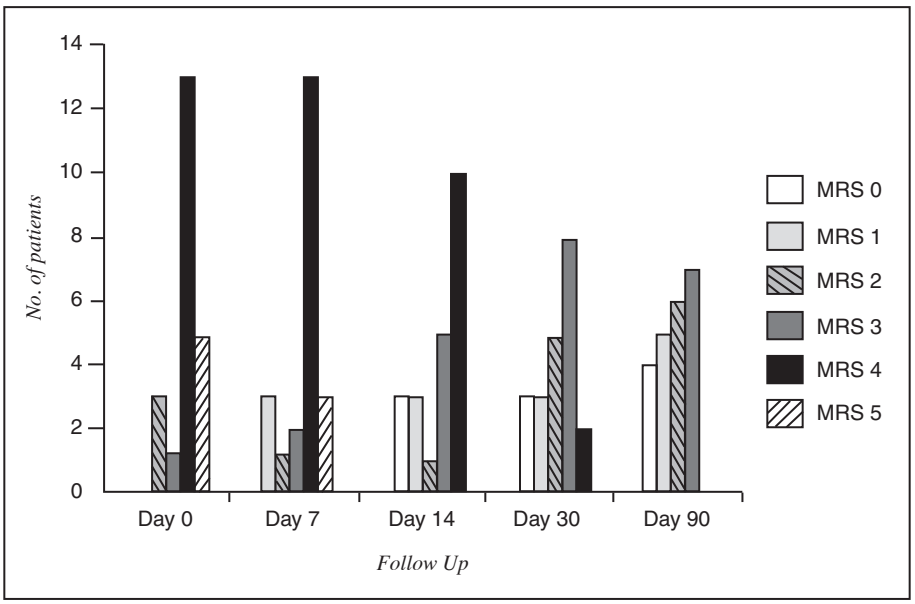

Figure 1. Modified Rankin Scale at various days of follow up

hours of onset of stroke and improvement at 14 days was 52, 64 and 64 percent at doses of 20, 30 and 60 mg per day of edaravone respectively.[10] On the basis of this study, the appropriate dose was considered to be 30 mg twice daily for 14 days.

Use of edaravone appeared to be safe in acute ischemic stroke as there was no adverse reaction in any of our patients though EABIS group reported insignificant skin rashes and abnormal liver function in the edaravone group. There are few case reports of acute renal failure and fulminant hepatitis associated with edaravone administration and therefore careful monitoring of renal and liver functions is warranted while using this drug.[11-12]

The limitations of this study are the small sample size, no placebo group and that no blinding of the clinician was done. However, the physiotherapist assessing the improvement was blinded to the treatment that the patient was receiving.

However, the results of the present study suggest that edaravone treatment may be safe and effective in providing early and sustained neurological improvement in patients with acute ischemic stroke. Larger randomized, double blind, case-controlled studies are required to confirm this.

Table 2: Clinical outcome of patients

Scale	Baseline	7 days	14 days	30 days	90 days
Mean NIHSS score	10.62±8.86	6.62 ± 7.48*	5.12±6.03*	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†

NIHSS: National Institute of Health Stroke Scale; GCS: Glasgow Coma Scale; MRS: Modified Rankin Scale; * - $p<0.05$, † - $p<0.005$, ‡ - p=Not Significant

REFERENCES

1. H Yoshida, H Yanai, Y Namiki, K Fukatsu-Sasaki, N Furutani, N Tada. Neuroprotective effects of edaravone: a novel free radical scavenger. *CNS Drug Rev* 2006; 12(1):9-20.
2. Suda S, Igarashi H, Arai Y, Andou J, Chishiki T, Katayama Y. Effect of edaravone, a free radical scavenger on ischemic cerebral edema assessed by Magnetic Resonance Imaging. *Neurol Med Chir (Tokyo)* 2007; 47:197-201.
3. *Edaravone* Acute Brain Infarction Study Group. Effect of a novel free radical scavenger, *edaravone* (*MCI-186*), on acute brain infarction. *Cerebrovasc Dis* 2003; 15:222-9.
4. Mishina M, Komaba Y, Kobayashi S, *et al*. Efficacy of edaravone, a free radical scavenger for the treatment of acute lacunar infarction. *Neurol Med Chir (Tokyo)* 2005; 45:344-8.
5. Inatomi Y, Takita T, Yonehara T, *et al*. Efficacy of edaravone in cardioembolic stroke. *Internal Medicine* 2006; 45(5):253-7.
6. Toyoda K, Fujii K, Kamouchi M, *et al*. Free radical scavenger, edaravone, in stroke with internal carotid artery occlusion. *J Neurol Sci* 2004; 221(1-2):11-7.
7. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull WHO* 1976; 54:541-53.
8. Goldstein LB, Jones MR, Matchar DB, *et al*. Improving the reliability of stroke subgroup classification using the Trial of ORG10172 in Acute Stroke Treatment (TOAST) criteria. *Stroke* 2001; 32(5):1091-8.
9. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. *Stroke* 1999; 30(8):1538-41.
10. Otomo E, Tohgi H, Kogure K, *et al*. Clinical efficacy of a free radical scavenger, MCI-186, on acute cerebral infarction: Early phase II clinical trial. *Ther Res* 1998; 19: 531-52.
11. Abe M, Kaizu K, Matsumoto K. A case report of acute renal failure and fulminant hepatitis associated with edaravone administration in a cerebral infarction patient. *Ther Apher Dial* 2007; 11(3):235-40.
12. Hishida A. Clinical analysis of 207 patients who developed renal disorders during or after treatment with edaravone reported during post-marketing surveillance. *Clin Exp Nephrol* 2007; 11(4):292-6.