Intravenous Thrombolytic Therapy for Acute Ischemic Stroke: The Experience of A Community Hospital

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Abstract-

Background and Purpose: Tissue plasminogen activator (tPA) is a standard therapy for acute ischemic stroke (AIS) but only limited data are noted in Taiwan. The purpose of this study was to assess the safety, feasibility, and efficacy of treatment in a community hospital setting.

Methods: We retrospectively reviewed the medical records of all patients who had received intravenous tPA therapy from 1998 to 2007 in our hospital. We compared the characteristics, complications, and outcomes in our patients with those of patients in the National Institute of Neurological Disorders and Stroke (NINDS) trial.

Results: A total of 43 patients were reviewed with a mean age of 63 years and a male predominane (64%). The median pretreatment National Institutes of Health Stroke Scale score was 18. In our patients, cardioembolism was the leading course of the strokes. The mean time from stroke onset to treatment was 134 minutes, and the mean door-to-computed tomography-time was 34 minutes while the mean door-to-needle time was 93 minutes. Within 36 hours symptomatic intracerebral hemorrhage occurred in two patients (4.7%). Four patients (9.3%) developed brain herniation with fatality. At follow-up, fourteen patients (33%) had a favorable outcome on the modified Rankin Scale (0-1). Patient outcome was not significantly different from that in the NINDS trial.

Conclusion: Although the number of patients with AIS receiving tPA in this study was small, thrombolytic therapy can be performed safely and effectively by physicians in the community hospital setting.

Key Words: Ischemic stroke, Thrombolytic therapy, Tissue plasminogen activator

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INTRODUCTION

The use of intravenous tissue plasminogen activator (tPA) is now a standard therapy for acute ischemic stroke (AIS) in selected patients. The approval of tPA in treating stroke patients within three hours of onset was based primarily on the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study

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Group trial[1]. The tPA treatment for AIS patients was shown to be beneficial despite a symptomatic intracerebral hemorrhage (ICH) rate of 6.4%. Several studies supported the safety of thrombolytic therapy in clinical practice[2]. Overall, the proportion of stroke patients who actually received tPA therapy varied widely in different community practices[3-6].

Stroke remains one of the major causes of death in Taiwan. Unfortunately, there have been scarce data on thrombolytic therapy for stroke in Taiwan[7,8]. In one study, Lien et al.[7] found that a high percentage of violations to the NINDS protocol led to high incidences of symptomatic ICH and low chances of a favorable functional outcome. Therefore, we presented our experience with intravenous tPA for AIS by assessing the feasibility of a 3-hour time window and comparing the safety data and outcome with those described in the NINDS trial.

METHODS

Chia-Yi Christian Hospital (CYCH) serves an area that includes Chiayi City, Chiayi County, southern Yunlin County, and northern Tainan County with a population of approximately 1,000,000 people. There are seven other regional hospitals in this area. Around 600 patients are admitted each year with a diagnosis of AIS.

We retrospectively reviewed the medical records of all patients who were treated with intravenous tPA for AIS at our hospital from 1998 to 2007. Stroke patients who presented to our emergency room (ER) were screened by an emergency doctor to determine eligibility for thrombolytic therapy. All potentially eligible patients were then examined by a neurologist. Treatment decisions were made by the neurologist mainly based on the NINDS protocol. After 2004, the tPA usage criteria of The Bureau of National Health Insurance (BNHI) was also taken into account. The pretreatment clinical severity was measured by the neurologist using the National Institutes of Health Stroke Scale (NIHSS). Intravenous tPA was administered at a dose of 0.9 mg/kg. After being admitted to an intensive care unit, patients were surveyed for the risk factors of strokes. We performed neuroimaging studies 24 to 36 hours following thrombolysis for each patient. Extracranial and intracranial circulation was examined by means of color-coded duplex sonography.

Using a standardized data extraction form, we recorded patient demographics, risk factor profiles, blood pressure, laboratory parameters, time of symptom onset, time of arrival at the ER, time to computed tomography (CT), time to tPA administration, and medications. We also documented all complications related to the tPA therapy. We classified stroke subtypes according to Trial of Org 10172 in Acute Stroke Treatment criteria[9] and the Oxfordshire Community Stroke Project[10]. Functional outcomes were obtained from the medical records three months after stroke onset or at the last visit by using the modified Rankin scale (mRS). A score of 0 or 1 on mRS was considered to be a favorable outcome.

To compare our data with those from the NINDS treatment cohort, χ^2 tests or Fisher's exact tests were used. Differences in continuous variables were compared by use of the Student's *t* test.

