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Low-dose intravenous recombinant tissue plasminogen activator in acute ischemic stroke without large vessel occlusion screened by 3T MRI

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Abstract. – OBJECTIVE: Globally, there are more than six million deaths due to cerebrovascular disease, which is the second leading cause of death. Although the imaging findings of magnetic resonance imaging (MRI) are more accurate than computed tomography for acute ischemic stroke (AIS), it is uncommon in recombinant tissue plasminogen activator (rTPA) treatment. Alteplase is not only strongly recommended treatment for acute ischemic stroke within 4.5 hours, but also decreases the disability and mortality rate. Besides, low-dose rTPA was associated with significant reductions in symptomatic intracerebral hemorrhage (sICH), compared with standard one. However, the benefits of low-dose rTPA for the treatment of AIS without large vessel occlusion (LVO) have not been fully demonstrated. We evaluated whether the low-dose rTPA in AIS without LVO could improve prognosis in patients three months post-treatment.

PATIENTS AND METHODS: This was a cross-sectional study on patients with AIS treated within 4.5 hours of symptom onset admitted to Can Tho S.I.S General Hospital between February 2019 and July 2021. The eligibility criteria were patients aged > 18 years treated with low-dose rTPA (0.6 mg/kg) and screened by 3T MRI. Patients with a pre-hospital modified Rankin score (mRS) ≥ 2 points, intracranial hemorrhage, LVO, or ≥ 3 microbleeds on brain MRI were excluded. The primary outcomes were the favorable outcome rate at three months and safety, which were evaluated by the rates of intracranial hemorrhage and mortality at three months.

RESULTS: This study enrolled 92 eligible patients between February 2019 and July 2021. Their National Institute of Health Stroke Scale (NIHSS) scores were 7.5 ± 3.7 at admission, 3.3 ± 3.5 at discharge or seven days after discharge, and 2.2 ± 2.8 at three months. Their mRS were 2.9 ± 0.8 at admission, 1.4 ± 1.3 at discharge or seven days after discharge, and 1.1 ± 1.1 at three months. Elevated cardiac enzymes, age ≥ 75 years, and body mass index ≥ 25 were associated with increased poor outcomes at three months. While AIS was more common in men than women, a similar number of men (33.3%) and women had poor mRS. Three patients had complications associated with low-dose rTPA treatment: one (1.1%) had intracranial hemorrhage, one (1.1%) had new infarcts, and one (1.1%) had gastrointestinal bleeding. No deaths occurred within three months.

CONCLUSIONS: Our study indicates the efficacy and safety of low-dose rTPA treatment for AIS without LVO within 4.5 hours. Patient selection for rTPA by 3T MRI decreased complications and mortality.

Key Words:
Low-dose, Alteplase, AIS, MRI.

Introduction

The cerebrovascular disease causes more than six million deaths globally and is the second leading cause of death after ischemic heart disease[1]. In addition, up to 50% of stroke survivors do not regain functional independence, and 20% require facility care three months after stroke onset[2]. Intravenous recombinant tissue plasminogen activator (IV rTPA) is the only drug approved by the US Food and Drug Administration to treat reperfusion in patients with acute ischemic stroke (AIS)[3]. Prerequisites for treating rTPA include: excluding bleeding and demonstrating salvageable tissue[4]. Results from the National Institute of Neurological Disorders and Stroke (NINDS) trial showed an additional 13% improvement in neurological function in ischemic stroke patients

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entirely or almost entirely at three months when IV rTPA treatment was given within three hours[5]. IV rTPA within 4.5 hours is currently the standard treatment for patients with AIS based on the European Cooperative Acute Stroke Study (ECASS) III results[6]. Some evidence indicates that low-dose fibrinolytic therapy is equally effective and tends to reduce the rate of bleeding complications and disability compared to standard doses[7-9]. However, there is limited data on giving low-dose IV rTPA to patients with AIS without large vessel occlusion (LVO) within 4.5 hours. Therefore, we conducted a study to determine whether it is safe and effective to use rTPA treatment for AIS without LVO within 4.5 hours by 3T magnetic resonance imaging (MRI).

