Original Paper

Thrombolysis in Chinese Ischemic Stroke Patients with Renal Dysfunction

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Key Words

Ischemic stroke · Intracerebral hemorrhage · Renal dysfunction · Thrombolytic therapy

Abstract

Background: Current data concerning the relationship between renal function and clinical outcome among stroke patients treated with intravenous thrombolytic therapy are conflicting. Our aim is to analyze whether the clinical outcome of Chinese ischemic stroke patients treated with thrombolytic therapy is affected by the presence of renal dysfunction. **Methods:** Chinese patients who received intravenous thrombolytic therapy for acute ischemic stroke were recruited. Renal dysfunction was defined as an estimated glomerular filtration rate (eGFR) <90 ml/min/1.73 m². The primary outcome was independent function (modified Rankin Scale, mRS, 0–2) at 3 months, while secondary outcomes included early improvement of the National Institute of Health Stroke Scale (NIHSS) score of ≥4 points at 24 h, symptomatic intracerebral hemorrhage (ICH) within 36 h of treatment and 30-day mortality. **Results:** A total of 199 patients were recruited, of whom 51.3% had renal dysfunction. There were no significant differences in functional independence at 3 months, NIHSS improvement at 24 h post-thrombolysis and 30-day mortality between patients with or without renal dysfunction. Multivariate analysis showed that eGFR as a continuous variable was not an independent risk factor for symptomatic ICH. **Conclusion:** Chinese ischemic stroke patients with renal dysfunction who received thrombolytic therapy had clinical outcomes similar to those without renal dysfunction.

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Introduction

Chronic kidney disease is shown to be associated with an increased risk of stroke [1, 2]. Moreover, renal dysfunction is also an independent predictor of long-term mortality and poor outcome in patients suffering from acute stroke [3, 4]. Intravenous thrombolytic therapy is a

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proven effective therapy for acute ischemic stroke patients. However, there is a small but definite increased risk of intracerebral hemorrhage (ICH) [5, 6].

Acute ischemic stroke is associated with unfavorably altered fibrin clot properties. Patients with renal failure were shown to have plasma fibrin clots that were less permeable and less susceptible to fibrinolysis than clots from healthy individuals. On the other hand, small-vessel cerebrovascular disease, microbleeds and platelet dysfunction described in patients with renal dysfunction may predispose patients to a higher risk of hemorrhage [7–11]. As a result, it is still uncertain whether it is the bleeding or thrombotic risk that will be more severely affected by renal dysfunction in acute stroke patients receiving thrombolytic therapy.

Currently, the data concerning the relationship between renal function and outcome among stroke patients who were treated with intravenous thrombolytic therapy are conflicting [12–20]. A recently conducted meta-analysis including 14 studies (n = 53,553 patients) has not revealed any significant difference in the odds of poor outcome or ICH between patients with and without renal dysfunction; while the risk of mortality after thrombolytic therapy was significantly higher in patients with renal dysfunction [21]. However, the majority of patients of these studies were from the Western populations and >50% of the data from the meta-analysis were from a US multicenter cohort study with 44,410 participants. Since racial differences in blood coagulation fibrinolysis factors can result in differences in responses to thrombolytic therapy [22, 23], the findings obtained from studies in Western populations may not be replicable in Chinese patients. As a result, we performed a retrospective cohort study to determine the effect of renal dysfunction on clinical outcome in our Chinese ischemic stroke patients treated with intravenous tissue plasminogen activator (tPA).

