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Predictors of hemorrhagic complications after intravenous thrombolysis in acute cerebral infarction patients

A single-center study of 391 cases

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Abstract

For patients with ischemic stroke, intravenous (IV) thrombolysis with Urokinase within 6 hours has been accepted as beneficial, but its application is limited by high risk of hemorrhagic complications after thrombolysis. This study aimed to analyze the risk factors of hemorrhagic complications after intravenous thrombolysis using Urokinase in acute cerebral infarction (ACI) patients.

Total 391 consecutive ACI patients were enrolled and divided into 2 groups: the hemorrhagic complications group and the non-hemorrhagic complications group. The related data were collected and analyzed.

Univariate analysis showed significant differences in prothrombin time, atrial fibrillation (AF), Mean platelet volume, large platelet ratio (L-PLR), triglyceride (TG), Lactate dehydrogenase, alanine aminotransferase (ALT), high-density lipoprotein, and baseline National Institute of Health Stroke Scale score between the hemorrhagic complications and the non-hemorrhagic complications group ($P < .1$). Multivariate logistic regression analysis indicated that AF (odds ratio [OR] = 2.91, 95% confidence interval [CI] = 1.06–7.99 $P = .039$) was the risk factor of hemorrhagic complications, while ALT (OR = 0.27, 95% CI = 0.10–0.72 $P = .009$) and TG (OR = 0.16, 95% CI = 0.06–0.45 $P = .000$) were protective factors of hemorrhagic complications.

For patients with AF and lower levels of ALT or TG, the risk of hemorrhagic complications might increase after ACI.

Abbreviations: ACI = acute cerebral infarction, AF = atrial fibrillation, ALT = alanine aminotransferase, CT = computed tomography, IVT = intravenous thrombolysis, rt-PA = recombinant tissue plasminogen activator, TG = triglyceride.

Keywords: acute cerebral infarction, alanine aminotransferase, atrial fibrillation, hemorrhagic complications, triglyceride, urokinase

1. Introduction

Acute cerebral infarction (ACI) is the most common clinical cerebrovascular disease. ACI is caused by sudden arterial occlusion that blocks blood supply to the brain.[1] In the past few decades, clinical trials have shown that patients who received intravenous thrombolysis had significantly reduced disability at 3 months compared with patients who received placebo.[2,3] At present, the use of recombinant tissue plasminogen activator (rt-PA) intravenous thrombolysis in the treatment of ACI has become a clinical standard in the world.[4] In developing countries such as China, Urokinase is used more frequently than rt-PA, mainly because rt-PA is not covered by medical insurance and Urokinase is cheaper.[5] A limited number of studies performed with Urokinase have reported improvements in recanalization and neurological outcomes similar to those achieved with treatments with rt-PA.[6,7] However, Urokinase intravenous thrombolysis has a risk of hemorrhage. Patients with severe hemorrhage usually have a poor prognosis, with a mortality rate as high as 90%.[8] Up to now, most studies have focused on cerebral hemorrhage as a complication of intravenous thrombolysis. Although the symptoms of peripheral hemorrhage can affect the survival of patients after urokinase intravenous thrombolysis, few people discuss events related to peripheral hemorrhage.

Hemorrhagic complications include hemorrhagic transformation, gastrointestinal bleeding, urethral bleeding, skin and mucous membrane bleeding, and gum bleeding. In this study, we analyzed the predictors of hemorrhagic complications after urokinase

intravenous thrombolysis, which can predict the probability of hemorrhage before intravenous thrombolysis, and pay more attention to thrombolytic situation and prognosis of the patients.

2. Materials and methods

The study was approved by the ethics committee of the Zhaoqing Gaoyao People's Hospital, and written informed consent was obtained from all patients. A total of 391 patients with ACI received Urokinase thrombolysis therapy from January 2013 to October 2019. Urokinase 150×10^4 U diluted with 100 mL saline for patients with weight more than 50 kg and 100×10^4 U for patients with weight less than 50 kg was injected intravenously with in 1 hour. All patients were divided into a hemorrhagic complications group and a non- hemorrhagic complications group. Any hemorrhagic transformation was found by a head Magnetic Resonance Imaging or computed tomography (CT) scan after thrombolysis. Baseline patient information was collected including demographics, past-history, complications and the index of coagulation system and other blood test before intravenous thrombolysis (IVT).

