Using Recombinant Tissue Plasminogen Activator to Treat Acute Ischemic Stroke in China

Analysis of the Results From the Chinese National Stroke Registry (CNSR)

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Background and Purpose—Little is known about intravenous recombinant tissue plasminogen activator (rtPA) use in China. By accessing the Chinese National Stroke Registry (CNSR), the rate of intravenous rtPA use was reviewed. We specifically examined the issues of prehospital and in-emergency department delay and compared them with the published data from developed countries.

Methods—Funded by Chinese government, CNSR is the only nationwide stroke registry that includes 132 urban hospitals. All patients eligible for intravenous rtPA were included for analysis. We then compared the onset-to-needle time and door-to-needle time in the emergency department in China with those in developed countries.

Results—From September 2007 to August 2008, 14,702 patients with ischemic stroke were entered into CNSR. Among 11,675 patients with known time of stroke onset, 2,514 (21.5%) presented to the emergency department within 3 hours, 1,469 (12.6%) were eligible for thrombolytic treatment, and 284 (2.4%) were finally treated, 181 (1.6%) of them with intravenous rtPA. The median onset-to-needle time was 180 (interquartile range, 150 to 228) minutes; the median door-to-needle time was 116 (interquartile range, 70 to 150) minutes; the median imaging-to-needle time was 90 (interquartile range, 60 to 129) minutes. Patients who were younger, presented to the emergency department quicker, with higher National Institutes of Health Stroke Scale scores, having higher income, and better education had a better chance of receiving intravenous rtPA.

Conclusions—Approximately 1 in 5 patients with stroke presenting within 3 hours received thrombolytic therapy. The onset-to-needle time, door-to-needle time, and especially imaging-to-needle time were significantly longer than those in developed countries. Reducing prehospital and in-emergency department response time would help increase intravenous rtPA use in China. (Stroke. 2011;42:1658-1664.)

Key Words: registries ■ stroke ■ thrombolytic therapy

Stroke is the second leading cause of death after cancer in the world.1 However, stroke has become the leading cause of death among all diseases in China, which has one fifth of the total population in the world. Currently, >7 million Chinese have strokes, and approximately 65% of them are ischemic. Rising incidence and morbidity of stroke have created a heavy burden to the Chinese healthcare system.2-4 Since its approval in the United States in 1996, intravenous recombinant tissue plasminogen activator (rtPA) has been used in treating acute ischemic stroke (AIS) for >15 years in developed countries.5 With the reported rate of using rtPA between 1.2% and 9%,6-8 their experiences have identified many barriers of giving rtPA such as prehospital or in-hospital delay, short treatment time window, and lack of hospital infrastructure and readiness. Delay in presentation is the most common reason for exclusion. Many studies found that only approximately 20% to 25% of patients with acute stroke arrived in the hospital within 3 hours.6,9,10

In 2001, rtPA treatment for AIS was approved by the State Food and Drug Administration of China. However, little is known about its use in China. As the 1 and only government-funded national registry, the Chinese National Stroke Regis-
try (CNSR) has offered the opportunity to study how stroke care is delivered in China. Based on the data entered into the CNSR, we analyzed how intravenous rtPA has been used in China.

Methods

Registry Design and Site Selection
CNSR, sponsored by the Ministry of Health of China, is an ongoing national registry of patients presenting to hospitals with acute cerebrovascular events. Initiated in 2007, CNSR was designed to examine the current status of stroke care in China. The data would be used to help developing strategies to improve stroke care.

The following criteria were used to select the hospitals as a CNSR site: (1) targeting 1% of the total 13,372 general hospitals in China; (2) having at least 1 stroke neurologist; (3) at least 2 sites are included from each of the 32 provinces and 4 municipalities in China; (4) commitment to participate voluntarily; and (5) ability to conduct research. A total of 242 hospitals were included initially; 187 agreed to participate; 132 were finally selected by the CNSR steering committee. The majority (75.8%) of these hospitals were tertiary care hospitals. The size of neurology ward ranged from 30 to 187 beds (median, 64). Approximately 52.4% had stroke units and 63.8% had neurology coverage in the emergency departments (EDs). CT scan was available 24/7 in 99.2% of the study sites. Other than the availability of ED and digital subtraction angiography, all 132 sites were comparable in terms of hospital sizes, infrastructure, personnel, and available diagnostic procedures.