RESULTS

Forty-three patients (27 men, 16 women) received intravenous tPA for AIS from 1998 to 2007. These represented 0.8% of all ischemic stroke patients admitted to CYCH. The ratio increased from 0.2% in 1998 to 1.6% in 2007. The mean age was 63 years, which was younger than that in the treatment group of the NINDS trial. The median pretreatment NIHSS score was 18 (range from 6 to 32). As compared with the stroke risk factors in the NINDS trial, more patients had atrial fibrillation (AF) and fewer patients were on aspirin at the time of stroke (Table 1). In contrast to the results of the NINDS trial however, most of our patients (79%) suffered from cardioembolic strokes (Table 2). AF was seen in 27 patients (63%), mechanical valve replacement in 2 (4.7%), myocardial infarction within 4 weeks in 2 (4.7%), atrial myxoma in 2 (4.7%), and sick sinus syndrome in 2 (4.7%).

Symptomatic ICH during the first 36 hours occurred in 2 patients (4.7%), both of whom were male and nondiabetic. The rate of symptomatic ICH did not differ sig-

Table 1. *Patient characteristics in CYCH and comparison with NINDS*

Characteristic	CYCH (n = 43)	NINDS, Part II (n = 168)
Age, mean (SD), year *	63 (13)	69 (12)
Male, %	64	57
NIHSS, median (range)	18 (6-32)	14 (2-37)
Blood pressure, mmHg		
Systolic, mean (SD)	150 (29)	153 (22)
Diastolic, mean (SD)	86 (16)	85 (14)
Glucose, mean (SD), mg/dL	134 (55)	149 (66)
Stroke risk factors, %		
Hypertension	77	67
Atrial fibrillation **	63	20
Diabetes mellitus	21	20
Hyperlipidemia	56	–
Prior strokes	19	12
Smoking	28	27
Prior aspirin use *	19	40

*: P < 0.01; **: P < 0.0001; SD: standard deviation; CYCH: Chia-Yi Christian Hospital; NINDS: National Institute of Neurological Disorders and Stroke.

Table 2. *Stroke subtypes and clinical stroke classifications of ischemic strokes*

Variable, %	CYCH (n = 43)	NINDS, Part II (n = 168)
Stroke subtype		
Small-vessel occlusive	0	14
Large-vessel occlusive	5	39
Cardioembolic	79	45
Undetermined/other	16	2
Clinical syndromes		
TACI	61	
PACI	30	
POCI	9	
LACI	0	

TACI indicates total anterior circulation infarct; PACI: partial anterior circulation infarct; POCI: posterior circulation infarct; LACI: lacunar infarct; CYCH: Chia-Yi Christian Hospital; NINDS: National Institute of Neurological Disorders and Stroke.

nificantly from that (6.4%) in the NINDS trial (P = 0.55). One of them, a 51-year-old man, had AF and took aspirin regularly. He underwent craniectomy with removal of the hematoma[11]. He had moderate disability, graded 3 on the mRS, at three months after a stroke. The other patient was 74 years old and had signs of early infarct on CT scan. He received conservative treatment and his mRS remained at a level of 3 at three months following his stroke. One patient (2.3%) suffered from asymptomatic ICH. Another two patients (4.7%) experienced hemorrhages at other sites. Both of them had gum bleeding and one had facial bruising.

Four patients were treated beyond the three-hour time window (185, 190, 205, and 224 minutes respectively). The pretreatment CT revealed hypodensity involving more than 1/3 of the middle cerebral artery territory in one patient. One patient had a favorable outcome and none of them experienced symptomatic ICH. Another 30-year-old man, with mechanical valve replacement and AF, developed clinical symptoms and signs of brain stem infarction. His pretreatment NIHSS score was 32, which was against the tPA usage criteria of BNHI. However, he had a full return to normal function before discharge.

The mean time from stroke onset to treatment was 134 minutes (range: 30 to 224 min). The mean door-to-CT time was 34 minutes and the mean door-to-needle time was 93 minutes. There was no relationship between the time from stroke onset to ER arrival and the door-to-needle time. Although a neurologist was on call around the clock for potential thrombolytic cases, he/she usually stayed at the hospital only in weekdays during daytime hours. Therefore, we tried to determine if the time intervals to action were different depending on whether the neurologist was at the hospital when he/she was paged. For those patients who presented to the ER, the onset-to-needle time, onset-to-door time, and door-to-needle time were similar. However, there was significant difference in the door-to-CT time (P = 0.02). It took a longer time for patients who arrived at our ER during daytime on weekdays to finish the CT scan (Fig. 1).