Patients and Methods

Patients

This retrospective descriptive cross-sectional study collected data using a pre-designed study case sample. It included patients with AIS treated within 4.5 hours of symptom onset admitted to Can Tho S.I.S General Hospital between February 2019 and July 2021. Its eligibility criteria included patients aged > 18 years treated with low-dose rTPA (0.6 mg/kg) and screened by 3T MRI. Patients with a pre-hospital modified Rankin score (mRS) ≥ 2 points, intracranial hemorrhage, LVO, or ≥ 3 microbleeds on brain MRI were excluded. The primary endpoints included both a satisfactory outcome rate defined by mRS of 0-2 and safety evaluated by the rates of symptomatic intracranial hemorrhage and mortality at three months. Figure 1 shows the patients' selection process.

Informed consent was obtained from all patients' representatives after a detailed explanation of the procedures. The study protocol was approved by the Ethics Council for Biomedical Research at Can Tho S.I.S General Hospital (approval number: 5721A/QD-S.I.S; dated April 28, 2021). All procedures involving human participants were performed according to the ethical standards of the institutional and national research committees and the 1964 Declaration of Helsinki and its later amendments.

Variables were retrospectively collected from the medical records of eligible patients at admission, at fibrinolytic therapy, after 24 hours, after seven days, at discharge, and after three months. Then, a researcher assessed patients' National Institute of Health Stroke Scale (NIHSS) scores at admission, 72 hours, and three months after a stroke via telephone. In addition, a researcher obtained medical history information from medical records, including medical history, blood tests, and MRI results.

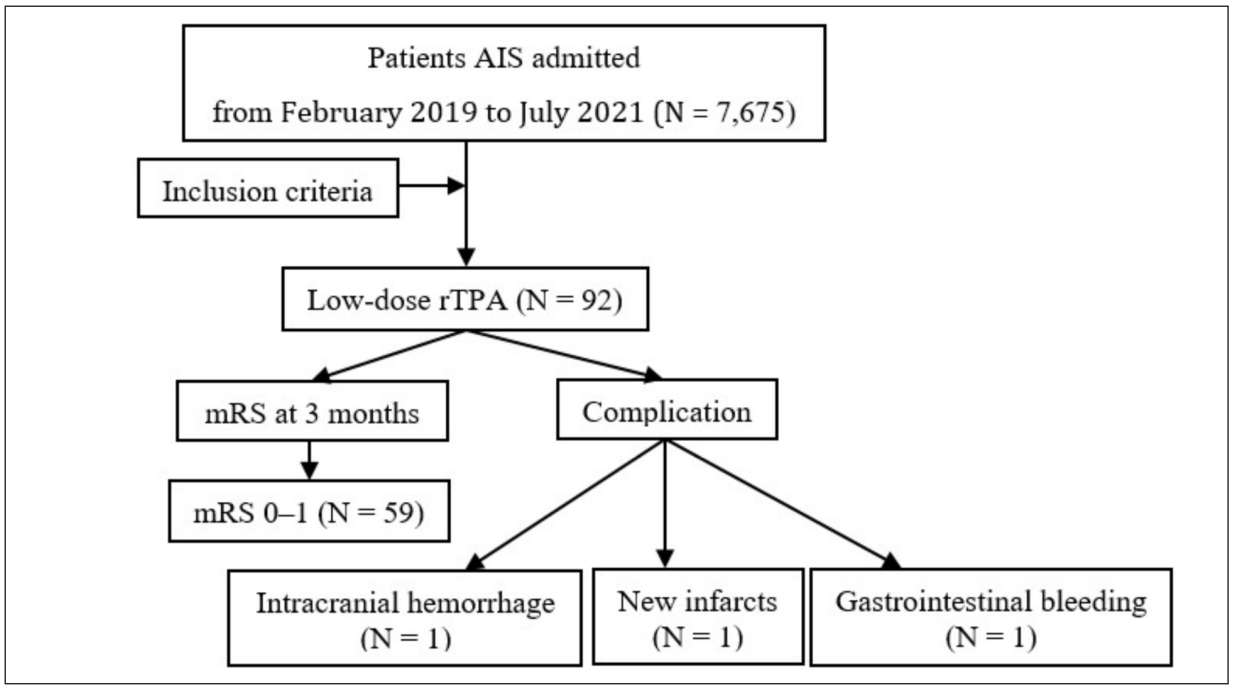

Figure 1. Flow-chart of patient selection in the study.