The inclusion criteria were: patients suffered from ACI without coma within 6 hours[9–12]; age range between 18 and 85 years old; low density ischemic lesions were not observed via head CT scanning with cerebral hemorrhage eliminated; not pregnant; and patient or family members sign informed consent form.

The exclusion criteria were: patients with single attack of transient ischemic attack, rapid improvement of stroke and minor functional impairment; patients with subarachnoid hemorrhage via past history and CT scanning; prolonged blood pressure elevation (systolic blood pressure ≥185 mm Hg or diastolic blood pressure ≥110 mm Hg); patients showed hemorrhage, brain edema, arteriovenous malformation and tumor via CT; patients with infective endocarditis; patients received anticoagulant or heparin within 48 hours before stroke; patients suffered from arterial puncture within 7 days, major surgery or trauma within 14 days, and active continuing hemorrhage; and patients with blood system diseases, hemorrhagic diathesis, and coagulation disorder; international normalized ratio > 1.5; platelet < 100×10^9/L; Suffering from chronic diseases except hypertension, atrial fibrillation, diabetes. The flow chart for case selection was shown in Figure 1.

All the data were analyzed by SPSS V.19 version. Quantitative data in normal distribution were analyzed and compared by the t test between 2 groups. The enumeration data were analyzed using the Fisher exact test or the χ^2 test. Logistic regression analysis was applied to analyze the influencing factors for hemorrhagic complications.
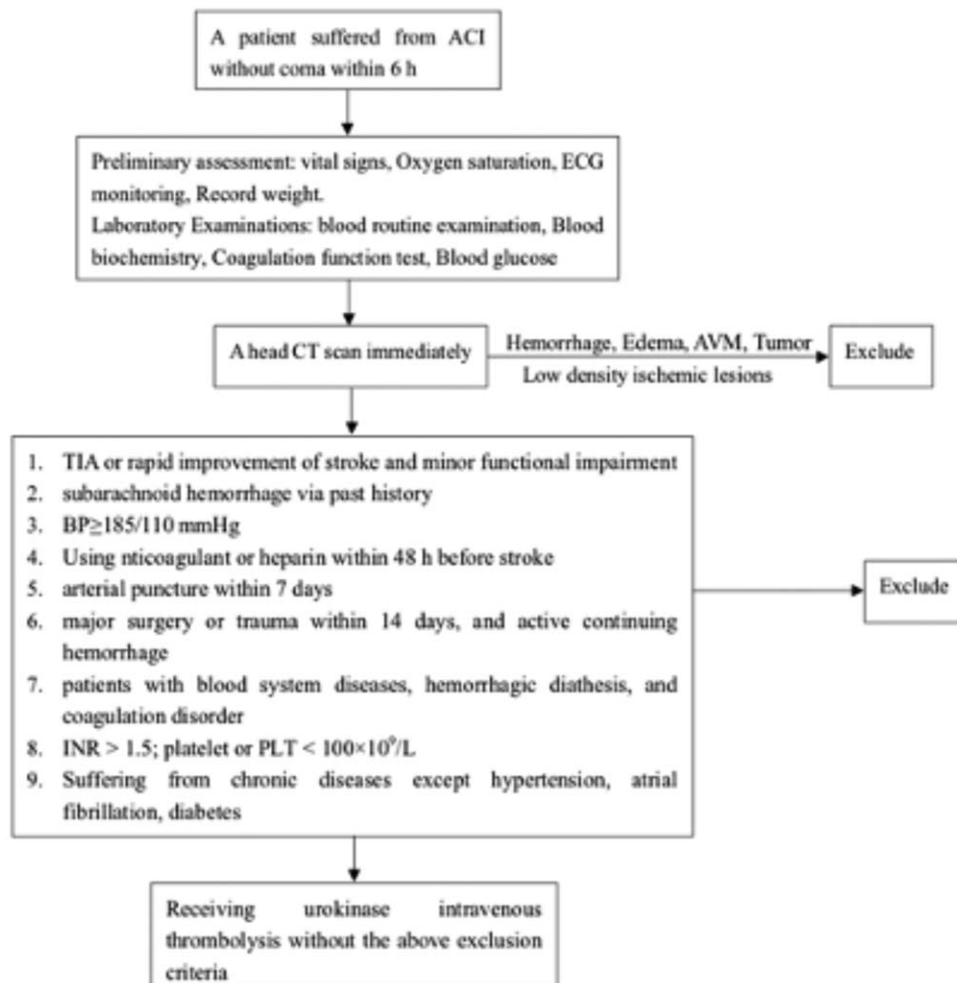

Figure 1. Flow chart of filtering cases.

