Increased Use of Thrombolytic Therapy and Shortening of In-Hospital Delays Following Acute Ischemic Stroke: Experience on the Establishment of a Primary Stroke Center at a Community Hospital

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Abstract-

Purpose: To improve and standardize stroke care, the establishment of primary stroke centers (PSCs) has been advised. Thrombolytic therapy has been proved to improve the outcome of acute ischemic stroke (AIS). We assessed the use of thrombolytic therapy before and after setting up a PSC at a community hospital.

Methods: In November 2007, a PSC was established at our hospital. Following guidelines based on national recommendations, we administered intravenous tissue plasminogen activator (tPA) to patients who met the criteria. To study the effects of the establishment of the PSC on tPA treatment rates, we examined our database of stroke patients dating back to January 2004.

Results: Before the establishment of the PSC, there have been 2420 patients admitted to our hospital diagnosed with AIS. Only 1.2% of these patients were treated with intravenous tPA. Following the establishment of the PSC, 2.8% of 1151 AIS patients were treated with tPA. Time of patient arrival to patient treatment was also diminished.

Conclusion: The establishment of the PSC significantly increases the usage of tPA treatment. Furthermore, response time to patient cases was also quicker. However, for maximum effectiveness, the public still needs to be made more aware of the risks of stroke and the importance of seeking medical care at the first signs of stroke.

Key Words: ischemic stroke, primary stroke center, thrombolytic therapy

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INTRODUCTION

Intravenous tissue plasminogen activator (tPA) is the only approved treatment for acute ischemic stroke (AIS). However, it should be administered within 3 hours of stroke onset according to most guidelines for acute stroke treatment, including Taiwan Guidelines for the Management of Stroke[1]. The narrow time window

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limits the use of thrombolytic therapy. Furthermore, the physicians' fear of legal liability due to the serious adverse effects of tPA, poor public awareness of stroke symptoms, and a lack of training for both neurologists and emergency medicine physicians in the use of the treatment are among the potential reasons preventing its use[2]. In Taiwan, The Bureau of National Health Insurance (BNHI) approved the reimbursement for the use of tPA on patients with AIS in January 2004. However, a 2006 national survey of stroke center status in Taiwan revealed that less than 1% of patients with AIS received thrombolytic therapy[3].

To increase the use of tPA, widespread creation of primary stroke centers (PSCs) has been recommended[4]. Two major goals for a PSC are to improve the level of care and to standardize certain aspects of acute care provided to the stroke patients[4,5]. The Brain Attack Coalition (BAC) has identified 11 key elements that are necessary for establishing a PSC[4]. These elements can be subdivided into patient care areas and support services. The former group consists of an acute stroke team, a stroke unit, written care protocols, a well-trained emergency department, neurosurgical services, and an integrated emergency response system. The latter group includes availability and interpretation of computed tomography (CT) scans 24 hours everyday and rapid laboratory testing, administrative support and strong leadership, measures for outcome and quality improvement, and continuing education. Through these efforts, the use of tPA could be increased and hence the outcomes of stroke could be improved. In the experience of the US, the establishment of a PSC at a community hospital substantially increased the proportion of stroke patients receiving thrombolytic therapy[6]. We tried to determine whether this experience can be reproduced at a community hospital in Taiwan.

METHODS

Our hospital serves an area with a population of approximately 1,000,000 people. It did not have an acute stroke team until November 2007, when this hospital established its PSC following the published recommendations as closely as possible[4]. The existing laboratory, neuroimaging, and neurosurgical resources were adequate to support a PSC. The acute stroke team consisted of neurologists only, who were on call around the clock for potential thrombolytic cases. Written protocols for acute stroke, with the emphasis on the initiation of urgent diagnostic tests and rapid notification of the stroke team, were developed and implemented. Documents of these protocols were available in the emergency department (ED). Since tPA should be used within the 3-hour time window, the stroke code was activated only for patients who arrived within two hours of stroke onset, sparing one hour for the completion of neuroimaging and laboratory studies. ED physicians screened patients to determine the eligibility of thrombolytic therapy based on the tPA usage criteria of the BNHI. When the initial evaluation did not reveal a contraindication and CT did not show hemorrhage, the neurologist on the acute stroke team was notified. Treatment decisions were made by the neurologist. Stroke educational activities related to stroke diagnosis and treatment, with focus on patient evaluation by the National Institutes of Health Stroke Scale (NIHSS), tPA use, and post-thrombolytic care were held for ED personnel and nursing staff in our stroke unit.