Case Enrollment and Target Population
From September 2007 to August 2008, the registry recruited consecutive patients who met the following criteria: (1) >18 years of age; (2) with any of the following conditions within 14 days of the index event: ischemic stroke, transient ischemic attack, intracerebral hemorrhage, or subarachnoid hemorrhage; (3) direct admission to the hospital from a physician’s clinic or ED; (4) written informed consent available from the patient or legal guardian; and (5) a patient with a diagnosis of stroke within 14 days of presentation.

Data Collection and Management
All research coordinators and study investigators were trained and certified to assess National Institutes of Health Stroke Scale (NIHSS) scores and modified Rankin Scale before the beginning of the trial. Trained research coordinators at each site reviewed medical records daily and identified, consented, and enrolled all eligible patients. A paper-based registry form developed by the advisory panel was used for data collection. Information collected included patient demographics, use of emergency medical services, the time of symptom onset and arrival at the ED, initial brain imaging, NIHSS scores, prestroke modified Rankin Scale, medical history, diagnosis, stroke management, and discharge status. Type of thrombolytics and doses, intravenous (IV), intra-arterial (IA), or IV and IA combination, treatment time, and reasons for not giving thrombolytic therapies were also recorded.

At each site, all data elements from each paper-based registry form were manually checked for completeness, correct coding, and proper application of diagnostic algorithm by a research specialist who had experience in clinical medicine from an independent contract research organization throughout the study period. A professional data processing company was responsible for the computer data entry. Beijing Translational Medicine Research Center (BTMRC), an independent research organization, served as the data analysis center.

Definition of Subjects Eligible for IV rtPA and the Dosages
The criteria used to select the eligible patient were based on the Michigan Acute Stroke Care Overview & Treatment Surveillance System (MASCOTS), which was a statewide hospital-based stroke registry.\(^3\) Patients who were eligible for IV rtPA treatment must be within 3 hours of stroke onset with no evidence of hemorrhage on the initial brain image and had no documented reasons for not being given IV rtPA.

We tracked the dosage used in all the centers in our registry. Some of the reasons why the patients were not treated with the 0.9 mg/kg rtPA were studied.

Survey on Reasons Causing In-ED Delay
To determine the factors associated with in-ED delay, we designed a substudy to examine any delay of door-to-needle time beyond 60 minutes. Items of this survey include (1) the process of obtaining consent; (2) completion of laboratory tests; (3) waiting for imaging interpretation; (4) waiting for family to purchase rtPA; and (5) others.

Statistical Analysis
For descriptive analysis, proportions were used for categorical variables; median with interquartile range (IQR) was used for continuous variables. Differences between IV rtPA-treated subjects and nontreated subjects were tested using nonparametric Kruskal-Wallis test for continuous variables and using the \( \chi^2 \) or Fisher exact test for categorical variables. Univariate logistic regression analysis was used to identify the demographic or clinical factors associated with the use of IV rtPA such as age, gender, education, marital status, type of health insurance, average monthly income per capita, NIHSS score on admission, prestroke MRS score at admission, onset to ED arrival time, medical history, antiplatelet/anticoagulant drug use before onset, admission ward, and the number of beds in neurology department. Unadjusted ORs and their corresponding 95% CIs were reported. To identity factors independently associated with the use of IV rtPA, multivariate logistic regression analysis was performed using backward selection method with significance level of \( P<0.05 \). The potential factors were selected from the univariate logistic analysis with overall association \( P<0.02 \), which was equivalent to maximize the model information criteria (Akaike information criterion). Type III adjusted ORs and the 95% CIs were reported.

The types of healthcare insurance were grouped into 3 categories: basic/government health insurance, rural cooperative insurance, and self-pay. The time of onset to ED arrival was divided into 3 intervals: <1 hour, 1 to 2 hours, and 2 to 3 hours. The severity of the presenting symptoms at admission was categorized into 3 levels by the NIHSS scores: <4, 4 to 14, and >14. For all analysis, a 2-tailed probability value of \(<0.05\) was considered significant and analyses were performed using SAS 9.1.3 (SAS Institute Inc).

