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Effects of edaravone on early outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen activator

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ABSTRACT

Background: We investigated whether edaravone could improve early outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen activator (rtPA).
Methods: We conducted a retrospective cohort study using the Japanese Diagnosis Procedure Combination database. We identified patients admitted with a primary diagnosis of ischemic stroke from 1 July 2010 to 31 March 2012 and treated with rtPA on the same day of stroke onset or the following day. Thereafter, we selected those who received edaravone on the same day of rtPA administration (edaravone group), and those who received rtPA without edaravone (control group). The primary outcomes were modified Rankin Scale (mRS) scores at discharge. One-to-one propensity-score matching was performed between the edaravone and control groups. An ordinal logistic regression analysis for mRS scores at discharge was performed with adjustment for possible variables as well as clustering of patients within hospitals using a generalized estimating equation.
Results: We identified 6336 eligible patients for inclusion in the edaravone group (n = 5979; 94%) and the control group (n = 357; 6%) as the total population. In 356 pairs of the propensity-matched population, the ordinal logistic regression analysis showed that edaravone was significantly associated with lower mRS scores of patients at discharge (adjusted odds ratio: 0.74; 95% confidence interval: 0.57–0.96).
Conclusions: Edaravone may improve early outcomes in acute ischemic stroke patients treated with rtPA.

1. Introduction

Thrombolysis with recombinant tissue plasminogen activator (rtPA) is an established therapy for acute ischemic stroke patients [1]. At the same time, however, previous *in vivo* studies have demonstrated that tPA has toxic effects toward brains under ischemia, such as expanding the infarct volume [2,3].

Edaravone is a free radical scavenger and neuroprotectant given a grade B recommendation for use in acute ischemic stroke patients in the Japanese guideline for the management of ischemic stroke [4]. Some *in vivo* and *in vitro* studies have suggested that edaravone attenuated the tPA-related neurotoxicity [5–7]. Thus, there is a possibility that edaravone may improve the neurological outcomes in acute ischemic stroke patients treated with rtPA. However, clinical data supporting the effectiveness of edaravone were based on limited studies with small samples [8,9]. We therefore investigated whether edaravone could improve early outcomes of acute ischemic stroke patients treated with rtPA, using a Japanese national inpatient database.

2. Material and methods

2.1. Data source

We conducted a retrospective cohort study using the Diagnosis Procedure Combination (DPC) database, which is a Japanese nationwide administrative claims and discharge abstract database. In total, 1075 hospitals, including all 82 university teaching hospitals, participated in the database in March 2012. The total number of recorded patients was approximately 7 million in 2011, which represents approximately 50% of all acute care inpatient hospitalizations in Japan. The database contained patients' general demographics, diagnoses, drugs used, surgical and medical procedures, hospital discharge status, and some detailed clinical data for specific diseases including date of stroke onset, modified Rankin scale (mRS) scores, and Japan Coma Scale

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(JCS) scores for stroke patients. The primary diagnosis on admission, pre-existing comorbidities, and complications occurring after admission, were separately recorded with International Classification of Diseases and Related Health Problems, Tenth revision (ICD-10) codes and text data in the Japanese language. Drugs and procedures were recoded with the dates of their use or implementation. Physicians in charge were responsible for recording the diagnoses with reference to the medical charts.

This study was approved by the Institutional Review Boards and Ethics Committee of the University of Tokyo. Informed consent was waived owing to the anonymous nature of the data.

2.2. Patient selection and data

We identified patients who were admitted to hospitals with a primary diagnosis of ischemic stroke from 1 July 2010 to 31 March 2012, and received rtPA on the same day of stroke onset or the following day. We included patients who received rtPA on the following day of stroke onset because some patients may have suffered stroke little before midnight and received rtPA soon after midnight. Thereafter, we selected those who received edaravone on the same day of rtPA administration (edaravone group), and those who did not receive edaravone during hospitalization (control group). During the study period, intravenous rtPA administration was approved in Japan at a dose of 0.6 mg/kg and only for patients within 3 h after stroke onset, based on the Japan Alteplase Clinical Trial [10]. Intravenous edaravone administration was approved at a dose of 30 mg twice a day within 14 days [11]. The diagnosis of ischemic stroke was identified by ICD-10 code I63.x. The exclusion criteria were: pre-existing comorbidities of chronic renal failure (ICD-10 code N18.x or N19); presentation in a coma at admission; and initial edaravone use on the next day of rtPA administration or later. We excluded patients with chronic renal failure because edaravone had a warning of the risk of renal disorder development [12]. We excluded patients in a coma in accordance with two previous randomized control trials on the efficacy of radical scavengers [11,13]. A comatose state was identified by JCS scores of 100–300. The JCS is a scale for impaired consciousness that is widely used in Japan [14,15]. A score of 0 indicates alert consciousness, single-digit scores of 1–3 indicate mildly impaired consciousness with spontaneous eye-opening, double-digit scores of 10–30 indicate moderately impaired consciousness with eye-opening when patients receive stimuli, and triple-digit scores of 100–300 indicate coma. The JCS is well-correlated with the Glasgow Coma Scale [16].