Since January 2004, when tPA was reimbursed by the BNHI for treatment of AIS, we have kept a database of patients receiving thrombolytic therapy. From November 2007 we registered all stroke patients who were admitted to the hospital. We prospectively collected information about demographic data, type of stroke each patient experienced, type of treatment provided, presentation times, treatment times, laboratory results, radiological times and findings, results of stroke scale, risk factors, complications, disposition, and measurement of outcomes. To evaluate the safety of thrombolytic therapy, we defined symptomatic intracranial hemorrhage (SICH) as any hemorrhage plus a neurological deterioration of ≥ 4 points on the NIHSS baseline or from the lowest NIHSS value after baseline to 7 days or leading to death[7,8]. The data collection had been approved by the Institutional Review Board of the hospital. Reports of time intervals and barriers to treatment

were communicated to the ED staff on a monthly basis.

For those patients who received thrombolytic therapy before and after the establishment of PSC, we compared their time intervals between arrival at the ED and action and outcome. To determine whether more stroke patients were transported to our hospital earlier, we retrospectively reviewed the medical records of all patients admitted with a diagnosis of AIS from November 2006 to October 2007 and recorded the time of onset, ED arrival, and completion of brain CT. Median values of the time intervals were used for descriptive statistics because of their non-normal distributions. Comparison of median values was done with the Mann-Whitney test. The T test was used to evaluate differences in continuous variables and either the chi-square test or Fisher's exact test were used for proportion data. A value of $p < 0.05$ was regarded as significant.

RESULTS

From January 1, 2004 to October 31, 2007, a total of 2420 patients were admitted to the hospital with a diagnosis of AIS. Twenty-nine patients (1.2%, 95% confidence interval [CI], 0.8% to 1.7%) were treated with intravenous tPA. During the 20 months after the establishment of the PSC in November 2007, 32 patients (2.8%, 95% CI, 2.0% to 3.9%) out of 1151 patients diagnosed with AIS were treated with intravenous tPA. The rate of tPA use was significantly increased with establishment of PSC (Table 1). The pretreatment NIHSS scores were comparable between these two groups (median 18 vs. 15). The median door-to-CT time decreased from 21 minutes to 16 minutes and the median door-to-needle time significantly decreased from 85 minutes to 67 minutes. The median onset-to-needle time decreased from 128 minutes to 110 minutes. SICH occurred in 2 patient (6.9%, 95% CI, 1.9% to 22.0%) before PSC and in 4 patients (12.5%, 95% CI, 5.0% to 28.1%) after PSC. Before PSC, 8 patients (27.6%) had a favorable outcome (modified Rankin scale [mRS] ≤1), and 11 (37.9%) recovered functional independence (mRS ≤2) at 3 months or last seen. After PSC, 10 patients (31.3%) had a favorable outcome, and 15 (46.9%) recovered functional independence.