The essential safety outcomes were the rate of symptomatic intracranial hemorrhage, as defined by the National Institute for Neurological Disorders and Stroke (NINDS) criteria[10], the rate of extracranial bleeding, and all-cause mortality.

We describe two typical cases with acute ischemic stroke that received low-dose rTPA in our study. A 47-year-old male presented to the local hospital with the onset of right hemiparesis and central facial palsy. He presented with consciousness and an NIHSS score of nine. He was transferred to Can Tho S.I.S General Hospital three hours after onset and was administered alteplase (0.6 mg/kg). MRI recorded new infarcts in the left posterior limb of the internal capsule and near the left lateral ventricle. His mRS recovered fully after five days (Figure 2).

A 59-year-old male presented to the local hospital with the onset of right hemiparesis, dizziness, aphasia, and dysphagia. He presented with consciousness and an NIHSS score of 12. He was transferred to Can Tho S.I.S General Hospital two hours after onset and were administered alteplase (0.6 mg/kg). MRI recorded a new medullary infarction. His mRS recovered fully after six days (Figure 3).

Statistical Analysis

The data were processed and analyzed using the STATA statistical software (version 14.0; StataCorp

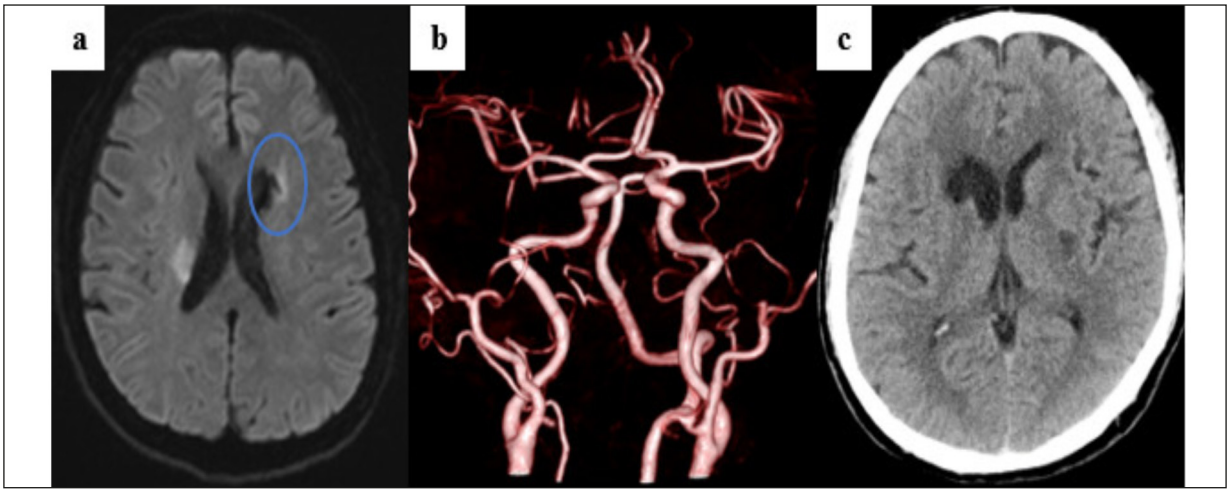

Figure 2. The first case. **a**, Diffusion-weighted imaging (DWI) shows new infarcts in the left posterior limb of the internal capsule and near the left lateral ventricle (blue circle). **b**, Magnetic resonance angiography (MRA) shows no left LVO in the anterior circulation. **c**, The postoperative computed tomography (CT) scan did not indicate intracranial hemorrhage.

