

Safety and efficacy of extending intravenous thrombolysis treatment for acute ischemic stroke in Taiwan

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Abstract

Recombinant tissue plasminogen activator (rt-PA) is the most effective treatment for acute ischemic stroke and the exclusion criteria of rt-PA has been revised to extend its application. However, in Taiwan, National Health Insurance (NHI) did not follow the latest international consensus due to safety concerns. The present study investigated whether extending the application of rt-PA in Taiwan was safe and effective. The medical records from the Shuang Ho hospital stroke registry between August 2009 and December 2016 were retrospectively reviewed. Post rt-PA intracranial hemorrhage (ICH) and modified Rankin Scale (mRS) score at 3-month after stroke were the primary and secondary outcomes, respectively. Differences were analyzed through Fisher's exact test and Student's *t* test. A *p*-value of <0.05 was considered statistically significant. Overall, there were 243 patients categorized into two groups: NHI exclusion criteria adherence (*n* = 160) and non-adherence (*n* = 83). There was no significant difference in the risk of post rt-PA ICH (12.50% in adherence group, 4.82% in non-adherence group, *p*=0.07). Among the non-adherence group, 10 patients breached the latest international exclusion criteria and none of them experienced post rt-PA ICH. However, among patients with moderately severe stroke, the odds of mRS ≤ 2 at 3-month were significantly lower in non-adherence group. This study demonstrated that extending administration of rt-PA in Taiwan was safe but the functional outcome after moderate stroke was not as favorable as adherence group. Old age, long onset-to-treatment time and less efficacy of lower dose of rt-PA were the possible factors for the difference in outcome.

INTRODUCTION

Acute ischemic stroke (AIS) is the leading cause of chronic disability.¹ Currently, recombinant tissue plasminogen activator (rt-PA) remains the most effective noninvasive treatment for AIS within the treatment time window.²⁻⁷ However, its most harmful side effect is post rt-PA intracranial hemorrhage (ICH), which results in prolonged hospital stay and increased mortality.⁸ The risk of post rt-PA ICH is approximately 6%, which is 10 times higher than that in patients with AIS without rt-PA.²

Since the early clinical trials for rt-PA, a number of exclusion criteria have been established to lower the risk of post rt-PA ICH.² Since then, there were numerous clinical trials attempting to extend the application of rt-PA and revise the

exclusion criteria.⁹ The latest American Heart Association/American Stroke Association (AHA/ASA) guideline was based on recent evidence of the safety and efficacy of rt-PA under various specific conditions. In this version, old patients (age > 80 years) and those with severe stroke (National Institutes of Health Stroke Scale [NIHSS] score > 25) are only excluded if their onset-to-treatment time is 3.0–4.5 hours.¹⁰

However, these revisions were not followed by all the medical care bodies around the world. In Taiwan, due to safety considerations, National Health Insurance (NHI) exclusion criteria for rt-PA in AIS is formulated according to the very first edition of international guideline² and has remained unchanged. The clinical use of rt-PA was mainly in adherence to the Taiwan NHI criteria. However, some patients who were non-adherent to

the exclusion criteria but were eligible according to the latest international guideline did received rt-PA treatment after consent was obtained. For example, since 2015, to shorten the door-to-needle interval, rt-PA treatment had been initiated before the results of laboratory examinations have become available, except blood glucose results. In some patients, because of incomplete medical history (such as good health and activities of daily living before event), rt-PA treatment has been given to patients with a history of ICH, intracranial meningioma, an onset-to-treatment time of 3.0–4.5 hours, those older than 80 years, or with very severe stroke.

In fact, a recent Taiwanese study showed a symptomatic post rt-PA ICH of 7% among the NHI exclusion criteria adherence patients¹¹, which was higher than the Western countries. In addition, although numerous studies demonstrated the off-label rt-PA application was safe and provided favorable outcome^{12–15}, there were limited published data available from Asia. This study is based on the data from a single university-affiliated hospital in Taiwan to demonstrate the safety and efficacy of extending rt-PA application in AIS patients who were non-adherent to the Taiwan NHI exclusion criteria.