Table 1. *Patients with thrombolytic therapy before and after the establishment of primary stroke center*

	1/1/2004-10/31/2007	11/1/2007-6/30/2009	*P* value
Hospitalized ischemic stroke (total)	2420	1151	
Treated with tPA, n (%)	29 (1.2)	32 (2.8)	< 0.001
Age, y	62.8 ± 14.3	64.5 ± 11.9	0.620
Female, n (%)	10 (34.5)	7 (21.9)	0.392
Hypertension, n (%)	23 (79.3)	26 (81.3)	1.000
Diabetes mellitus, n (%)	6 (20.7)	12 (37.5)	0.172
Serum glucose, (mg/dL)	138.1 ± 57.4	168.6 ± 69.9	0.076
Aspirin before admission, n (%)	2 (6.9)	8 (25.0)	0.085
Pretreatment NIHSS, median	18	15	0.218
Interval times, median; min			
Door-to-CT	21	16	0.045
Door-to-needle	85	67	0.016
Onset-to-needle	128	110	0.058
Outcome			
SICH, n (%)	2 (6.9)	4 (12.5)	0.674
mRS ≤ 1, n (%)	8 (27.6)	10 (31.3)	0.786
mRS ≤ 2, n (%)	11 (37.9)	15 (46.9)	0.606

CT = computed tomography; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; SD = standard deviation;SICH = symptomatic intracerebral hemorrhage; tPA = tissue plasminogen activator.

Table 1. *Arrival times and percentage of thrombolytic therapy before and after the establishment of primary stroke center*

	11/1/2006-10/31/2007	11/1/2007-6/30/2009	*P* value
Hospitalized ischemic stroke (total)	693	1151	
Time from onset to door			
≤ 2 h, n (%)	106 (15.3)	229 (19.9)	0.0131
≤ 3 h, n (%)	133 (19.2)	276 (24.0)	0.0166
Treated with tPA			
Of total, n (%)	11/693 (1.6)	32/1151 (2.8)	0.1123
Of arrival ≤ 2 h, n (%)	11/106 (10.4)	32/229 (14.0)	0.3869

tPA = tissue plasminogen activator.

During the 12 months before the establishment of PSC, 19.2% of patients presented to the ED within 3 hours of symptom onset and 15.3% within 2 hours. After the establishment of PSC, 24.0% of patients arrived at ED within 3 hours and 19.9% within 2 hours (Table 2).

After the establishment of the PSC, for the 229 patients who presented within 2 hours of symptom onset, 14.0% (32/229) were treated with intravenous tPA, which accounted for 68.1% (32/47) of patients eligible for thrombolytic therapy. The remaining 15 patients who did not receive thrombolytic therapy either refused the treatment or were delayed in the diagnosis and management. Among the 182 patients who were not eligible according to the BNHI tPA usage criteria, the reason for nontreatment included sugar greater than 400 mg/dL in 4 patients, age older than 80 in 41, NIHSS score < 6 in 106, NIHSS score > 25 in 19, platelet < 100,000 in 3, INR > 1.3 in 2, prior stroke with diabetes mellitus in 34, onset with seizure in 6, and high blood pressure in 60. Time from patient arrival at hospital to time of brain CT completion decreased from a median of 37 to 21 minutes (3-month running average). Time of arrival to evaluation by acute stroke team decreased from a median of 77 minutes to 56 minutes.

DISCUSSION

To improve the proportions of thrombolysis use for AIS, some interventions may be helpful. Among the 11 major criteria for the establishment of PSCs recommended by the BAC, seven were associated with increased tPA use, including written care protocols, integrated emergency medical services, organized emergency departments, continuing medical education, availability of an acute stroke team, existence of a stroke unit and rapid neuroimaging services[9]. Another study conducted in Taiwan indicated routine tPA protocol in the emergency room and supervision by the stroke center director increased the administration of tPA significantly[10]. Before the establishment of the PSC, we did not have a standard care pathway for stroke patients presented to the ED and ED staffs were not well trained in acute stroke care regarding the use of thrombolysis. So ED staffs might fail to identify all potentially eligible stroke patients and to treat them with high priority. By following the aforementioned recommendations for the PSC, we achieved a 2.3-fold increase in the proportion of stroke patients treated with tPA. Thirty-two patients were treated, representing 2.8% of all ischemic stroke cases, 14.0% of those patients who presented to the hospital within 2 hours of symptom onset, and 68.1% of eligible patients.