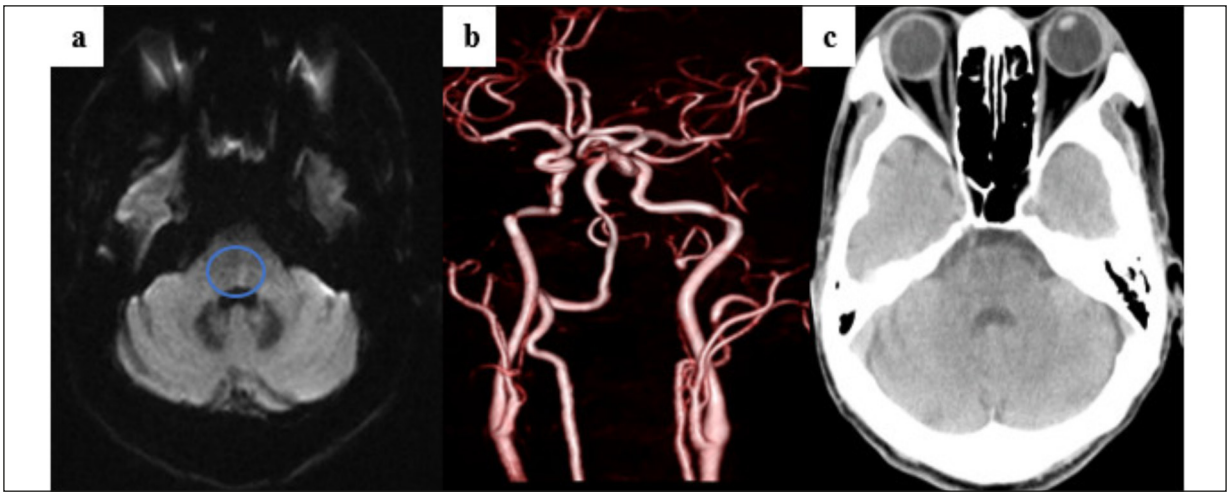

Figure 3. The second case. **a**, DWI shows a new medullary infarction (blue circle). **b**, MRA shows no LVO in the posterior circulation. **c**, The postoperative CT scan did not indicate intracranial hemorrhage.

LLC, TX, USA). Qualitative variables are expressed as percentages and compared using the χ^2 test or Fisher's exact test (when the expected frequency in any one variable box is < 5). An odds ratio (OR) was calculated to evaluate the factors' degree and direction of influence. A multivariable logistic regression model was used to analyze the variables impacting functional independence at three months. A p-value < 0.05 was considered statistically significant with appropriate 95% confidence intervals (CIs).

Results

There were 7,675 patients with AIS admitted to the Emergency Department of Can Tho S.I.S General Hospital from February 2019 to the end of July 2021, of which 145 received thrombolytic therapy (1.9%). This study included 92 patients with AIS treated with low-dose fibrinolysis alone who met its inclusion criteria. It excluded 53 patients with AIS treated with fibrinolysis therapy who did not meet its sample criteria.

As shown in Table I, rates were higher in males than females (34.8%). The subjects' average age was 64.4 ± 12.3 years. Their clinical manifestations were varied: 96.7% had weakness/hemiplegia, 78.3% had difficulty speaking, 54.4% had hemisensory syndrome, 25% had a language disorder, 66.3% had cranial nerve palsy, and 15.2% had a consciousness disorder. Among patients, 27.2% were overweight-obese, and 44.6% smoked (all male). The time from onset to hospital admission was 150.6 ± 62.9 minutes, with 65.2% of patients hospitalized within < 180 minutes of onset. The time to obtain MRI results was 35.0 ± 11.2 minutes. After hospitalization, the time to bolus rTPA was 57.3 ± 15.6 minutes, the intensive care unit stay length after rTPA was 46.4 ± 111.4 hours, and the total hospital stay length was 7.6 ± 6.9 days. The Alberta Stroke Programme Early CT Score (ASPECTS) was evaluated on diffusion-weighted imaging (DWI): the rate of anterior circulation was 80.4%, the average ASPECTS was 8.2 ± 0.7, and the average posterior circulation ASPECTS was 8.3 ± 0.6. Hospitalization time would have been shortened if patients went directly to the hospital (p = 0.030) or the distance between stroke patients and the hospital for stroke treatment was < 60 km (p = 0.006) (Table II).

The NIHSS scores were 7.5 ± 3.7 at admission, 3.9 ± 3.5 at 24 hours after rTPA treatment, 3.3 ± 3.5 at discharge or after seven days, and 2.2 ± 2.8 at three months. The mRS scores were 2.9 ± 0.8 at admission, 1.8 ± 1.2 at 24 hours after rTPA treatment, 1.4 ± 1.3 at discharge or after seven days, and 1.1 ± 1.1 at three months (Figure 4).