METHODS

Patient selection

This retrospective study was approved by the Joint Institutional Review Board of Taipei Medical University (N201705044), and informed consent was waived. Medical records from Shuang Ho hospital stroke registry between August 2009 and December 2016 were reviewed. During this study period, 243 patients with AIS received intravenous rt-PA and had complete medical records. They were included in this analysis.

All patients had undergone noncontrast head computed tomography (CT) before rt-PA was given and were closely monitored for 24 hours after rt-PA treatment. In addition, either head CT with CT angiography or brain magnetic resonance (MR) imaging with MR angiography was performed within 72 hours after rt-PA.

The patients' information procured from the medical records included age; sex; history of hypertension, diabetes mellitus, atrial fibrillation, and stroke; onset-to-treatment time; post rt-PA ICH, as defined by the criteria of the European Cooperative Acute Stroke Study II¹⁶; initial NIHSS score; and 3-month post-stroke modified Rankin scale (mRS) scores. The overall post rt-PA

ICH rates and the odds of a favorable outcome (assessed by a 3-month mRS score of ≤ 2) were the primary and secondary outcomes, respectively. The patients were categorized into two groups: NHI exclusion criteria adherence ($n = 160$) and non-adherence ($n = 83$). In all patients in the adherence group, the dosage of rt-PA was standard 0.9mg/kg whereas low dose of rt-PA (0.6mg/kg) was given to nonadherence group due to safety and financial concerns.

All CT/MR results were analyzed by two independent neurologists. The 3-month post-stroke mRS score at followed up was through telephone interview or outpatient records.

Statistical analyses

All analyses were performed using SPSS (v 19; SPSS Inc., Chicago, IL, USA) for Windows 10. Continuous variables are presented as means \pm standard deviations, and categorical variables were calculated as percentages. Differences were analyzed using the Student's *t* test or Fisher's exact test. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Table 1 presented the demographic data of both groups. Not surprisingly, patients in the NHI exclusion criteria non-adherence group were significantly older and exhibited longer onset-to-treatment time. Regarding to safety, non-adherence group did not had higher risk of post rt-PA ICH (adherence group: 12.5%; non-adherence group: 4.82%, $p = 0.070$). Although the initial NIHSS between groups was identical, the 3-month post-stroke mRS score was higher in the non-adherence group (adherence group: 2.63 ± 1.94 ; non-adherence group: 3.27 ± 2.00 , $p = 0.016$) and the odds of good outcome after stroke (3-month $mRS \leq 2$) were significantly lower in nonadherence group (adherence group: 51.25%; non-adherence group: 37.35%, $p = 0.043$).

In the non-adherence group, the main reasons of exclusion criteria violation were age > 80 ($n = 48$), mild stroke (NIHSS < 6) or rapid improvement ($n = 14$), onset-to-treatment more than 3 hours ($n = 13$), severe stroke (NIHSS > 25 , $n = 8$) and miscellaneous ($n = 10$). Some of the patients had more than one violations. Furthermore, there were 10 patients violating the latest guideline of rt-PA application. Among them, 4 patients violated the guideline of a prolonged treatment window (3.0–4.5 hours) accompanied by other factors (age > 80 years, $n = 3$; NIHSS score > 25 ,

Table 1: Demographic data of NHI exclusion criteria adherence and non-adherence groups

