Clinical Neurology and Neurosurgery 167 (2018) 157–161

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Effects of edaravone, the free radical scavenger, on outcomes in acute cerebral infarction patients treated with ultra-early thrombolysis of recombinant tissue plasminogen activator

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ARTICLE INFO

Keywords:
Edaravone-acute cerebral infarction-recombinant tissue plasminogen activator-thrombolysis

ABSTRACT

Objectives: Edaravone, a free radical scavenger, alleviates blood-brain barrier disruption in conjunction with suppression of the inflammatory reaction in acute cerebral infarction. Thrombolysis with recombinant tissue plasminogen activator (rtPA) is an established therapy for acute cerebral infarction patients. The purpose of this study was to assess the effects of edaravone on outcomes in acute cerebral infarction patients treated with ultra-early thrombolysis of iv-rt-PA.

Patients and Methods: We conducted a retrospective cohort study using the database of Ningbo First Hospital. We identified patients who were admitted with a primary diagnosis of acute cerebral infarction and treated with intravenous rtPA(iv-rtPA) within 3 h of symptom onset from March 1st in 2014 to October 31st in 2016.Thenceforth,the patients were divided into 2 groups by treatment with(edaravone group) or without edaravone(non-edaravone group). Glasgow Coma Scale (GCS) scores and mRS score at admission were used. Clinical background, risk factors for acute cerebral infarction hemorrhagic transformation, 7-day mortality, recanalization rate, bleeding complications and blood rheology indexes were collected. We also collected the following factors: National Institutes of Health Stroke Scale scores, barthel index.

Results: 136 patients treated without edaravone during hospitalization were selected in non-edaravone group while edaravone group included 132 patients treated with edaravone during hospitalization. The patient baseline distributions were well balanced between non-edaravone group and edaravone group. The rate of hemorrhagic transformation in non-edaravone group was higher than that in edaravone group ($P < 0.05$). The NIHSS scores 7 days and 14 days after symptom onset were higher in non-edaravone group than in edaravone group (both $P < 0.05$). Edaravone group showed a higher recanalization rate and a lower bleeding complications rate at discharge than the non-edaravone group (both $P < 0.05$). The differences of all the blood rheology indexes between the two groups were statistically significant (all $P < 0.05$).

Conclusions: Edaravone may improve outcomes of acute cerebral infarction patients treated with ultra-early thrombolysis of iv-rt-PA.

1. Introduction

Acute cerebral infarction is the most common subtype of stroke which is a major cause of morbidity and disability in industrialized countries. Recently, studies have demonstrated that the mortality of hospitalized patients with acute cerebral infarction is about 3.3%–5.2% at 1 months after onset and about 9%–9.6% at 3 months after onset in China [1,2]. Owing to risk of hemorrhagic transformation (HT) after cerebral infarction, thrombolysis of iv-rt-PA at ultra-early stage which was within 3 h after stroke onset can effectively improve clinical curative effect and prognosis of patients. Recombinant tissue type plasminogen activator(rt-PA) as the most effective thrombolytic drugs used in stroke patients could convert plasminogen into active plasmin. However, rtPA is known to be neurotoxic, such as increasing leukocytic infiltration and free radical reactions in infarcted areas [3, 4]. Edaravone, a free radical scavenger, alleviates blood-brain barrier disruption in conjunction with suppression of the inflammatory reaction in acute cerebral infarction [5]. At present, the research about the clinical efficacy of ultra-early thrombolysis of rt-PA combined with edaravone in the treatment of acute cerebral infarction was limited. The aim of this study was to investigate the effects of edaravone on outcomes in acute cerebral infarction patients treated with ultra-early thrombolysis of iv-rt-PA.

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https://doi.org/10.1016/j.clineuro.2018.02.026
Received 13 December 2017; Received in revised form 2 February 2018; Accepted 19 February 2018
Available online 24 February 2018
0303-8467/

2. Patients and methods

2.1. Patients

We conducted the retrospective study using the database of Ningbo First Hospital. Our cohort study retrospectively evaluated 268 patients (134 men, 134 women) with acute cerebral infarction who were admitted to Ningbo First Hospital, Neurosurgery Departments, from March 1st in 2014 to October 31st in 2016 (3 years and 8 months). The diagnosis of acute cerebral infarction was identified according to the criteria of Guidelines for the Diagnosis and Treatment of Acute cerebral infarction specified by the Chinese medical association [6]. Treatments for cerebral infarction other than edaravone were administrated according to established guidelines, with no other restrictions imposed. A standardized protocol for emergency thrombolysis for acute cerebral infarction was established. All patients were received iv-rtPA therapy with low-dose alteplase (0.6 mg/kg) within 3 h after stroke onset. We selected those who were administered edaravone with a dosing regimen of 30 mg was drip-infused intravenously over a 30-minute period on the same day of rtPA administration, and this process was repeated twice a day for 2 weeks (edaravone group, n = 132). Edaravone as a neuroprotective agent was approved for the treatment of acute cerebral infarction within 24 h of the onset of symptoms by Chinese Society of Neurology in April 2015. Then all patients admitted to our hospital after April 2015 received edaravone twice daily by intravenous drip infusion for 14 days, except for contraindications. Thereafter, during hospitalization those not received edaravone were selected as non-edaravone group(n = 136). The inclusion criteria was as follows: all patients were first-episode admitted within 3 h of the onset of symptoms and confirmed by CT or MRI; weakness in the upper or lower limbs, disability with mRS score < 2 before onset. The exclusion criteria was: age < 18 years; presentation in a coma on admisson; slight or severe neurologic deficits on admission (NIHSS score, ≤ 6or≥ 23); contraindications for edaravone treatment, including severe liver disease, kidney dysfunction (ICD-10 code N18.x or N19); serious comorbidities, like heart disease, malignant tumor or intracranial hemorrhage; serious infection-related complications or autoimmune disease; use of antibiotics, steroids or nonsteroidal anti-inflammatory drugs. Because edaravone had a warning of the risk of liver disease and renal disorder development [7]. A comatose state was identified by Glasgow Coma Scale (GCS) which is widely used [8].