Results

Demographics of the Patients Studied
A total of 22,216 patients with acute cerebrovascular events were entered into the registry during the 12-month study period. Of these registered patients, 14,702 (66.2%) were diagnosed with AIS on admission; 5221 (23.5%) had intracerebral hemorrhage; 1387 (6.2%) had transient ischemic attack; 767 (3.5%) had subarachnoid hemorrhage; and 1392 (6.2%) had cerebral hemorrhage; 1387 (6.2%) had transient ischemic attack; 767 (3.5%) had subarachnoid hemorrhage; and 1392 (6.2%) had intracerebral hemorrhage. Initiated in 2007, CNSR was designed to maximize the model information criteria (Akaike information criterion). Type III adjusted ORs and the 95% CIs were reported.

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The mean age was 65.0 ± 14.4 years and 39.3% were female. Of the registered patients, 14,702 patients with ischemic stroke, 7579 (54.1%) arrived at the ED by taxi, 2782 (18.9%) by emergency medical services, 2717 (18.5%) by private car, 378 (2.5%) by bikes/tricycles, and 884 (6.0%) by other means. Approximately 3027 (20.6%) were excluded because of missing baseline data (n = 176) and stroke onset time was unclear (n = 2851). Among patients with documented accurate onset time, the median onset-to-door time was 26.0 (IQR, 7.5 to 68.0) hours. The onset time of stroke was clear in 2514 (2514 of 11,675 [21.5%]) patients who presented to the ED within 3 hours of symptom onset (Figure 1).
Data on the Use of rtPA

A total of 1469 (1469 of 2514 [58.4%]) patients had no contraindications to thrombolysis and were therefore eligible for IV rtPA. Among them, 181 (181 of 1469 [12.3%]) received IV rtPA, 8 (8 of 1469 [0.5%]) had IA or IV+IA rtPA, and 95 (95 of 1469 [6.5%]) received IV or IA urokinase. In the IV rtPA group, 102 (56.35%) received 0.9 mg/kg rtPA and 79 (43.65%) received lower doses. Among them, 45 (56.96%) patients received 0.6 to 0.8 mg/kg tPA because the treating physicians felt that such a dosage range was also effective; 31 (39.24%) patients received total of 50 mg because these patients could not afford higher doses. Infusion was stopped in 3 patients because their neurological conditions deteriorated.

For 1045 patients presenting within 3 hours of onset but did not get rtPA, the reasons for not treating are listed in Table 1.

The median onset-to-needle time in CNSR was 180 (IQR, 150 to 228) minutes (Figure 2). The median door-to-needle time was 116 (IQR, 70 to 150) minutes (Figure 3A). The median imaging-to-needle time was 90 (IQR, 60 to 129) minutes (Figure 3B). The median onset-to-needle time in the study was longer than those seen in developed country registries, including the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) registry and Registry of the Canadian Stroke Network (31 hospitals in 8 provinces)\textsuperscript{13} (Figure 2). The door-to-needle time in the EDs between China and developed countries was also compared. The time in CNSR was longer than those in SITS-MOST, Ethos,\textsuperscript{14} and Registry of the Canadian Stroke Network registries (Figure 3A).

The In-ED Delay Substudy

Eighteen (13.64%) tertiary care hospitals and 14 (10.61%) secondary care hospitals participated voluntarily in the sub-study of reasons of in-ED delaying door-to-needle time beyond 1 hour; 344 (59.4%) of the 579 patients arriving at the ED within 3 hours of symptomatic onset were eligible for thrombolytic therapy. Among 344 patients, 45 (13.1%) did receive the treatment within 3 hours from onset, but the door-to-needle time was beyond 1 hour in 37 (82.22%) patients. The most common reasons documented by the physician for the in-ED delay included the time needed to obtain consent (n=16 [43.24%]), delay in completing labo-
ratory tests (n=1045 [24.32%]), waiting for the family to purchase rtPA (n=1080 [21.62%]), and others (n=444 [10.81%]).

