Gender Differences in Effect on Patients with Acute Ischemic Stroke Following Thrombolysis: a 11-year Cohort Study in Northern Taiwan

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Introduction: Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) has been the most effective treatment in selected patients with acute ischemic stroke (AIS) since it was approved by the Food and Drug Administration in 1996. Several studies showed that only 1-7% of all AIS patients received thrombolysis and around 15-20% of patients arriving hospitals within 3 hours were not treated with IV rt-PA. In Asia, IV rt-PA has not been widely adopted despite the 3 million AIS-related deaths annually relative to Western populations. Without thrombolysis, women are more likely to have a poorer outcome than men in the natural history of AIS. A systematic review, however, shows that female stroke patients have similar or better clinical outcomes compared to their male counterparts following intravenous thrombolysis. Noticeably, majority of studies assessing gender effect on thrombolysis have been conducted in Western populations and it remains unclear whether Asian men and women with AIS would benefit differently from IV rt-PA. We aim to determine whether there is a gender difference in outcomes among Asian AIS patients following IV rt-PA.

Methods : Our hospital is a 1200-bed tertiary care and teaching hospital in the Taipei metropolitan area of northern Taiwan. A retrospective cohort was established using its single-center stroke registry database from July 2005 to December 2016. During this period, AIS patients receiving IV rt-PA within a three-hour time window from stroke onset were enrolled. The study was approved by a local institutional review board. Baseline data include age, sex, pertinent medical and medication history, blood pressure, glucose, baseline National Institute of Health Stroke Scale (NIHSS) score, and stroke etiological subtypes classified as per TOAST (trial of ORG 10172 in acute stroke treatment) criteria, time from symptom onset, to emergency department (ED) arrival (OTA), to thrombolysis(OTT), and time from arrival to thrombolysis (ATT). The primary outcome was 90-day excellent functional outcome as normal or nearly-normal recovery defined by a modified Rankin Scale (mRS) score of 0-1. Safety outcomes included mortality and symptomatic intracranial hemorrhage (sICH). Symptomatic ICH is defined as any clinical deterioration in neurologic status within days following thrombolysis and documented by a follow-up CT (computed tomography) or MRI (magnetic resonance imaging) scan showing new hemorrhage consistent with the new or worsening clinical symptoms and signs.

Results: From July 2005 to December 2016, 345 patients receiving thrombolysis within 3 hours from symptoms onset were analyzed and 142 (41.2%) were women. Relative to men (M), women (F) were significantly more likely to be older (mean age: M 63.0 vs F 67.1 years old; p=0.001), have more atrial fibrillation (M 42.4% vs F 62.6%; p=0.001), more baseline NIHSS score of > 20 (M 10.8% vs F 21.8%; p=0.006), more cardioembolic (CE) strokes (M 42.9% vs F 62.7%; p=0.001). 63 men (31.0%) and 36 women (25.3%) had an excellent functional outcome, defined as modified Rankin Scale score of 0-1 at 90-days after thrombolysis. There are no gender differences in both crude (p=0.252) and adjusted odds ratio (p=0.965) of the excellent functional outcome after adjusting for age, glucose, hypertension, atrial fibrillation, stroke subtypes, dyslipidemia, baseline NIHSS score, and time from symptom onset to thrombolysis. Noticeably, women waited significantly longer than men from hospital arrival to thrombolysis (p=0.01).

Table 1. Baseline Characteristics of Men Versus Women with AIS receiving IV rt-PA

	All patients (n=345)	Male (n=203)	Female (n=142)	p value
Age (years), mean (SD)	64.7 (11.7)	63.0 (11.8)	67.1 (11.0)	0.001
History of				
Hypertension, [n (%)]	231 (67.7)	138 (68.3)	93 (66.9)	0.81
AF ¹ , [n (%)]	172 (60.6)	86 (42.4)	86 (60.6)	0.001
DM ² , [n (%)]	105 (30.6)	58 (28.6)	47 (33.6)	0.34
Dyslipidemia, [n (%)]	231 (67.7)	138 (68.3)	93 (66.9)	0.784
Ischemic heart disease, [n (%)]	91 (26.5)	55 (27.1)	36 (25.7)	0.776
Valvar heart disease, [n (%)]	51 (14.9)	25 (12.4)	26 (18.6)	0.114
Ever smoker, [n (%)]	129 (37.8)	118(58.4%)	11(7.9%)	<0.001
Antiplatelet agents, [n (%)]	165 (47.8)	90 (44.3)	75 (52.8)	0.121
Clinical manifestation				
Baseline NIHSS				
Mean(SD)	13.4 (6.0)	12.7 (5.8)	14.4 (6.0)	0.008
>20, [n (%)]	53 (15.4)	22 (10.8)	31 (21.8)	0.006
MAP ³ (mmHg), mean (SD)	107.7 (19.6)	106.5 (19.4)	109.2 (19.9)	0.226
Blood glucose (mg/dl), mean(SD)	146.3 (60.6)	145.6 (63.6)	147.4 (56.0)	0.789
Blood glucose >110 mg/dl, [n (%)]	241 (69.9)	137 (64.5)	104 (73.2)	0.252
Stroke etiological subtype ⁴				<0.001
Cardioembolic, [n (%)]	176 (51.0)	87 (42.9)	89 (62.7)	
Large-vessel occlusive, [n (%)]	124 (35.9)	93 (45.8)	31 (21.8)	
Lacunar/ undetermined, [n (%)]	45 (13.0)	23 (11.3)	11 (15.5)	
Process measures (minutes), mean(SD)				
Symptom onset to arrival (OTA)	45.6(26.4)	44.9 (25.8)	46.5 (27.3)	0.588
Arrival to treatment (ATT)	70.8 (25.9)	67.9 (23.6)	75.0 (28.5)	0.012
Symptom onset to treatment (OTT)	116.6 (31.7)	113.1 (30.6)	121.5 (32.8)	0.016

Table 2. Comparisons of Excellent Functional, Safety Outcomes

Outcome	All patients (n=99)	Male (n=63)	Female (n=36)	Crude OR (95% CI)	p value	Adjusted OR ³ (95% CI)	p value
mRS 0-1 at 90 days ² , [n (%)]	99 (28.7)	63 (31.0)	36 (25.4)	0.75 (0.47, 1.22)	0.252	0.99 (0.57, 1.72)	0.965
sICH ² , [n (%)]	28 (8.2)	17 (8.4)	11 (7.9)	0.94 (0.43, 2.07)	0.879	0.69 (0.29, 1.64)	0.400
Death, [n (%)]	27 (7.8)	11 (5.4)	16 (11.3)	2.22 (0.99, 4.93)	0.051	1.63 (0.69, 3.89)	0.268

Table 3 Modified Rankin Scale at 3 months in Taiwanese cohort, randomized controlled trials and other post-market studies

Conclusion : The study found that there is no difference in the excellent recovery between the Taiwanese men and women with AIS following IV rt-PA within three hours. The nullified result suggests Asian women with AIS benefited more from thrombolysis than men. However, in-hospital delay caused women with AIS to receive thrombolysis than men until the additional action was taken. Continuous efforts are required to address potential gender inequality in stroke-related treatments especially when women could benefit more from the thrombolysis than men.