2.2. Data selection

The data about risk factors for acute cerebral infarction including hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, atrial fibrillation, type of cerebral infarction, responsible occluded vessel and smoking status were used. The cerebral infarction subtypes were divided into four groups: cardiogenic embolism; atherothrombosis; lacunar; others or unspecified. We also collected other clinical backgrounds, blood pressure, blood glucose and D-dimer before treatment. We took knowledge of whether patients took antihypertensive drugs, including diltiazem and nicardipine, both of which are commonly used for acute cerebral infarction patients in China, as symptom onset. Urgent use of antihypertensive drugs helped to realize blood pressure of patients at admission. GCS and mRS scores at admission indicating the post-stroke neurological status were used. We defined normal function as mRS scores of 0–1. The effect of drug and acute stroke care to prevent complications is generally achieved within the first 7 days so we collected 7-day mortality in two groups [9].

Hemorrhagic transformation on brain CT in 14 days after stroke onset was collected which was categorized into hemorrhagic infarction (HI) or parenchymal hematoma(PH) based on the European Cooperative Acute Stroke Study II(ECASS II) criteria: (1) HI-1: small petechiae along the margins of the infarct; HI-2: more confluent petechiae within the infarct area but without a space-occupying effect; (2) PH-1: hemotoma in 30% of the infarcted area with some slight space-occupying effect; and PH-2: dense hemotoma in 30% of the infarcted area with substantial space-occupying effect or hemotoma out of the infarcted area [10]. We also collected the following factors: NIHSS scores indicating neurologic deficit and barthel index (BI) on admission, on the seventh day and the fourteenth day, and mRS scores at discharge indicating functional outcome in the two groups. Recanalization rate and bleeding complications at discharge were evaluated [11]. The length of hospital staying was collected. We also compared with the blood rheology indexes before and after treatment (at discharge), including high shear whole blood viscosity, low shear whole blood viscosity, plasma viscosity, hematocrit rate, fibrinogen.

2.3. Statistical analysis

Statistical analyses were performed using SPSS 22.0 software for Windows (SAS Institute, Cary, NC). Characteristics of patients are reported as mean ± standard deviation (SD). The unpaired Student t test or χ^2 test were used. A multiple logistic regression analysis was used for comparison of characteristics between the patients with and without recanalization. Differences were considered significant at P < 0.05. This study was approved by the ethics committee of our hospital.

3. Results

The median age was 70 years in patients receiving rtPA alone or rtPA + edaravone.136 patients treated without edaravone during hospitalization were selected in non-edaravone group while edaravone group included 132 patients treated with edaravone during hospitalization. The baseline clinical characteristics, risk factors for acute cerebral infarction, type of cerebral infarction, responsible occluded artery and smoking status were shown in Table 1.The patient baseline distributions were well balanced between non-edaravone group and edaravone group. Among the 370 patients in two groups, no significant intragroup differences in male/female ratio, mean age, or body mass index were detected as well as in mean blood pressure($P > 0.05$).The smoking rate tended to be higher in the edaravone group than in the non-edaravone group, although the difference was not significant ($P > 0.05$).In terms of risk factors, GCS and mRS score, no intragroup differences were found($P > 0.05$).No intragroup differences in blood glucose and D-dimer on admission were noted($P > 0.05$).The two groups used similar drugs other than edaravone during hospitalization after symptom onset. Steroids or nonsteroidal anti-inflammatory drugs were not used in patients in either group. The usage rate of antihypertensive drugs and time of rtPA treatment after onset are not different in both groups($P > 0.05$).

Table 2 shows hemorrhagic transformation in 14 days after symptom onset. The rate of hemorrhagic transformation in the non-edaravone group was significantly higher than that in the edaravone group($\chi^2 = 4.588$,$P = 0.024$,Table 2).However there was no significant difference seen in HI1, HI2, PH1 or PH2 between Edaravone group and non-edaravone group, respectively($P > 0.05$).

The NIHSS score on admission was not different in both groups,but the NIHSS scores on the 7th day and the 14th day after symptom onset were significantly higher in those receiving rtPA alone than in those receiving rtPA + edaravone($P < 0.05$,Table 3). The BI 14 days after symptom onset were significantly lower in non-edaravone group than in edaravone group ($P < 0.05$).Patients with mRS scores of 0–1 at discharge in edaravone group were more than those in non-edaravone group($P > 0.05$).Patients with mRS scores of 4–6 at discharge in edaravone group were less than those in non-edaravone group($P > 0.05$).

Edaravone group showed a higher recanalization rate ($P < 0.05$) and a lower bleeding complications rate at discharge($P > 0.05$) than the non-edaravone group. There were no significant differences in asymptomatic and symptomatic intracerebral hemorrhage rates between two groups($P > 0.05$).The median duration of hospitalization