As shown in Table III, regarding clinical outcomes after three months, disability risk was fivefold higher for patients with increased troponin enzyme (p = 0.04) than those without.

Clinical outcomes at three months were not significantly associated with an NIHSS ≥ 10 at admission, hyperglycemia or anemia factors, decreased glomerular filtration rate, leukocytosis,

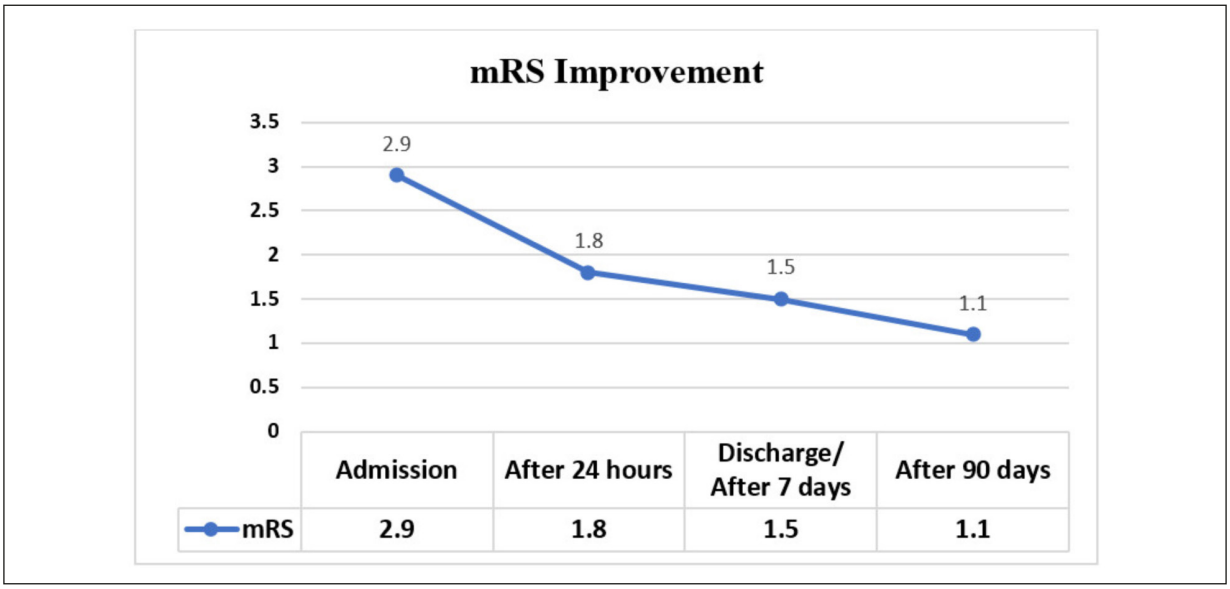

Figure 4. The change in mRS with time.

Table I. Study subjects' general characteristics.

Features	n	Percent (%)
Aged ≥ 75	18	19.5
Male	60	65.2
Clinic		
Weakness on one side	89	96.7
Dysarthria	72	78.3
Sensory loss	50	54.4
Aphasia	23	25.0
Cranial nerve paralysis	61	66.3
Consciousness decrease	14	15.2
BMI > 25	25	27.2
History		
Hypertension	72	78.2
Stroke	15	16.3
diabetes	13	14.1
Dyslipidemia	12	13.0
Smoking	41	44.6
MRI		
Anterior cerebral circulation	74	80.4%
posterior cerebral circulation	18	19.6%
Subclinical on admission		
Hyperglycemia	16	17.4%
Decreased eGFR	5	5.4%
Increased troponin	9	9.8%
Hyper leukemia	36	39.1%
Anemia	10	10.9%
Hospitalization < 180 minutes from onset	70	76.1
Direct hospital admission	79	85.9
Distant from onset place to hospital ≤ 60 km	60	65.2

BMI: Body Mass Index; MRI: magnetic resonance imaging.