Variables That Impact the Rate of Treatment

In univariate logistic analysis, statistically significant differences were detected between the IV rtPA treatment group (181 patients) and untreated group (1185 patients) in the following variables: age, hypertension, education, types of health insurance, average monthly income per capita, NIHSS scores on admission, onset to ED time, ED arrival mode, and admission destination (Table 2).

In age subgroups, younger patients (18 to 45 years old) were more likely to receive thrombolytic treatment than other age subgroups (46 to 65 years, 66 to 75 years, and >75 years). Compared with patients with <4 NIHSS scores, patients with 4 to 14 NIHSS scores on admission were 4 times more likely to receive IV rtPA, whereas patients with >14 NIHSS scores on admission were 7 times more likely to get thrombolytic treatment. Also, earlier onset to ED arrival time significantly increased the odds of receiving IV rtPA. Compared with arriving 2 to 3 hours after the onset, patients arriving earlier than 2 hours received IV rtPA more frequently (OR, 2.17; 95% CI, 1.45 to 3.2 and OR, 1.57; 95% CI, 1.03 to 2.4, respectively). In addition, there was a significantly higher rate of giving rtPA to patients who had better education and higher average monthly income.

Patients were able to get brain scans quickly on arrival in the ED in China, which was similar to the findings in the developed countries. However, there was a significant delay following variables: age, hypertension, education, types of health insurance, average monthly income per capita, NIHSS scores on admission, onset to ED time, ED arrival mode, and admission destination (Table 2).

Results of the final multivariate model identifying factors associated with IV rtPA use are shown in Figure 4. Age, education, average monthly income per capita, NIHSS scores on admission, and onset to ED arrival time remained significant in multiple regression analysis after adjustment for other potential factors.

Figure 2. Comparison of onset-to-needle times for patients receiving intravenous recombinant tissue plasminogen activator (IV rtPA) among different registries. Data are shown in median time (minutes); Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): 285 centers in 14 countries; Registry of the Canadian Stroke Network (RCSN): 31 hospitals in 8 provinces; Ethos in the United States: 86 hospitals in 23 states; China National Stroke Registry (CNSR) in China: 132 hospitals in 32 provinces.

Table 1. Reasons Documented for Not Giving IV rtPA to 1045 Patients Within 3 Hours of Symptom Onset

<table>
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<tr>
<th>Reasons (n=1045)*</th>
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<tr>
<td>Age &gt;80 y</td>
<td>139 (13.30%)</td>
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<tr>
<td>Stroke too severe (NIHSS &gt;25)</td>
<td>56 (5.36%)</td>
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<td>Stroke symptoms had significantly improved before rtPA therapy</td>
<td>437 (41.82%)</td>
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<td>Major early infarct signs involving greater than one third of the middle cerebral artery territory on the CT scan</td>
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<td>Uncontrolled hypertension</td>
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<td>Known history of ICH, brain aneurysm, or hemorrhagic diathesis within the last 6 mo</td>
<td>18 (1.72%)</td>
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<td>Blood glucose &lt;50 or &gt;400 mg/dL</td>
<td>2 (0.19%)</td>
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<td>Platelet count &lt;100 000/mm³</td>
<td>3 (0.29%)</td>
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<td>PT (INR) &gt;1.4, PT &gt;15, or APTT &gt;40 s</td>
<td>6 (0.57%)</td>
</tr>
<tr>
<td>Time window became &gt;3 h because of delay in hospital</td>
<td>712 (68.13%)</td>
</tr>
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<td>Consent was not available</td>
<td>171 (16.36%)</td>
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*Record regarding the reasons why rtPA was not administered to patients with ischemic stroke within 3 hours of symptom onset was designed as a multi-item check box. Thus, physicians could choose >1 contraindication. No. of patients with documented contraindications to thrombolysis was noted separately from the no. of reasons for not giving thrombolytic drug.

**IV indicates intravenous; rtPA, recombinant tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time.**

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between the completion of the brain imaging and the administration of IV rtPA (Figure 3B).