Patients and Methods

All consecutive Chinese patients who received intravenous tPA therapy for acute ischemic stroke within a time window of 3 h from December 1, 2008 to November 30, 2013 at the Queen Elizabeth Hospital, a tertiary care hospital in Hong Kong, were recruited in the study. Our inclusion criteria for thrombolytic therapy were largely adapted from the National Institute of Neurological Disorders and Stroke (NINDS) trial [5]. National Institute of Health Stroke Scale (NIHSS) scores were calculated. Investigations including blood tests and urgent noncontrast cerebral computed tomography (CT) were performed. The extent of hypodensity or swelling resulting from acute ischemic edema on baseline CT was quantified with the methods described in the Alberta Stroke Program Early CT Score Study (ASPECTS) [24]. Each eligible patient would receive a single intravenous alteplase dose of 0.9 mg/kg, with 10% given as a bolus, followed by a continuous intravenous infusion of the remainder over 1 h. No dose adjustment was made for renal function. A follow-up cerebral CT scan would be performed 24 h post-tPA and in situations of neurological deterioration.

Baseline demographic data and clinical variables were retrieved from patients' records. Based on the serum creatinine level measured on admission, the estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (MDRD) equation for Chinese patients [25]: $\text{eGFR (ml/min/1.73 m}^2\text{)} = 186 \times \text{Pcr}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.233$. Patients were divided into two groups based on the eGFR: (1) renal dysfunction group with $\text{eGFR} < 90 \text{ ml/min/1.73 m}^2$ and (2) normal GFR group with $\text{eGFR} \geq 90 \text{ ml/min/1.73 m}^2$.

The primary clinical outcome was independent function (modified Rankin Scale, mRS, 0–2) at 3 months. The secondary outcomes were early improvement of NIHSS score of ≥ 4 points at 24 h post-tPA treatment, symptomatic ICH within 36 h of tPA treatment and 30-day mortality. Symptomatic ICH was defined according to the ECASS (European Cooperative Acute Stroke Study) definition [26]. The study was approved by our local ethics committee.

Statistical Analyses

The software SPSS (SPSS 20.0, IMB Corp.) was used to perform the statistical analyses. Continuous data were expressed as means $\pm$ standard deviation (SD), and categorical data were expressed as percentages.

Table 1. Baseline characteristics, clinical parameters and clinical outcomes of patients with and without renal dysfunction

	Renal dysfunction group (n = 102)	Normal GFR group (n = 97)	p value
Age, years	72 ± 8.2	62 ± 11.6	<0.001
Male gender	66 (64.7)	60 (61.9)	0.77
Hypertension	72 (70.6)	41 (42.3)	<0.001
Diabetes mellitus	27 (26.5)	13 (13.4)	0.02
Hyperlipidemia	40 (39.2)	16 (16.5)	<0.001
Ischemic heart disease	19 (18.6)	3 (3.1)	<0.001
Atrial fibrillation	37 (36.3)	15 (15.5)	<0.001
History of smoking			0.12
Yes	14 (13.7)	18 (18.6)	
No	59 (57.8)	63 (64.9)	
Unknown	29 (28.5)	16 (16.5)	
Prior stroke	11 (10.8)	13 (13.4)	0.67
Prior use of antiplatelet	48 (47.1)	20 (20.6)	<0.001
SBP, mm Hg	149 ± 25	149 ± 24	0.98
DBP, mm Hg	81 ± 17	84 ± 17	0.24
Blood glucose, mmol/l	7.9 ± 3.8	7.2 ± 3.1	0.17
eGFR, ml/min/1.73 m ²	71.9 ± 14.8	114.8 ± 26.0	0.006
NIHSS score on admission	15.4 ± 8.6	11.6 ± 6.3	<0.001
Time from symptom onset to tPA, min	140 ± 41	147 ± 47	0.25
Symptomatic ICH	8 (7.8)	0 (0)	0.007
Asymptomatic ICH	21 (20.6)	11 (11.3)	0.09
mRS 0–2 at 3 months	57 (55.9)	61 (62.9)	0.31
NIHSS improvement ≥ 4 at 24 h	15 (14.7)	11 (11.3)	0.53
30-day mortality	14 (13.7)	5 (5.2)	0.05

Values are expressed as means ± SD or n (%). SBP = Systolic blood pressure; DBP = diastolic blood pressure.