Table II. Factors affecting the amount of time spent in the hospital before admission

		Onset to hospital > 180 mins	Onset to hospital ≤ 180 mins	n (%)	OR (CI 95%)	p
Distant from onset place to hospital	> 60 km	13 (40.6%)	19 (59.4%)	32 (100%)	3.9(1.3-12.0)	0.006
	≤ 60 km	9 (15.0%)	51 (75.0%)	60 (100%)		
Patient transportation to hospital	Indirectly	8 (61.5%)	5 (38.5%)	13 (100%)	3.7 (1.1-15.6)	0.029

dyslipidemia, history of diabetes, history of smoking, history of stroke, or history of hypertension.

Three patients experienced complications after rTPA treatment. One (1.1%) had an asymptomatic intracranial hemorrhagic transformation. One (1.1%) had moderate cerebral edema due to a progressive cerebral infarction; despite concurrent pneumonia during treatment, this patient was on stable treatment and was discharged after tracheostomy with an mRS of 4 at three months. One (1.1%) had gastrointestinal bleeding within 24 hours of rTPA administration. Other complications, such as fatalities, urinary hemorrhage, and angioedema, were not reported after IV rTPA treatment.

Discussion

In our study, we had a good proportion of patients with neurological rehabilitation (64.1%), equivalent to an mRS score of 0-1 at three months, meaning they could return to a daily routine or only have minor functional limitations. In addition, one case (1.1%) of asymptomatic intracerebral hemorrhage occurred. Their hemorrhagic transformation occurred during hospitalization within the first 24 hours after treatment; the patient's clinical status was almost unchanged, and there was no increased NIHSS score during their hospital stay. In addition, one case (1.1%) of gastrointestinal bleeding occurred within 24

Table III. Factors affecting disability outcomes after three months.

		mRS > 1	mRS ≤ 1	OR (KTC 95%)	p
BMI (kg/m^2)	≥ 25	15	10	4.1 (1.4-12.1)	0.003
	< 25	18	49		
NIHSS	≥ 10	11	11	2.2 (0.7-6.5)	0.40
	< 10	22	48		
Age	≥ 75	6	12	0.87 (0.24-2.87)	0.8
	< 75	27	47		
Gender	Male	20	40	0.73 (0.28- 2.0)	0.49
	Female	13	19		
Leukocytes (cells)	> 10^9/L	10	26	0.6 (0.2-1.5)	0.14
	≤ 10^9/L	23	33		
Glycemia (mg%)	> 180	4	12	0.5 (0.1-2.0)	0.31
	≤ 180	29	47		
Anemia	Yes	3	7	0.7 (0.1-3.6)	0.68
	No	30	52		
eGFR (mL/min/1.73 m^2)	≤ 45	2	3	1.2 (0.1-11.1)	0.84
	> 45	31	56		
Increased troponin (pg/ml)	Yes	5	2	5.1 (0.8-55.5)	0.04
	No	28	57		
History of stroke	Yes	6	9	1.2 (0.3-4.4)	0.715
	No	27	50		
History of diabetes	Yes	6	7	1.7 (0.4-6.4)	0.404
	No	27	52		
History of dyslipidemia	Yes	4	8	0.9 (0.2-3.6)	0.844
	No	29	51		
History of hypertension	Yes	27	45	1.4 (0.4-5.0)	0.536
	No	6	14		
History of smoking	Yes	15	25	1.1 (0.44-2.91)	0.77

BMI: Body Mass Index; NIHSS: National Institute of Health Stroke Scale.

hours after rTPA treatment. None of our cases of hematuria and angioedema were observed after rTPA treatment. One patient (1.1%) had moderate malignant cerebral edema resulting in acute progressive cerebral infarction (Table IV).

There were many reasons for the different results in the abovementioned studies[3,6,7]. Firstly, we only selected patients without LVO. Therefore, the infarct volume was usually small, and the neurological deficit was not severe. Secondly, the value of a brain examination by MRI was better than one by computed tomography (CT), although MRI took a long time to complete. An MRI DWI sequence allowed us to assess accurately the characteristics of ischemic lesions. Therefore, the pseudo-strokes could be ruled out with this sequence. In addition, MRI helped to evaluate cerebral microhemorrhages, which could increase intracerebral hemorrhages after rTPA treatment. CT cannot detect cerebral microhemorrhages. Furthermore, MRI could be used to assess previous cerebral injury; this helped us to consider the rTPA decision. Thirdly, rTPA was used with a low dose (0.6 mg/kg). There was no difference in neurological recovery after three months between the low and standard doses in the enhanced Control

Table IV. Complications after rTPA treatment.

