



## Clinical Study

# Direct access to a hospital offering intravenous thrombolysis therapy improves functional outcome of acute ischemic stroke patients



Dae-Hyun Kim<sup>a,b</sup>, Jae-Kwan Cha<sup>a,b,\*</sup>, Hyun-Seok Park<sup>b</sup>, Jae-Hyung Choi<sup>b</sup>, Myung-Jin Kang<sup>b</sup>, Jae-Taeck Huh<sup>b</sup>

<sup>a</sup> Department of Neurology, College of Medicine, Dong-A University, 1, 3-ga Dongdaesin-dong, Seo-gu, Busan 602-715, Republic of Korea

<sup>b</sup> Busan-Ulsan Regional Cardiocerebrovascular Center, Busan, Republic of Korea

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## ABSTRACT

Referral from other hospitals is one of the primary causes of delayed thrombolysis therapy after acute ischemic stroke (AIS). We aimed to evaluate whether direct access to a hospital offering intravenous thrombolysis therapy was associated with good functional outcome in AIS patients treated with thrombolysis. We enrolled patients who received intravenous thrombolysis within 3 hours of symptom onset at our stroke center. We divided these patients into two groups: those with a direct admission to our stroke center and those with indirect admission by referral from other community hospitals. We investigated onset-to-door time and onset-to-recombinant tissue plasminogen activator (rtPA) time according to admission mode. We then assessed the association between a direct admission and favorable outcome at 90 days. A total of 232 patients (mean age of 66.6 years, median National Institutes of Health Stroke Scale score of 10) were included. A total of 48.7% of AIS patients treated with intravenous thrombolytic therapy were transferred from other hospitals. Patients who were directly admitted to our stroke center had a shorter onset-to-door time (61 versus 120 minutes,  $p < 0.001$ ) and onset-to-rtPA time (103 versus 155 minutes,  $p < 0.001$ ) than those referred from other hospitals. Direct admission was associated with a good outcome with an odds ratio of 2.03 (95% confidence interval 1.051–3.917,  $p = 0.035$ ), after adjusting for baseline variables. Thrombolysis after direct admission to a hospital offering intravenous thrombolysis therapy could shorten onset-to-rtPA time and improve stroke outcome in patients with AIS.

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## 1. Introduction

Intravenous recombinant tissue plasminogen activator (rtPA) treatment within 3–4.5 hours of stroke onset improves the chances of neurological recovery and functional independence after ischemic stroke [1,2]. Despite the approval of thrombolytic therapy for the treatment of acute stroke, the estimated rate of rtPA use is extremely low at approximately 2–5% of all ischemic strokes [3–5]. The most common reason why patients with acute ischemic stroke (AIS) do not receive rtPA is delayed arrival to the hospital [6].

A previous analysis has shown that the greatest benefit comes from earlier intravenous thrombolysis with the net benefit diminishing over time [7–9]. Delayed hospital admission interferes with early thrombolytic therapy in patients with AIS. Even when rtPA is administered within 3–4.5 hours after stroke onset, the onset-to-rtPA time is subsequently prolonged in AIS patients arriving at an emergency room (ER) late after onset compared with those with

shorter onset-to-door time. This is because the time of hospital admission is prolonged [10]. An important factor associated with delayed arrival to hospital is the referral pattern [11–13]. Referral after previous initial medical contact significantly prolongs not only the admission time to the hospital where thrombolysis is available but also the time to thrombolytic treatment after AIS [12,14–17]. Thus, patients with AIS with direct access to a hospital where intravenous thrombolysis is available could have better outcome after thrombolysis treatment.

This study was designed to evaluate whether direct admission to a hospital offering intravenous thrombolysis therapy could influence the functional outcome in patients with AIS receiving thrombolytic in a single, large, stroke center located in an urban setting.

## 2. Materials and methods

Our hospital is a 1000 bed general teaching hospital located in Busan, a highly industrialized metropolitan area (a population of

\* Corresponding author. Tel.: +82 51 240 5570; fax: +82 51 244 8338.

E-mail address: [nrcjk65@gmail.com](mailto:nrcjk65@gmail.com) (J.-K. Cha).

3.7 million people, area 765.64 km<sup>2</sup>, including 10 fire fighting blocks) on the east coast of South Korea. Our hospital is a tertiary care facility with over 600 patients with AIS or transient ischemic attack admitted through the ER each year. In February 2009, our hospital implemented a stroke code activation system to effectively perform acute stroke treatment along with its establishment as a comprehensive stroke center. Acute stroke expertise is provided 24 hours a day, 7 days a week. We also established a hotline system in conjunction with the Korean Emergency Medical Information System (1339) for prehospital notification whenever it is felt that a stroke patient required emergency care at other general hospitals [18]. The primary role of the 1339 system is to connect a patient who is in need of an emergency intervention or operation in community hospitals with appropriate available hospitals. We accepted all admission applications from other institutes.