Continuous data were analyzed by Student's t test to detect the difference between groups if the data were normally distributed; otherwise, the Mann-Whitney test would be used. Categorical data were analyzed by χ^2 test or Fisher's exact test. Clinical variables which were significantly associated with functional independence (mRS 0–2) at 3 months were detected using univariate analysis. Then, with respect to these variables, we determined which of them were independent predictors of functional outcome by multivariate logistic regression analysis using a backward and stepwise elimination method. A p value <0.05 was defined as statistically significant.

Results

A total of 199 Chinese patients were recruited in our study. The mean age was 67 ± 11 years. The mean admission NIHSS score was 14 ± 7.8 . The mean eGFR was 92.8 ± 28.1 ml/min/1.73 m². About half of our patients (102/199, 51.3%) had renal dysfunction (defined as eGFR <90 ml/min/1.73 m²). Amongst them, only 20 patients (10.1%) had eGFR <60 ml/min/1.73 m². The mean eGFR was 114.8 ± 26.0 ml/min/1.73 m² in the normal GFR group and 71.9 ± 14.8 ml/min/1.73 m² in the renal dysfunction group. None of our patients was on dialysis. The clotting profile and the platelet count of all patients were within normal reference range.

The baseline characteristics and clinical parameters are shown in table 1. Patients in the renal dysfunction group were significantly older, with a higher prevalence of hypertension,

diabetes mellitus, hyperlipidemia, atrial fibrillation, ischemic heart disease and history of antiplatelet use. They also had a significantly higher NIHSS score on admission. There was no significant difference in the mean time from symptom onset to tPA treatment between the two groups.

The clinical outcomes are shown in table 1. There was no significant difference in the proportion of patients who achieved mRS 0–2 at 3 months and early symptomatic improvement of NIHSS by ≥ 4 points. A total of 8 patients (4%) in our cohort developed symptomatic ICH and all of them were in the renal dysfunction group ($p = 0.007$). The renal dysfunction group also had a borderline higher 30-day mortality ($p = 0.05$).

Using multivariate logistic regression analysis, neither eGFR nor the presence of renal dysfunction was shown to be an independent factor for our primary outcome of mRS 0–2 or secondary outcomes of symptomatic ICH, NIHSS improvement at 24 h or 30-day mortality. The predictors of functional independence at 3 months (mRS 0–2) in our patients were the absence of a history of cerebrovascular disease (OR 3.56, 95% CI 1.27–9.99, $p = 0.016$), lower NIHSS (OR 1.11, 95% CI 1.06–1.16, $p < 0.001$) and the absence of early infarct signs on cerebral CT scan on admission (OR 4.27, 95% CI 2.20–8.25, $p < 0.001$).

Discussion

There have been conflicting results in different studies concerning the effect of renal dysfunction on the bleeding risk and efficacy of intravenous thrombolytic therapy in patients with acute ischemic stroke. A study by Lyrrer et al. [12] showed poorer functional outcome at 3 months for mild renal impairment (eGFR < 90 ml/min/1.73 m²), with an increased odds of poor functional outcome (mRS 3–6) for every 10 μ mol/l elevation in serum creatinine by 12.7%. In another study, moderate renal impairment (GFR < 60 ml/min) was associated with a decrease in efficacy of thrombolytic therapy, based on NIHSS scoring at 24 h and 7 days, but no significant difference in terms of risk of symptomatic ICH and in-patient mortality when compared with the normal renal function group [13]. A lower GFR, however, was shown to be associated with both poor 3-month neurological outcome and symptomatic ICH in a large European multicenter study [14]. Severe renal impairment (eGFR < 30 ml/min) was also associated with symptomatic ICH in two studies, but the impact on functional outcome or mortality was not studied [18, 19]. In a Japanese multicenter study, an increased risk of symptomatic ICH, poor functional outcome and death was found in patients with renal dysfunction (defined as eGFR < 60 ml/min/1.73 m²) even if a lower dose of tPA (0.6 mg/kg) was administered [15]. On the other hand, in other studies including one performed in Taiwan, eGFR < 60 ml/min/1.73 m² had no association with symptomatic ICH, functional outcome or mortality [16, 17]. In addition, in a US multicenter study involving 44,410 patients, eGFR < 60 ml/min/1.73 m² was not associated with risk-adjusted symptomatic ICH or serious systemic hemorrhage and did not significantly vary by renal dysfunction stage for either of these primary end points in multivariable analyses. However, patients with eGFR < 60 ml/min/1.73 m² were more likely to die in the hospital and have an unfavorable discharge functional status than those with normal renal function [20]. The difference in ethnicity of the study population, the cutoff value of eGFR for definition of renal impairment and the definition for the outcome measures made generalization of the results obtained from these studies difficult.