Two patients in our series were inpatients at the time of stroke onset. Both patients were admitted for other

medical problems. It took 88 and 106 minutes from stroke onset to CT, and 140 minutes from stroke onset to treatment. Both CT and treatment were delayed for the ward patients.

At the time of hospital discharge, 29 patients (67%) experienced a 4-point or more improvement in the NIHSS score. At the time of follow-up, 14 patients (33%) had a favorable outcome on the mRS (Fig. 2), which was not significantly different from the data of NINDS treatment group at 3 months (P = 0.35). Four patients (9.3%) died before discharge, which was lower than the mortality rate (17%) at 3 months in the NINDS trial but no statistical significance was noted (P = 0.22). All of them died of herniation due to cerebral edema without any hemorrhagic transformation (HT).

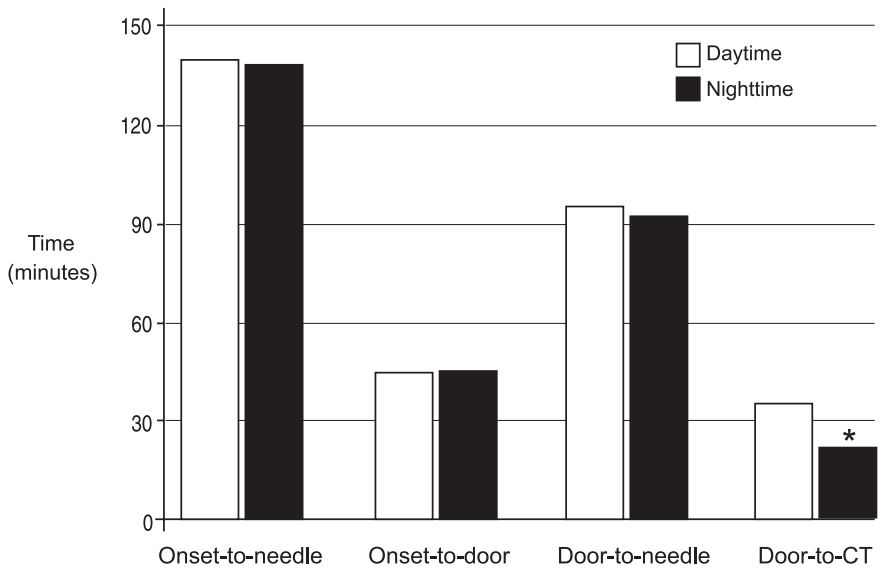

Figure 1. For patients with acute ischemic stroke directly presenting to the ER, the time intervals were similar whether they arrived during daytime or nightime on weekdays except for the door-to-CT time. (*P = 0.02).

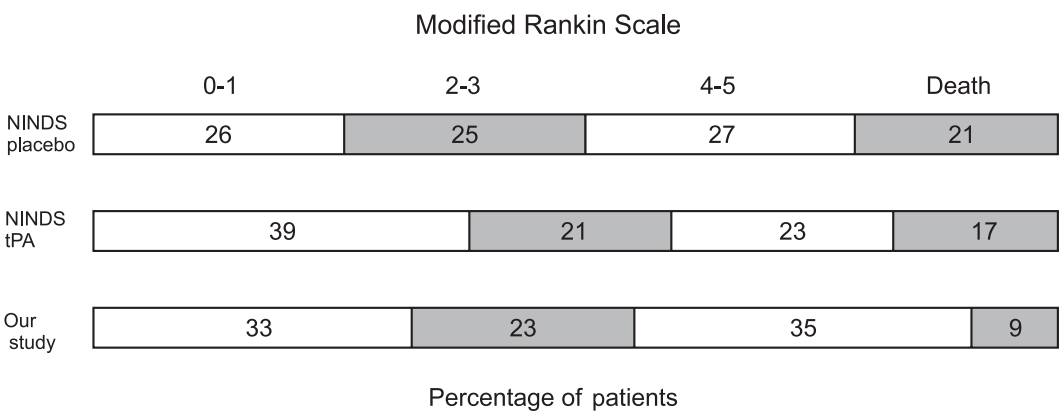

Figure 2. Functional outcome of CYCH patients at follow-up compared with patients in NINDS trial at three months.

DISCUSSION

Controlled multicenter trials have proved the efficacy of IV tPA treatment in selected cases of AIS[1,12]. The feasibility of this therapeutic option in clinical practice has been assessed in other community-based studies[3-6]. Our data showed some differences in comparison with the results of other studies.