	Our study (%)	ENCHANTED (%)	ECASS 3 (%)	NINDS (%)
ICH (total/ symptomatic)	1.1	1.0 (Low dose)/2.1 (standard dose)	27.0	10.6
	0		2.4	6.4
Mortality	0	8.5 (Low dose)/10.3 (standard dose)	7.7	17.3
Extracranial bleeding	1.1	-	-	-
Angioedema	0	-	-	-

of Hypertension and Thrombolysis Stroke (ENCHANTED) and low-dose rTPA studies[3,11].

Cases of minor non-embolic stroke usually have mild symptoms (low NIHSS). However, whether a mild stroke is actually "mild" remains controversial since prospective data show that 30% of these patients are functionally disabled at 90 days after the stroke. The causes of these disabilities are either inadequate initial assessment of functional impairment or the worsening of cerebral infarction, in addition to multiple comorbid conditions in one patient leading to adverse events, including recurrent stroke.

When comparing CT and MRI use in managing ischemic stroke, studies[4,6,7,12] have shown that MRI is better than CT for detecting acute ischemia, especially in sensitivity to ischemic stroke. The risk of intracranial hemorrhage is higher after IV rTPA therapy with multiple microbleeds. Dannenberg et al[13] showed that the frequency of intracranial hemorrhage was 3.8% in patients with no or single microbleeds, 21.1% in patients with 2-4 microbleeds, and 30.0% in patients with ≥ 5 microbleeds.

In addition, a cerebral hemorrhage history is a contraindication factor increasing the risk of cerebral hemorrhages after fibrinolytic therapy in stroke patients11. CT cannot evaluate microhemorrhages or accurately assess the stage and nature of older brain lesions. MRI with susceptibility-weighted imaging or T2* and fluid-attenuated inversion recovery sequences can accurately assess microhemorrhage lesions and determine the timing of acute or chronic bleeding from older hemorrhagic lesions that are challenging to assess with CT[8].

MRI examinations can cover the whole brain without radiation, especially the posterior fossa area. In previous generations of MRI, the main limitation was the more time-consuming and challenging aspect of testing. However, 3T MRI has a total imaging time similar to CT. Capturing basic pulse sequences in acute stroke assessment takes about 12 minutes, including vascular examination. This speed is a remarkable advantage over previous generations of MRI (which took 20-30 minutes) in shortening the brain survey time for stroke patients. Therefore, MRI can provide accurate diagnoses in routine stroke emergencies regardless of the time of onset and symptom severity, even with nonexpert radiologists[8].

It is time-consuming for stroke patients before being admitted to the hospital, accounting for ~70% of total reperfusion treatment time. Nepal et al14 indicated that a hospitalization distance from stroke onset to the acute stroke center of < 20 km reduces time to reperfusion treatment (OR = 7.9, 95% CI: 3.8-16.5, $p < 0.05$). Time to reperfusion therapy was reduced when patients were immediately admitted to a comprehensive stroke center (OR = 4.2, 95% CI: 2.09-8.66, $p < 0.05$). If this time was optimized, the time for reperfusion therapy could be significantly shortened. In our study, wait times for hospitalization were significantly shorter when patients went directly to the hospital for stroke treatment without a referral ($p = 0.030$) or lived < 60 km from the hospital ($p = 0.006$). The time before admission was highly influenced by various factors, including the first aid knowledge of patients and their family members to identify a stroke (including about the golden hour for AIS), distance from stroke onset to a stroke center, convenience and availability of transportation, and taking an ambulance to the hospital[15]. Therefore, community-based interventions can spread awareness and improve public understanding of stroke, the golden hour for stroke, and engender the proper attitude about recognizing stroke patients. In addition, establishing widespread stroke centers with modest baseline capacity that can give IV rTPA and move patients to a higher center when needed and improving emergency services can improve stroke patient care, limiting their disability and death.

The most important role of alteplase is that it can help stroke patients regain nerve function and return to regular life. According to the NINDS study, IV alteplase treatment resulted in satisfactory neurological recovery in 13% of patients, equivalent to an mRS score of 0-1 at three months[16].