Racial differences in blood coagulation fibrinolysis factors can result in racial differences in responses to thrombolytic therapy which may lead to different clinical outcomes in Chinese ischemic stroke patients after tPA therapy [22, 23]. Our patients in the renal dysfunction group (defined as eGFR < 90 ml/min/1.73 m²) were older and more likely to have hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, atrial fibrillation, prior

antiplatelet use and a higher NIHSS score on admission. Many of these variables, namely age, hypertension, diabetes mellitus, prior use of antiplatelet agents, baseline NIHSS and early infarct changes on CT imaging have been found to be independent prognostic indicators for symptomatic ICH in different studies [27]. After multivariate logistic regression analysis, neither the serum creatinine level nor the presence of renal dysfunction were independent risk factors for 3-month functional independence, early NIHSS improvement, symptomatic ICH or 30-day mortality in our Chinese ischemic stroke patients receiving tPA therapy.

In our study, 60.2% of patients had mRS 0–2 at 3 months. This was comparable with the results of the SITS-MOST study (54.8%) [28] and TTT-AIS study (53.4%) [23]. Previous history of stroke, higher baseline NIHSS and early infarct changes on cerebral CT scan, but not renal dysfunction, were found to be independent predictors of poor functional outcome in our Chinese ischemic stroke patients receiving tPA therapy. In addition, 4% of patients developed symptomatic ICH in our study, a figure that was similar to that of the TTT-AIS study [23]. The bleeding risk after tPA may be further enhanced in patients with renal dysfunction due to the presence of endothelial and platelet dysfunction [8–11]. In our study, patients with renal dysfunction tend to develop more symptomatic ICH when compared with patients in the normal renal function group, which could be related to the differences in baseline demographic and clinical characteristics. In fact, eGFR as a continuous variable was not an independent risk factor for symptomatic ICH in multivariate regression analysis. Based on our study, the presence of mild renal dysfunction should not discourage physicians from using tPA in Chinese ischemic stroke patients, provided that the patients be closely monitored for bleeding complications. However, it cannot be confirmed whether tPA administration is still safe in patients with severe renal dysfunction and whether a lower dose of tPA should be used in our Chinese patients. Studies with a larger number of patients are required for further verification.

Our study has several limitations. First, it was a retrospective, nonrandomized study and it was possible that other unidentified confounders might have influenced the outcomes. Moreover, the sample size and event rates were small, limiting the statistical power of our study. The small sample size also limited our ability to further study the effect of lower eGFR strata such as eGFR <60 ml/min/1.73 m² or even <30 ml/min/1.73 m². In our cohort, only 10.1% of patients had eGFR <60 ml/min/1.73 m². Furthermore, the eGFR was based on the serum creatinine at presentation which might not truly represent a steady state, thus potentially leading to wrong classification. In addition, urine protein was not routinely estimated in our center and we might miss cases with renal dysfunction. Finally, we did not compare the influence of renal dysfunction on stroke outcome between tPA-treated patients and non-tPA-treated patients.

In conclusion, our study showed that Chinese ischemic stroke patients with renal dysfunction who received thrombolytic therapy had clinical outcomes in terms of good functional neurological outcome similar to those without renal dysfunction. Mild renal dysfunction should not be a reason discouraging the use of tPA in carefully selected stroke patients with close monitoring of bleeding complications, though further large scale studies are required for further clarification.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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