The most common etiology of strokes in our series was cardioembolism, which was secondary to AF in most patients. In contrast to the data of NINDS trial, the patients with cardioembolic stroke considerably outnumbered the cases due to other etiologies (Table 2). The most common clinical syndrome was total anterior circulation infarct. There was no case of lacunar infarct in our series. In the NINDS trial, patients with cardioembolic stroke had less chance to achieve a favorable outcome than those with lacunar infarct. The predominance of cardioembolic stroke could explain the higher pretreatment NIHSS scores and lower rate of favorable outcome in our series. Strokes secondary to cardioembolism usually produce maximal deficit at onset and are prone to causing decreased consciousness due to massive infarction such as total anterior circulation infarct[13]. Patients with severe neurologic deficits tended to present to the ER early after symptom onset[14,15]. As a result they were more likely to arrive in time for thrombolytic therapy. On the contrary, lacunar strokes typically produce mild symptoms at onset which are probably neglected by patients and family members in Taiwan. Consequently, patients with lacunar strokes may have a longer delay between symptom onset and arrival at the ER. We found a similar distribution of etiologies in a Japanese study[16], in which 77.7% of their patients suffered from cardioembolic strokes. This implies that education of general population about stroke identification and immediate response to strokes can result in a better outcome.

In a meta-analysis of safety data from 15 open-label studies[2], symptomatic ICH occurred at 36 hours in only 5.2% of patients, suggesting that tPA is potentially safe in clinical practice. Protocol violation may predispose patients to symptomatic ICH[17-19]. Other factors which can predict symptomatic ICH include stroke severity, mass effect or hypodensity in head CT and old age[20,21]. Although we had four patients with time violations, one with large hypodensity on CT, and one with severe initial symptoms, no patients suffered from symptomatic ICH. The rate of symptomatic ICH in our series was 4.7%, which was comparable to that in the NINDS trial. Some may have concern about the racial differences in thrombolytic effect and hemorrhagic complications by using tPA[22,23]. A dose of tPA at 0.6 mg/kg was used in Japan [16]. Nevertheless, our experience showed that a dose of 0.9 mg/kg was safe.

While HT is a natural consequence of cerebral infarction and it happens in up to 71% of cardioembolic strokes[13], in our study, HT only occurred in 7.0 % of our patients despite the predominance of cardioembolic strokes. The incidence of HT on CT after a cardioembolic stroke increases with the time[24]. Within 24 hours after stroke onset, the percentage of HT could be as low as 5%[25]. Since we performed the second neuroimaging study between 24 and 36 hours after strokes, we probably underestimated the incidence of HT especially for those patients who developed HT beyond 36 hours without clinical deterioration. In addition, early spontaneous recanalization in less than 6 hours after a cardioembolic stroke was associated with no HT[26] while the majority of tPA-indueced recanalizations occur during the first hour after treatment[27]. Based upon these observations, we speculated that the overall rate of HT after cardioembolic strokes might be reduced by successful treatement with tPA.

The mean door-to-CT time (34 minutes) and the mean door-to-needle time (93 minutes) were longer than those recommended by the NINDS. They recommend that from the time of arrival at the ER, a patient with AIS should undergo CT examination within 25 minutes and receive tPA within 60 minutes[28]. At CYCH, patients who arrived at the ER during nighttime hours were inclined to receive CT scans sooner. This might be because during the daytime, our CT services were preoccupied by scheduled examinations. However, the advantage of early CT examination at nighttime did not shorten the time intervals from door to treatment. This was probably due to delayed evaluation by the neurologists.

Physicians who are not neurologists tend not to give patients thrombolytic treatment[5]. Although the number of in-hospital strokes was small, two patients who had an in-hospital stroke had marked delays in CT examination. This might be due to unfamiliarity of a thrombolytic treatment in non-ER setting.

According to previous studies, predictors of good outcome after thrombolysis include milder baseline stroke severity, no history of diabetes mellitus, normal pretreatment blood sugar, normal pretreatment blood pressure, treatment within 90 minutes, and a normal CT scan[29-32]. The pretreatment NIHSS of our patients was slightly higher than those in the NINDS trial, but our mortality rate was lower although it did not reach statistic significance. The overall outcome at three months was comparable to that of the NINDS trial. This demonstrates that intravenous tPA is an effective treatment in our patients.

Despite academic acceptance of intravenous tPA therapy for AIS, many neurologists have been unwilling to use it in community practice settings[33]. Although our study has some flaws, including: a small number of patients, retrospective design, and lack of a control group, our data offer Taiwanese experience on tPA therapy. Furthermore the efficacy and safety results are consistent with those of multicenter trials. In conclusion, intravenous tPA can be a feasible, safe, and effective treatment for AIS in the community hospital setting by providing the protocol for physicians.

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