**Discussion**

Similar to the SITS-MOST data, our study showed that 1 in 5 (19.3%) patients with AIS received IV rtPA (12.3%), IA rtPA, or IV and IA rtPA (0.5%) or IV and IA urokinase (6.5%) when presenting to the ED within 3 hours in China. Overall, approximately 2% of all patients with acute AIS in this study were treated with thrombolytics, which was lower than the rate of treatment in Europe.\(^\text{15}\)

The majority (82.9%) of patients with AIS in CNSR arrived at the ED beyond 3 hours (median time, 26.0 hours). The median time from onset to treatment was 180 minutes, longer than that seen in developed countries.\(^\text{13,16}\) Many reasons were accountable for this concerning prehospital delay: inability to recognize stroke signs and symptoms by patients or their families, a wait-and-see attitude, and unwilling to call emergency medical services unless the stroke is severe.\(^\text{17}\) In the CNSR, more than half of the patients with AIS (54.1%)
arrived at the ED by taxi, and less than 1 in 5 (18.9%) used emergency medical services. For those who arrived at the ED quicker, they were likely to be treated.

The median door-to-needle time was 116 minutes, longer than that reported in the developed countries. However, the time between the ED arrival to CT or MRI scanning was similar to the reported time in the developed countries. It is especially concerning that the imaging-to-needle time was nearly twice as long in China. We have identified several factors that would be accountable for such a delay: a long process of obtaining consent, delay in completing laboratory testing, long wait for the family to buy rtPA, and physicians’ nihilistic attitude. It usually takes a long time to obtain written consent from the family because there is often a trust issue between the family and the treating physician in China. What is also of concern and perhaps unique in China is that the patients and their families of low socioeconomic status would have to find money to purchase the drug first before it could be given. Before 2008, the cost of rtPA was not covered by healthcare insurance in China. The price was close to 8500 Yuan ($1255 US) for a patient with an average body weight of 70 kg (5700 Yuan per ampoule containing 50 mg).

In CNSR, patients with a higher income (>1000 Yuan/month) were nearly twice likely to receive IV rtPA. The present study was conducted before the national healthcare insurance coverage of rtPA treatment for patients with AIS. The current condition may have improved because the healthcare insurance has covered rtPA treatment since 2008.

Many Chinese physicians are still concerned about the safety of using IV rtPA. They would overemphasize the adverse effect of rtPA such as symptomatic intracerebral hemorrhage. Such an attitude from the treating physician would have a negative impact on patients or their families, who would then likely refuse IV rtPA.

The reason that younger patients were more likely to receive rtPA is due to their better knowledge of rtPA and much higher expectation of a better outcome after stroke. It is a good example that better education would facilitate acute treatment of AIS.

Patients with more severe stroke were more likely treated with IV rtPA. The possible explanation was that there was the belief that severe strokes (NIHSS 4 to 25) may have a better benefit.18

Similar to previous reports by different countries in Asia,19,20 we also found that approximately 44% patients received doses 0.9 mg/kg in hospitals participating in CNSR. Besides the economic reason, the belief held by many physicians was that lower-dose rtPA (0.6 to 0.8 mg/kg) offered similar efficacy as doses of 0.9 kg/mg.20 This issue may need to be settled further by clinical trials in the future.

Limitations of the Study

There were several limitations in our study. The participating hospitals in CNSR were selected based on geographical differences. These study sites were tertiary care hospitals and therefore had more resources and stroke neurologists than smaller hospitals in rural areas. Because nearly 70% of populations in China live in rural areas and patients with stroke may go to rural hospitals first, it is likely that the rate of using IV rtPA could be even lower. Furthermore, only some hospitals participated in the in-ED delay substudy. Often time was documented by the estimation of the treating physicians. Therefore, there could be selection and information biases. A more comprehensive study of the reasons related to prehospital and in-ED delay would be needed and help to improve the thrombolytic use in China.

Conclusions

Based on the data from CNSR, the rate of using IV rtPA in China is lower than that in Europe. Many barriers that are unique to Chinese culture prevented more successful use of IV rtPA. Many challenges lie ahead in treating patients with AIS in China. Much work still needs to be done to improve the knowledge of stroke and available treatment for stroke among the public and healthcare professionals. In addition,
there is a need to better organize the healthcare delivery systems and better documentation. We plan to study this issue again once the interventions have been completed and hopefully, the rate of using IV rtPA to treat eligible patients with AIS will substantially improve in China.

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Disclosures
None.

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