	Adherence	Non-adherence	P value
Number	160	83	
Female	62 (38.75)	40 (48.19)	0.172
Age (y/o)	65.12±10.38	76.84±10.76	<0.001
Hypertension	133 (83.13)	69 (31.33)	1.000
Diabetes	52 (32.50)	26 (31.33)	0.886
Atrial fibrillation	49 (30.63)	28 (33.73)	0.664
Initial NIHSS	13.33±6.08	13.49±7.64	0.861
OTT (mins)	113.18±36.69	130.18±36.69	0.004
Post rt-PA ICH	20 (12.50)	4 (4.82)	0.070
3-month mRS	2.63±1.94	3.27±2.00	0.016
3-month mRS≤2	82 (51.25)	31 (37.35)	0.043

Abbreviation: NHI, National Health Insurance; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment; rt-PA, recombinant tissue plasminogen activator; ICH, intracranial hemorrhage; mRS, modified Rankin scale. Data was presented as either number (percentage) or mean±standard deviation.

n = 1). Four patients violated the guideline of low platelet count (<100,000/mm³), which happened because rt-PA treatment could not be delayed just to obtain complete laboratory examination results, except for blood glucose. Two patients violated the guideline in having an intracranial meningioma or failure to provide information on their past history of ICH at presentation. Post rt-PA ICH was not observed in these 10 patients, and 6 of them had mild disability (3-month mRS≤2) (Table 2).

Age and initial NIHSS were the most relevant indicators of functional disability after stroke. However, the present study was not able to exclude the effect of age while comparing the efficacy of rt-PA between groups since the age>80 was the main reason of non-adherence. Alternatively, when we grouped patients based on the severity of stroke. Among patients with minor stroke (initial NIHSS 0~7) or severe stroke (NIHSS≥16), the odds of good post-stroke outcome was similar between two groups. In patients with moderate stroke (initial NIHSS 8~15), the odds of good outcome of stroke was significantly lower in non-adherence group (adherence group: 60%, non-adherence group: 33.3%, *p*=0.014) (Table 3).

DISCUSSION

The present study revealed that there was no significant difference in the risk of post rt-PA

ICH between NHI exclusion criteria adherence and non-adherence groups. For patients with moderate stroke severity, the odds of a good functional outcome after stroke was less among non-adherence patients. The present study demonstrated that extending application of rt-PA was safe but the efficacy was not as good as NHI exclusion criteria adherence patients if the stroke severity was moderate.

The application of intravenous rt-PA was the gold standard of AIS treatment since the last two decades.² The initial exclusion criteria of intravenous thrombolysis was based on the early positive randomized control trials and expert opinions. However, these strict regulations resulted in limited or delayed treatment. For example, the requirement for coagulation profile prior to treatment may consume precious time and delayed the initiation of thrombolysis. In order to treat more eligible patients with AIS, several subsequent studies investigated the efficacy and safety of thrombolysis on AIS while extending the onset-to-treatment time from 3.0 to 4.5 hours and excluding certain contraindications, such as coagulation profile and the age limitation.^{5,7,9} Based on these modifications, a study using simplified criteria for thrombolysis had demonstrated the potential to increase the rate of thrombolysis by up to 25%.¹⁷ Nevertheless, the application rate of intravenous rt-PA for patients with AIS is still unsatisfactory, especially in East Asian

Table 2: Demographic data and clinical presentations of patients who violated latest exclusion criteria but still received rt-PA treatment.

	Age	Sex	NIHSS	OTT (min)	rt-PA (mg/Kg)	Infarct area	Post rt-PA ICH	3M mRS	Reasons of protocol violation
1	82	M	25	195	0.6	L't MCA	N	3	OTT >3 hours and age >80
2	81	M	14	205	0.6	R't MCA	N	2	OTT >3 hours and age >80
3	61	F	27	186	0.6	R't MCA	N	5	OTT> 3hours and NIHSS>25
4	82	F	6	211	0.6	Bilateral hemispheres	N	2	OTT >3 hours and age >80
5	73	M	17	81	0.6	BA	N	5	Low Platelet count
6	85	M	14	170	0.6	L't MCA	N	4	Low Platelet count
7	68	M	12	135	0.6	BA	N	1	Low Platelet count
8	66	M	18	51	0.6	L't MCA	N	1	Low Platelet count
9	61	F	6	105	0.6	DWI signal change (-)	N	1	Brain meningioma
10	64	F	20	140	0.6	L't MCA	N	2	Previous ICH history