Since intravenous tPA should be administered within the narrow 3-hour time window, a substantial proportion of patients who arrived early did not receive thrombolytic therapy owing to in-hospital delays, including delayed physician evaluation, neurologic consultation, neuroimaging and laboratory tests[11]. In-hospital delays can be shortened through the organization of a stroke team, the development of stroke pathways and the training of ED personnel[12]. The present study confirmed the reduction of door-to-CT, door-to-needle, and onset-to-needle

times by applying these measures. Nevertheless, the mean door-to-needle time (67 minutes) was longer than that recommended by the National Institute of Neurological Disorders and Stroke, which states that from the time of arrival at the ED, a patient with AIS should receive tPA within 60 minutes[13]. This could be caused by the delayed notification of the stroke team, the slow appearance of the team, and the lack of adequate personnel on the stroke team. The stroke team was activated after the completion of CT and the neurologists on this team usually stayed at home except for daytime hours in weekdays. According to the recommendations formulated by the BAC[4], the stroke team should include a physician and another health care professional and a member of the team should be at the bedside within 15 minutes of being called. Our acute stroke team did not fully meet the BAC recommended criteria for PSC and our tPA protocol still had room for improvement. We have reorganized the acute stroke team to include ED personnel and revised the tPA protocol to notify the neurologist soon after ED triage.

The shortening of onset-to-needle time should be associated with a better outcome[14]. However, the proportions of patients achieving favorable outcome or functional independence were similar before and after the setting up of the PSC. The small patient numbers may be insufficient to detect the difference. In addition, a nonsignificant increase in the occurrence of SICH in the present study might offset the benefit of shorter onset-to-needle time. The higher serum glucose level and higher proportion of prior aspirin use may contribute to the increased rate of SICH[15-17].

The proportions of thrombolysis use for AIS was still low as compared to the experience of other countries[6,18]. In these countries, the proportion of patients treated with tPA increased to about 10% of all ischemic stroke patients after organizational changes were implemented. However, their criteria for tPA usage was broader than those used in the present study. For example, elder patients up to 95 years of age and patients with milder stroke severity (NIHSS as low as 2) were treated. So another way to increase tPA use is the expansion of the usage criteria. In the present study, 182 of 229 patients who arrived within two hours were not eligible for thrombolysis. Most of them were not treated owing to old age or having mild stroke severity. In the Taiwan Guidelines for the Management of Stroke 2008, some suggestions have been made to modify the tPA usage criteria, such as inclusion of patients with initial NIHSS score ≥ 4[19].

Currently we only activate the stroke code when patients come to ED within two hours of symptom onset. After the establishment of the PSC, intravenous tPA for those ischemic patients admitted within 2 hours increased from 10.4% to 14.0%, which reflected the shortening of the hospital delay, i.e., the decrease in door-to-CT and door-to-needle times. If we want to treat patients arriving between 2 and 3 hours, more efforts should be done to expedite the clinical evaluation and CT scanning of these patients in order to administer tPA within the 3-hour time window. However, these can only increase patients treated by a small proportion because less than 20% (47/276) of patients arriving within 3 hours of stroke onset came to ED between 2 and 3 hours. Most patients with AIS postponed their search for medical help. Therefore, shortening of the prehospital delay has a great potential to increase the use of thrombolysis[20]. As in the present study, the increase in patients treated with tPA after the establishment of PSC was partly due to earlier presentation of stroke patients to the ED. This might be explained by increased public awareness of warning signs for stroke and the more rapid delivery of stroke patients to the hospital. In addition, more potential tPA candidates might have been preferentially transported to our hospital after we established the PSC. Stroke center designation and selective triage of acute stroke patients have been shown to improve the access to timely thrombolytic therapy[21].

In conclusion, the establishment of a PSC not only increased the use of tPA on patients with AIS but also improved the efficiency of the delivery of thrombolysis. To further improve the outcome of stroke patients by using thrombolytic therapy, programs that educate patients to seek treatment sooner after a stroke should be an integral component of stroke care.

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