Journal of Clinical Neuroscience 27 (2016) 74–79

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

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

Clinical Study

Direct admission to stroke centers reduces treatment delay and improves clinical outcome after intravenous thrombolysis

Dae-Hyun Kim [a], Hee-Joon Bae [b], Moon-Ku Han [b], Beom Joon Kim [b], Sang-Soon Park [c], Tai Hwan Park [c], Kyung Bok Lee [d], Kyusik Kang [e], Jong-Moo Park [e], Youngchai Ko [f], Soo Joo Lee [f], Jay Chol Choi [g], Joon-Tae Kim [h], Ki-Hyun Cho [h], Keun-Sik Hong [i], Yong-Jin Cho [i], Dong-Eog Kim [j], Jun Lee [k], Juneyoung Lee [l], Mi Sun Oh [m], Kyung-Ho Yu [m], Byung-Chul Lee [m], Hyun-Wook Nah [a], Jae-Kwan Cha [a,*]

[a] Department of Neurology, Dong-A University College of Medicine, 3-ga Dongdaesin-dong, Seo-gu, Busan 602-715, Republic of Korea
[b] Department of Neurology, Cerebrovascular Center, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
[c] Department of Neurology, Seoul Medical Center, Seoul, Republic of Korea
[d] Department of Neurology, Soonchunhyang University College of Medicine, Seoul, Republic of Korea
[e] Department of Neurology, Eulji General Hospital, Eulji University, Seoul, Republic of Korea
[f] Department of Neurology, Eulji University Hospital, Eulji University, Daejeon, Republic of Korea
[g] Department of Neurology, Jeju National University Hospital, Jeju, Republic of Korea
[h] Department of Neurology, Chonnam National University Hospital, Gwangju, Republic of Korea
[i] Department of Neurology, Ilsan Paik Hospital, Inje University, Goyang, Republic of Korea
[j] Department of Neurology, Dongguk University, Ilsan Hospital, Goyang, Republic of Korea
[k] Department of Neurology, Youngnam University Medical Center, Daegu, Republic of Korea
[l] Department of Biostatistics, Korea University College of Medicine, Seoul, Republic of Korea
[m] Department of Neurology, Hallym University College of Medicine, Anyang, Republic of Korea

ARTICLE INFO

Article history:
Received 14 January 2015
Accepted 4 June 2015

Keywords:
Acute ischemic stroke
Admission route
Interhospital transfer
Intravenous thrombolysis

ABSTRACT

We aimed to examine whether direct access to hospitals offering intravenous thrombolysis is associated with functional outcomes in patients with acute ischemic stroke treated with intravenous thrombolysis. We enrolled patients who received intravenous thrombolysis within 4.5 hours of symptom onset using a prospective multicenter registry database. Patients referred directly from the field to organized stroke centers were compared with those who were transferred from non-thrombolysis-capable hospitals in terms of clinical outcomes at 90 days after intravenous recombinant tissue plasminogen activator treatment. We also investigated onset-to-door time and onset-to-needle time according to admission mode. A total of 820 patients (mean age of 67.3 years and median National Institutes of Health Stroke Scale score of 9) were enrolled. Seventeen percent of patients with AIS who received intravenous thrombolytic therapy at 12 hospitals (n = 142) were transferred from other hospitals. The direct admission group had a shorter median onset-to-admission time (63 *versus* 121 minutes, $P < 0.001$) and onset-to-needle time (110 *versus* 161 minutes, $P < 0.001$) as compared with the indirect admission group. Direct admission was associated with a good outcome with an odds ratio of 1.57 (95% confidence interval: 1.02–2.39, $P = 0.036$) after adjustment for baseline variables. Direct admission to a hospital with intravenous thrombolysis facilities available at all times was associated with shorter onset-to-needle time and better outcome in patients with AIS undergoing thrombolytic therapy. Our findings support the implementation of regional stroke care programs transporting patients directly to stroke centers to promote faster treatment and to achieve better outcomes.

1. Introduction

In patients with acute ischemic stroke (AIS), intravenous recombinant tissue plasminogen activator (rtPA) within 4.5 hours of stroke onset is a treatment modality with a well established clinical benefit [1–3]. Several prospective randomized trials comparing tPA with standard treatment and pooled analyses have shown that there is a correlation between a shorter time from symptom onset to treatment and better outcomes [4–7].

* Corresponding author. Tel.: +82 51 240 5570; fax: +82 51 244 8338.
E-mail address: nrcjk65@gmail.com (J.-K. Cha).

http://dx.doi.org/10.1016/j.jocn.2015.06.038
0967-5868/

Patients with AIS should be referred to hospitals where thrombolysis is available as promptly as possible, which is essential for earlier intravenous rtPA treatment. However, this may be delayed in many patients with AIS. This is mainly due to a lack of public recognition of stroke symptoms or patients' failure to activate emergency medical services (EMS) [8–11]. Another reason for the delayed admission is that patients with AIS are transferred from initial visiting hospitals without receiving intravenous rtPA [12,13].

Referral from other hospitals might significantly prolong not only the onset-to-door (OTD) time to the thrombolysis-capable hospitals but also onset-to-needle (OTN) time after AIS. This leads to the speculation that patients who were indirectly admitted would suffer poor outcomes after receiving thrombolytic treatments as compared with those who were directly admitted, although both groups are given rtPA within 4.5 hours of stroke onset [14,15].