### 2.1. Patient selection

This study was based on a prospectively collected stroke registry. Consecutive patients with ischemic stroke and transient ischemic attack who were admitted to our stroke center within 7 days of symptom onset were enrolled in our stroke registry. During the study period, the treating physician decided whether to carry out an MRI or CT scan within the 3 hour time window, mainly on the basis of MRI availability (the preferred method). However, CT scan was performed if MRI was not immediately available or if the patient had a contraindication to MRI. MRI-specific exclusion criteria were well-developed fluid attenuated inversion recovery (FLAIR) changes within acute diffusion weighted imaging (DWI) lesions indicative of subacute infarction, and strongly hyperintense DWI signal changes involving more than 50% of the middle cerebral artery (MCA) territory. Clinical eligibility criteria for thrombolysis were applied according to the conventional National Institute of Neurological Disorders and Stroke (NINDS) criteria [1]. Follow-up CT scan or MRI was performed 24–48 hours after initiation of thrombolytic therapy. During admission, all patients were evaluated using a protocol that included 12 lead electrocardiography, chest radiograph, lipid profile and standard blood tests. Data including clinical manifestation, demographic data, medical history, presence of vascular risk factors, and treatment information were recorded in the stroke registry by two trained study nurses.

We identified patients with AIS who received intravenous thrombolytic treatment between January 2008 and March 2012 from our stroke registry. Of these, we enrolled only the patients who received rtPA within 3 hours of onset of symptoms because rtPA treatment within 3–4.5 hours of stroke onset was only approved in Korea in November 2011. We excluded patients who had an in-hospital stroke or less than 3 months of follow-up. Endovascular treatment was defined as additional intra-arterial thrombolytic therapy or mechanical clot retrieval therapy with intravenous thrombolysis.

### 2.2. Assessment of pre-hospital and in-hospital process

We obtained information about symptom onset time and the admission route to ER from patients, bystanders and the emergency rescue sheet recorded by paramedics. Based on the mode of admission, we divided patients into a direct admission group (those with a private, direct visit to our ER or with a direct admission to our ER by way of emergency medical services [EMS]) and an indirect admission group (those who were transferred to our ER after first visiting another hospital).

Onset of stroke was defined as the time when the patient or an observer first noted a neurological deficit or the last normal appearance in the case of unknown time of onset of symptoms. Upon admission to the ER, onset-to-door time (the time from onset

of symptoms to arrival at our stroke center), door-to-rtPA time (the time from ER arrival to rtPA start) and onset-to-rtPA time were recorded.

### 2.3. Clinical assessment and outcome measures

Initial stroke severity was determined by the National Institutes of Health Stroke Scale (NIHSS). The primary end point was a good functional outcome at 90 days, defined as a modified Rankin scale (mRS) score of  $\leq 2$ . Trained study nurses assessed the mRS at 90 days by telephone interview with the patients or their next of kin, or by hospital chart review. mRS values at 90 days were classified into good outcome (mRS 0–2) and poor outcome for independence (mRS 3–6). Symptomatic hemorrhagic transformation was defined as any hemorrhage associated with a 4 point increase in the NIHSS score.

### 2.4. Statistical analysis

Statistical significance of intergroup differences was assessed by chi-squared tests for categorical variables. Continuous variables were expressed as the mean  $\pm$  standard deviation or median and interquartile range, which were then compared using Student's *t*-test or the Mann-Whitney test as appropriate. To evaluate the relationship between the admission routes to our stroke center and clinical outcome, all potential factors were entered into a stepwise logistic regression model as dependent variables and inclusion was set at a univariate association with a probability value of  $\leq 0.1$ . Results are presented as odds ratio (OR) estimates of relative risk with 95% confidence intervals (CI). *p* values  $< 0.05$  were considered statistically significant.

## 3. Results

### 3.1. Demographic characteristics according to admission route

Of the 2698 patients who were registered in our stroke registry, a total of 249 patients with AIS receiving rtPA treatment (9.2%) within 3 hours after stroke onset were enrolled during the study period. A total of 17 patients were excluded because of in-hospital stroke ( $n = 9$ ) and loss to follow-up ( $n = 8$ ). Thus, a total of 232 patients were finally included in the study. Mean age of the patients was  $66.6 \pm 11.8$  years, 55.2% were male and the median NIHSS score was 10.

Baseline clinical characteristics according to admission route are shown in Table 1. Approximately half of patients with AIS receiving intravenous thrombolytic therapy ( $n = 113$ ) were transferred from other hospitals. The distance from the hospital requesting dispatch to our stroke center was  $24.0 \pm 24.4$  km (range, 2.9–153 km). Initial NIHSS score was lower in patients with a direct admission than those with referral from other hospitals (9 [6–14] versus 12 [7–17];  $p = 0.001$ ).

During the study period, the median door-to-rtPA time was 33 minutes. Median door-to-rtPA time was shorter in patients referred from other hospitals than in those with direct admission because of the reduction of intra-hospital processing time through pre-admission notification during patient transfer (31 minutes [18–41] versus 36 minutes [26–45];  $p = 0.013$ ) [18]. Nevertheless, the direct admission group had a shorter onset-to-door time (61 minutes [40–86] versus 120 minutes [90–139];  $p < 0.001$ ) and onset-to-rtPA time (103 minutes [74–135] versus 155 minutes [130–169];  $p < 0.001$ ) than the indirect admission group.

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