Original Article

A randomized controlled clinical trial to compare the safety and efficacy of edaravone in acute ischemic stroke

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Abstract

Background and Objective: Edaravone has potent antioxidant and free radical scavenger properties. Few Japanese studies had demonstrated its neuroprotective role in acute ischemic stroke (AIS). This study aims to evaluate the efficacy of edaravone in terms of functional outcome in a group of Indian patients of AIS. **Materials and Methods:** Fifty patients of AIS were randomly divided into two groups. The study group received 30 mg of edaravone twice daily for 14 days by infusion, while control group received normal saline infusion as placebo. Outcome assessment was done by the Modified Rankin Scale (MRS). MRS score ≤2 at 90 days was considered as a favorable outcome. **Results:** Of 25 patients, 18 (72%) had favorable outcomes (MRS ≤2) at 90 days in edaravone group, while 10 (40%) of 25 patients in placebo group had favorable outcome ($P < 0.005$). Two patients expired (one in each group) during treatment. The mean Barthel index increased from 41.20 ± 32.70 at baseline to 82.40 ± 18.32 at day 90 in edaravone group as compared with placebo group in which scores were 44.20 ± 22.76 at baseline and 68.20 ± 21.30 at day 90 ($P < 0.005$). **Conclusions:** We therefore conclude that edaravone effectively improves functional outcome in AIS.

Key Words

Edaravone, free radical scavenger, neuroprotection, stroke

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Introduction

Free radical generation after acute cerebral ischemia seems to contribute neuronal damage by activating lipoxygenase system. Edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazoline-5-one), a novel free radical scavenger, inhibits activation of lipoxygenase pathway in the arachidonic acid cascade and peroxidation of the phosphatidylcholine liposomal membrane *in vitro*.[1] Thus, edaravone may provide effective neuroprotection, prevent vascular endothelial injury, and delay neuronal death in transient cerebral ischemia and ischemic stroke.

Few Japanese studies have shown it to be efficacious in patients with acute ischemic stroke (AIS).[2-6] However, there is paucity of literature about the efficacy of edaravone outside Japan. The aim of this study was to investigate the effects of edaravone in terms of functional outcome in a group of Indian patients with AIS.

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Materials and Methods

A prospective open-labeled, randomized controlled pilot study was conducted in the Department of Neurology, Chhatrapati Shahuji Maharaj Medical University, Lucknow, a tertiary healthcare center in North India. The study was carried out between May 2009 and May 2010. A written informed consent was undertaken prior to inclusion in the study. The study was approved by the Institutional Ethics Committee and also registered in CTRI, India (CTRI/2009/091/000309, 23-04-2010).

Inclusion and exclusion criteria

The study included patients with AIS 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, history of stroke, those with severe hepatic disease, renal dysfunction, malignancy, pregnancy, or lactation were excluded from study.

Evaluation of patients

A detailed history taking, 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 done in all the patients.

Clinical assessment

Patients were formally assessed at enrollment and at 90 days by an experienced physiotherapist, who was blinded for the treatment given, using the Modified Rankin Scale (MRS) and the Barthel index (BI).[7] The stroke severity was assessed by the National Institute of Health Stroke Scale (NIHSS) and Glasgow Coma Scale. The patients were also assessed clinically by physician at day 14 and day 30. MRS score ≤2 at 90 days was considered as favorable outcome.

Imaging

On admission, all patients underwent computerized tomography (CT) using a Somatom Hiq CT scanner (Siemens) using 10 mm axial sections. 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), when required, for confirming diagnosis. Diagnosis of ischemic stroke was made according to the World Health Organization definition.[8] The stroke subtypes were classified as per the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) study criteria.[9]

Treatment

After inclusion, the patients were randomly divided into two groups according to computer-generated random sequences. The study group received 30 mg of edaravone dissolved in 100 ml of normal saline by infusion over 60 minutes twice daily for 14 days.[3] Control group received normal saline infusion as placebo. Both the groups also received standard therapy for ischemic stroke and other symptomatic treatment, whenever required.

Safety assessments

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.

Statistical analysis

We compared clinical outcome (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 outcome (MRS ≤2) were compared between two groups by Chi square test. For BI, the results were expressed as mean ± standard deviation and the mean were compared between two groups by independent *t* test. The final analysis was based on an "intention-to-treat" approach that included all randomized patients who received at least one dose of study medication. The level of significance was set at $P < 0.05$.

Results

A total of 72 patients having a clinical diagnosis of AIS of 6- to 72-hour duration were admitted during the study period, of which 50 patients were included in the study. Among excluded patients, 18 patients had 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 25 patients received normal saline infusion as placebo, as shown in Figure 1.

The baseline clinical characteristics of the study subjects are shown in Table 1. There were no significant differences for age, gender, frequency of diabetes, hypertension, coronary heart disease, smoking, baseline NIHSS score, BI, median MRS, or number of patients with MRS ≤2 on admission. Among edaravone group, 18 patients had large-artery atherosclerosis, 5 patients had small-artery occlusion, and 2 patients had cardioembolic stroke, whereas in placebo group, 16 patients had large-artery atherosclerosis, 6 patients had small-artery occlusion, and 3 patients had cardioembolic stroke. One patient in each of the placebo and edaravone group died at day 3 and day 5, respectively. Eighteen patients (72%) had favorable