Abbreviation: rt-PA, recombinant tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment; ICH, intracranial hemorrhage; MCA, middle cerebral artery; BA, basilar artery; mRS: modified Rankin scale.

countries.¹⁸⁻²¹ The risk of post rt-PA ICH in these countries may be higher, which raised the safety concern of extending rt-PA application.²²⁻²⁴ Alternatively, low dose of rt-PA (0.6mg/kg) had been widely used in Japan for elder patients and the safety had been confirmed.²⁵ In Taiwan, the NHI had yet to revise the exclusion criteria of the application of rt-PA since its first establishment, which limit the possibility of increasing application

rate of rt-PA in AIS patients. The present study demonstrated that patients who were not adherent to the NHI exclusion criteria but fulfilled the international consensus of rt-PA did not have a higher risk of post rt-PA ICH upon low dose treatment. Therefore, the NHI should consider modifying the exclusion criteria in accordance with the latest international consensus.

Other than safety, the efficacy of rt-PA was

Table 3: The odds of good functional outcome after stroke (3-month mRS≤2) among patients with mild (initial NIHSS 0~7), moderate (initial NIHSS 8~15) or severe (initial NIHSS ≥16) in two groups

Initial NIHSS	Adherence	Non-adherence	p-value
0~7	26 (72.2)	17 (70.8)	0.91
8~15	42 (60.0)	10 (33.3)	0.014
>16	14 (25.9)	4 (22.2)	0.20

Abbreviation: NIHSS: National Institutes of Health Stroke Scale

another important consideration. AHA/ASA has suggested a standard dosage of rt-PA for all patients.¹⁰ However, low-dose rt-PA was more popular in the Asian countries for older (age>80) subjects and those with delayed onset-to-treatment (3~4.5 hours) patients. The efficacy of low dose rt-PA in the old age had been investigated in Japan²⁵⁻²⁷, which demonstrated that the functional outcome after treatment was not as favorable as the younger patients. The present study showed a similar finding in the Taiwanese patients. Upon extending the application of rt-PA at lower dosage, the risk of post rt-PA ICH did not increase, but the functional outcome were less favorable than the NHI exclusion criteria adherence group.

The latest revised guidelines of rt-PA¹⁰ have excluded the use of the drug in patients with intracranial tumor, post-ICH history, and intracranial aneurysm. Nevertheless, some published studies have demonstrated the safety of rt-PA among these patients.²⁸⁻³⁴ Abnormal coagulation profile has remained a treatment contraindication. However, waiting for coagulation profile results is not only time-consuming but also the main cause of treatment delay. According to expert opinion, rt-PA application must not be delayed by waiting for laboratory examination results, except for blood glucose.³⁵ The present study enrolled 10 patients who violated the latest guidelines and received rt-PA treatment. Notably, none of these patients experienced post rt-PA ICH. In addition, they were not prone to having a poorer outcome. These results suggest that low dose rt-PA application can be considered if the same safety and efficacy are demonstrated for those specific group of patients.

The present study had some limitations. Because of its retrospective study design, the effects of rt-PA were not compared between patients with and without thrombolysis. Only the safety and outcomes were compared between NHI exclusion criteria adherence and non-adherence groups. The guideline-violating patients were biased as the use of drug requires the patient's and family's consent, they are likely to have higher socioeconomic status because their rt-PA would not be paid by the NHI), and likely to have better baseline daily activity.

In conclusion, the present study showed that extending rt-PA application in Taiwanese patients based on latest international guideline was safe, but the functional outcome after moderate stroke for the NHI exclusion criteria nonadherence patients may be less favorable.

DISCLOSURE

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Conflict of interests: None

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