We collected patients' pre-existing comorbidities including atrial fibrillation (I48) and heart failure (I50.x). As indicators of the post-stroke neurological status, the JCS scores and mRS scores at admission were used. In accordance with the ICD-10 codes recorded for the patients, the infarction subtypes were divided into three groups: arterial thrombosis (I630, I633); arterial embolism (I631, I634); and others or unspecified (I632, I635, I636, I638, I639). We examined whether patients received intravenous administration of antihypertensive drugs on the same day as stroke onset (urgent use of antihypertensive drugs) as an indicator of high blood pressure at admission. These drugs included diltiazem and nicardipine, both of which are commonly used for stroke patients in Japan [17]. We also collected the following factors: route of rtPA administration (intravenous or intra-arterial); admission to a Stroke Care Unit for at least 1 day during hospitalization; type of hospital (university hospital or community hospital); date of admission (weekday or weekend); and medications prescribed after admission including statins and eicosapentaenoic acid (EPA).

The primary outcomes of interest were mRS scores at discharge. We defined functional independence as mRS scores of 0–2. The secondary outcomes of interest were 7-day mortality, the occurrence of intracranial hemorrhage (ICH) after admission, and length of hospital stay. We chose 7-day mortality with reference to the understanding that provision of acute stroke care and prevention of complications are generally achieved within the first 7 days [18]. Intracranial hemorrhage was identified by ICD-10 codes I60.x, I61.x, I62.x, and I638 combined with the text data "hemorrhagic infarction".

2.3. Statistical analysis

We performed one-to-one propensity-score matching between the edaravone and control groups. This matching tried to enhance the baseline comparability between the two groups in this retrospective study. To estimate a propensity score for each patient, we used a logistic regression model for receipt of edaravone with adjustment for possible confounding variables including patient age, sex, pre-existing comorbidities on admission, JCS score at admission, mRS score at admission, infarction subtype, urgent use of antihypertensive drugs, route of rtPA administration, Stroke Care Unit admission, hospital type, date of admission, and medications prescribed during hospitalization. The C-statistic was calculated to evaluate the goodness-of-fit for the model. Each patient in the edaravone group was matched with a patient in the control group with the closest estimated propensity on the logit scale within a specified range ($\leq$0.25 of the pooled standard deviation of estimated logits) [19]. In both the total population and the matched population, categorical data were compared between the edaravone group and the control group using the chi-square test or Fisher's exact test as appropriate, while continuous data were compared using the Mann–Whitney U test. Ordinal logistic regression analyses were performed for mRS scores at discharge with adjustment for several variables as well as clustering of patients within hospitals using a generalized estimating equation. The threshold for significance was $P < 0.05$. All statistical analyses were performed using SPSS Statistics version 20.0 (IBM SPSS, Armonk, NY, USA).

3. Results

The selection process for the study cohort is described in Fig. 1. During the survey periods, 7591 patients with acute ischemic stroke were treated with rtPA on the same day or the following day of stroke onset. After excluding patients with chronic renal failure, in a coma, with missing data and with delayed use of edaravone, 6336 patients were eligible for our study as the total population. The edaravone group included 5979 (94%) patients, while the control group included 357 (6%) patients. By one-to-one propensity-score matching, 356 pairs of patients in the edaravone and control groups were selected. The C-statistic for goodness-of-fit was 0.68.

Table 1 shows baseline characteristics of the edaravone and control groups in the total population and the matched population. In the total population, the baseline characteristics were heterogeneous between the edaravone and control groups. The patients in the edaravone group were younger (median age [interquartile range]: 74 [66–81] years *vs.* 80 [71–85] years; $P < 0.001$), had a lower proportion of heart failure as a preexisting comorbidity (8.1% *vs.* 17.6%; $P < 0.001$), had less impaired consciousness at admission (51.9% *vs.* 54.9% with JCS scores of 1–3; 27.0% *vs.* 32.2% with JCS scores of 10–30; $P = 0.001$), and were more likely to be admitted to hospital on a weekday (74.0% *vs.* 66.9%; $P = 0.003$) compared with the patients in the control group. In the matched population, the patient baseline distributions were well balanced between the two groups.

Table 2 shows univariate comparisons of the outcomes in the matched population. The proportion of functional independence at discharge tended to be higher in the edaravone group than in the control group, although the difference was not significant (35.1% *vs.* 28.7%; $P = 0.06$). On the other hand, there were no significant differences between the two groups in 7-day mortality, the occurrence of ICH after admission, and length of hospital stay.

Table 3 shows the adjusted odds ratios of various factors in the matched population for mRS scores at discharge derived from the ordinal logistic regression analyses. Edaravone was significantly associated with reduction of mRS scores at discharge (adjusted