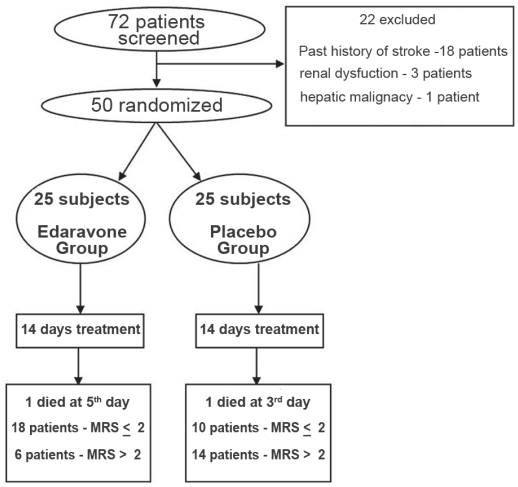

Figure 1: Flow of patient through the trial

Table 1: Baseline characteristics

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	: $P = 0.437$
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 : $P = 0.619$
Modified Rankin Scale ≤2	4	3	Fischer exact : $P = 1$
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 disease	6	5	χ^2: $P = 0.733$

*Indicate Mean ± Standard deviation; NIHSS = National Institute of Health Stroke Scale;

outcomes (MRS ≤2) at 90 days in edaravone group, while 10 patients (40%) had favorable outcome in placebo group, as shown in Figure 2. The mean MRS decreased from 3.84 + 1.17 at baseline to 2.04 ± 1.30 at 90 days in edaravone group. The mean MRS was 2.72 ± 1.33 at 90 days in placebo group. The difference in mean MRS was not significant in between two groups ($P = 0.059$), as shown in Table 2. The mean BI increased from 41.20 ± 32.70 at baseline to 82.40 ± 18.32 at day 90 in edaravone group as compared with 68.20 ± 21.30 at 90 days in placebo group, as shown in Figure 3. There was a significant difference ($P < 0.005$) between the groups in favor of edaravone, as shown in Table 2. Adverse reactions were observed in 3 patients (12.5%) in edaravone group and in 5 patients (20.8%) in placebo group. Such reactions in edaravone group consisted of skin rash in 1 patient, abnormal liver function in 1, and fever and abnormal renal function in 1 patient. In the placebo group, skin rash developed in 1 patient, abnormal renal function in 2, and fever and diarrhea in 2 patients. All of them recovered with treatment.

Discussion

The treatment of AIS is mainly centered on antithrombotic agents, such as antiplatelets, thrombolytics and anticoagulants, and neuroprotective agents such as free radical scavengers and antioxidants. The neuroprotective agents may block reperfusion injury and help in decreasing neuronal damage. In the present study, 18 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 functional outcome in favor of edaravone and also demonstrated its safety in Indian patients. The Edaravone Acute Brain Infarction Study (EABIS) Group also observed significant improvement in functional outcome in the edaravone group, as evaluated by the Modified Rankin Scale.[7]

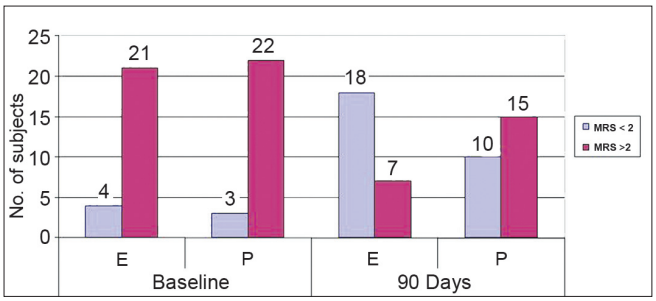

Figure 2: Number of subjects (MRS < 2 & >2) in edaravone (E) and placebo (P) group at baseline and 90 days

Table 2: 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: $P = 0.015$*

* indicate significant results.

In EABIS study, the time limit to treatment after the onset of AIS was kept between 6 and 72 hours and the dose of edaravone was 30 mg twice daily for 14 days.[3] In our study also, we followed the same dosing schedule and time criteria. An early phase II study involving edaravone had also demonstrated its efficacy up to 72 hours of onset of stroke. The improvement at 14 days was 52, 64, and 64% 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.

The major adverse reactions were skin rash, abnormal liver function, and renal dysfunction, but they were more frequent in the placebo group and all patients recovered with treatment. The safety of edaravone was also established in an Indian study where no adverse reaction was observed in any of the patients.[11] 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.[12,13]

The limitations of this study are the small sample size 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.

We therefore conclude that edaravone, a novel free radical scavenger, can provide safe and effective neuroprotection in AIS. Larger randomized, double blind, case-controlled studies are required to confirm this.

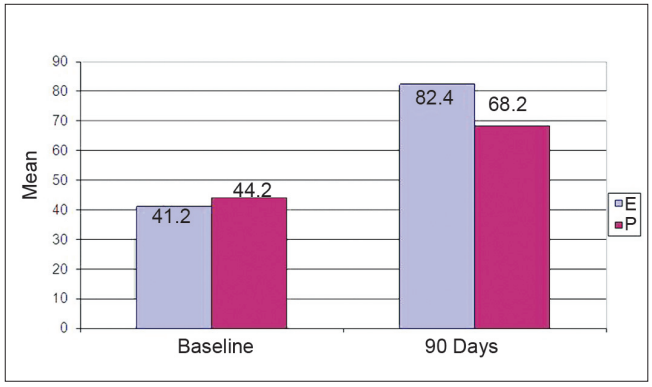

Figure 3: Barthel index in edaravone (E) and placebo (P) at baseline and 90 days

Table 3: Frequency of Modified Rankin Scale in edaravone and placebo groups at 90 days

Modified Rankin Scale	Frequency (%)	
	Edaravone	Placebo
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)

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