There are some data about the association between admission route and outcome after percutaneous coronary intervention in patients with ST-elevation myocardial infarction [16–18], but there is a paucity of such data in the AIS field. We demonstrated a correlation between direct admission to a hospital offering intravenous thrombolysis therapy and good outcomes after intravenous rtPA in a single Korean center [19]. This study was designed to evaluate whether direct admission to hospitals with intravenous thrombolysis facilities available at all times could affect the functional outcomes in patients with AIS receiving thrombolytic therapy within 4.5 hours of stroke onset in multiple Korean centers.

2. Methods

We used the database of the Clinical Research Center for Stroke-5 (CRCS-5), which is a web-based, prospective registry for consecutive patients with AIS admitted to 12 academic hospitals in Korea. All hospitals implemented a stroke code activation system to effectively perform acute stroke treatment. Stroke specialists were available 24 hours a day, 7 days a week during the study period. Details of the CRCS-5 registry database have been described previously [20]. The National Institutes of Health Stroke Scale (NIHSS) score was measured by neurologists at presentation. Modified Rankin Scale (mRS) at 90 days was obtained by direct assessment or by telephone interview with the patients or their relevant caregivers. Symptomatic hemorrhagic transformation was defined as any hemorrhage associated with a 4 point increase in the NIHSS. The data quality for clinical and laboratory information was monitored and audited regularly.

From the stroke registry database, we identified patients with AIS who were treated with intravenous rtPA within 4.5 hours of onset between January 2011 and December 2012. Eligibility criteria for this study were: (1) AIS arriving at the emergency room; (2) age >18 years; (3) no in-hospital stroke; (4) no or minimal prestroke disability defined as mRS score 0–2; (5) no transfer after intravenous rtPA at outside hospitals; and (6) availability of 3 month mRS outcome. We confirmed that OTD time, door-to-needle (DTN) time (the time from emergency room arrival to rtPA start) and OTN time were recorded upon admission in the database.

Based on the mode of admission, we divided our patients into two groups. The direct admission group was defined as patients referred directly from the field to thrombolysis-capable stroke centers with a private visit or by way of EMS. The indirect admission group included patients who were transferred from the field to the nearest hospital and were subsequently referred to the stroke centers.

Primary outcome was the proportion of mRS $\leqslant$ 2 outcomes at 3 months. We also compared baseline characteristics including OTD, DTN and OTN times between the two groups.

The CRCS-5 registry and design of this study were approved by the Institutional Review Boards of each hospital.

2.1. Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range [IQR]) and then compared using Student's t-test or the Mann–Whitney test, as appropriate. Categorical variables were presented as proportions and compared by the chi-square test.

When comparing the dichotomized outcomes of the proportions of mRS $\leqslant$ 2 between two groups, the chi-square test was used for unadjusted analyses and multiple logistic regression for adjusted analyses. All potential factors were entered into a stepwise logistic regression model as independent variables except for time factors. Covariates having $P < 0.1$ for good functional outcome in univariable analyses were selected for input into the multivariable models. Results are presented as odds ratio (OR) estimates with 95% confidence intervals (CI). P values < 0.05 were considered statistically significant.

3. Results

Of 10,501 patients with AIS registered in CRCS-5 data, 994 (9.5%) received intravenous rtPA treatment in 12 hospitals. Among them, we analyzed 820 after exclusion due to pre-stroke mRS > 2 (n = 72), follow-up loss (n = 14), in-hospital stroke with intravenous rtPA (n = 22) and intravenous rtPA after 4.5 hours of symptom onset (n = 66) (Fig. 1). Mean age was 67.3 ± 12.3 years, 59.7% were male and the median NIHSS score was 9 in the study population.

Among these patients, 678 (82.7%) were referred directly from the field to the organized stroke centers and 142 (17.3%) were transferred from non-thrombolysis-capable hospitals. A comparison of characteristics between the two groups is presented in Table 1.

The median OTD time was shorter for patients referred directly from the field (63 minutes; IQR: 39 to 105) as compared to patients transferred from the non-thrombolysis-capable hospitals (121 minutes; IQR: 98 to 152 minutes; $P < 0.001$). The median DTN time was 5 minutes longer in the direct admission group

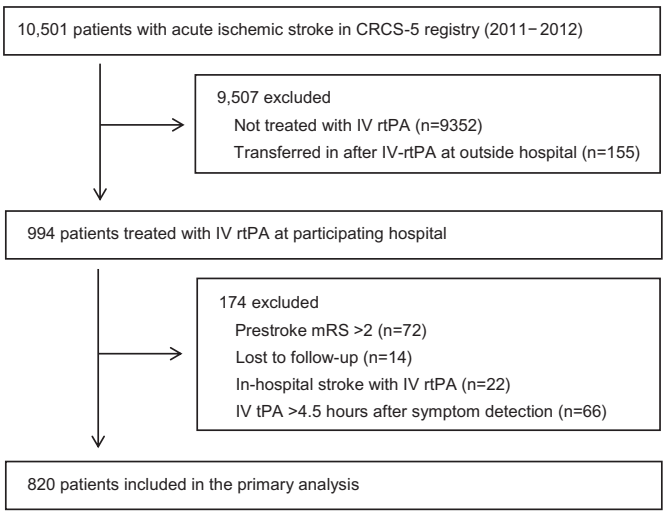

Fig. 1. Study population selection process.