Most patients in our study were hospitalized with moderate (NIHSS of 6-10; 41.3%) and severe (NIHSS > 10; 19.6%) neurological deficits. Their mean NIHSS at admission was 7.5 ± 3.7, and the median was 6. These are relatively low scores compared to the NINDS trial[18]. Due to our selection of patients without major embolisms, the brain injury area was usually small and accompanied by mild to moderate neurological deficits. IV rTPA was an essential treatment for significantly improving daily activities after stroke. After 24 hours of rTPA treatment, the mild neurological deficit group improved by 78.3%, with a mean NIHSS of 3.9 ± 3.5, while the moderate and severe neurological deficit groups improved by 15.2% and 6.5%, respectively. The neurological deficit improvement occurred within seven days or before discharge, with 79.4% of cases considered mild, and severe cases decreasing to 4.3%, with an average NIHSS of 3.3 ± 3.5.

Our three-month recovery was better than that with the standard dose in the ECASS III trial[16] (52.4%) and ENCHANTED trial (48.9%)[3,11]. This difference might be explained by the other studies[3,6,17] having a higher mean NIHSS at admission, which is associated with lower positive outcomes and higher mortality. For example, the NINDS trial had a mean NIHSS of 14, a good recovery of 39%, and mortality of 17%[18]. Similarly, the ECASS III trial[16] had a mean NIHSS of 11, a good recovery of 52.4%, and a mortality of 6.7%.

Symptomatic intracranial hemorrhage is the most serious complication of rTPA treatment due to its association with an increased risk of death or severe disability[19]. Symptomatic intracranial hemorrhage in the NINDS trial[18] was 6.4%, of which 36.36% occurred in the first 12 hours and the rest within the first 24 hours. Subsequent studies showed this rate to be lower; it was 2.1% in the ENCHANTED trial[3,4,11].

Our study's age factor was associated with increased worse clinical outcomes. We extended the treatment to those aged ≥ 80 years. We also found that age was a poor prognostic factor for recovery (p = 0.010). The fibrinolytic treatment window (time factor) in our study lasted up to 4.5 hours. The high bleeding rate was associated with a longer time. While there were factors in our study negatively affecting clinical outcomes, compared to previous studies[7,16], most patients had positive clinical outcomes after three months, and adverse effects from fibrinolytic therapy were considerably minimized. The significant distinction depended on the apparent evaluation of the ischemic lesions by 3T MRI and a low fibrinolytic therapy dose.

Our study was observational and retrospective. Since it had a small sample size, it did not show statistically significant differences. Confounding factors, such as the proportion of patients with a history of diabetes, atrial fibrillation on the electrocardiogram, and cardiovascular disease, might affect the outcome variable. We will continue to collect samples for analysis with larger numbers to identify more apparent factors for treatment.

Conclusions

We have provided additional evidence for the efficacy and safety of intravenous rTPA therapy given to patients with AIS within 4.5 hours, with a rate of hemorrhagic complications without symptomatic intracranial hemorrhage of 1.1%. No patients died within three months. A brain MRI-based brain examination at the time of admission and, ultimately, low-dose rTPA therapy could help reduce morbidity and mortality.

Acknowledgments
The authors are grateful to the study participants and the medical staff for their assistance.

Informed Consent
Informed consent was obtained from all patients' representatives after a detailed explanation of the procedures.

Ethics Approval
The study protocol was approved by the Ethics Council for Biomedical Research at Can Tho S.I.S General Hospital (approval number: 5721A/QD-S.I.S; dated April 28, 2021). All procedures involving human participants were performed according to the ethical standards of the institutional and national research committees and the 1964 Declaration of Helsinki and its later amendments.

Availability of Data and Materials
The datasets generated and/or analyzed during the current study are not publicly available due to privacy concerns, but are available from the corresponding author on reasonable request.

Authors' Contributions
Q.-S. Huynh, C.-C. Tran, and M.-D. Nguyen made a substantial contribution to acquisition, analysis, and data interpretation. Q.-S. Huynh and M.-D. Nguyen prepared, drafted, and revised the manuscript critically for important intellectual content. Each author gave the final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest
The authors declare that they have no conflict of interest.

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