Table 1

Basic information of the patients in 2 groups.

Variables	Non-hemorrhagic complications (n = 354) No. (%)	Hemorrhagic complications (n = 37) No. (%)	P value
Age (mean ± SD), yrs	67.17 ± 12.45	68.11 ± 10.76	.203
Gender, n (%)			.419
Male	155 (61.0)	20 (54.1)	
Female	99 (39.0)	17 (45.9)	
Smoking	96 (37.8)	13 (35.1)	.755
Drinking	36 (14.2)	6 (16.2)	.741
AF	212 (83.5)	23 (62.2)	.002*
Hypertension			.253
0	76 (30.0)	8 (21.6)	
1	9 (3.6)	4 (10.8)	
2	38 (15.0)	7 (18.9)	
3	130 (51.4)	18 (48.6)	
Diabetes mellitus	209 (82.3)	27 (73.0)	.177
Cerebral infarction (%)	209 (82.3)	34 (91.9)	.141
Severity of ICAS			.506
None or < 50%	10 (5.8)	0 (0.0)	
50% to 69%	79 (46.2)	6 (40.0)	
70% to 99%	31 (18.2)	4 (26.7)	
100%	51 (29.8)	5 (33.3)	

Values are median (IQR). AF = atrial fibrillation, ICAS = intracranial atherosclerotic stenosis, SD = standard deviation.

* $P < .05$.

3. Results

Total 391 patients were enrolled in our study, including 354 (90.5%) in the non-hemorrhagic complications group (mean age 67.17 ± 12.45 years; 155 males/ratio 61.0%) and 37 in the hemorrhagic complications group (mean age 68.11 ± 10.76 years; 20 males/ratio 54.1%).

Univariate analysis showed that there were no significant differences between the 2 groups in basic information such as gender, past history, drinking history, smoking history, and hypertension. However, atrial fibrillation (AF) was 1 variable that was significantly different between hemorrhagic complications group and non-hemorrhagic complications group (Table 1).

By analyzing the clinical and biochemical data, we observed that prothrombin time, Mean platelet volume, platelet-larger cell ratio, Lactate dehydrogenase, high-density lipoprotein and baseline National Institute of Health Stroke Scale score were significantly increased, whereas alanine aminotransferase (ALT) and triglyceride (TG) were significantly reduced in hemorrhagic complications group compared with non-hemorrhagic complications group ($P < .1$) (Table 2).

Next, we analyzed these factors using multiple logistic regression, choosing the following parameters: AF, prothrombin time ≥13.05 second, mean platelet volume ≥9.55 fl, platelet-larger cell ratio ≥19.6%, lactate dehydrogenase ≥180.5 IU/L, ALT ≥12.75 IU/L, TG ≥0.76 mmol/L, high-density lipoprotein ≥1.445 mmol/L, baseline National Institute of Health Stroke Scale score. The results showed that AF was risk factors and ALT and TG were the protective factors of hemorrhagic complications after IVT in acute cerebral infarction (Table 3).

4. Discussion

With continuous improvement of living conditions, ACI has become one of the most common diseases.[13] ACI has high morbidity and mortality rate, which has become one of the major diseases that endanger human health.[14,15] How to choose the best treatment has become a pivotal problem. At present, thrombolytic therapy has been the best intervention for ACI.[16] Most patients who receive urokinase thrombolysis have a good prognosis, compared with patients not receiving IVT.[12,17,18] However, hemorrhagic complication is one of the most serious complications of ACI. A total of 391 patients with ACI were included in this study, 37 of whom were confirmed to have hemorrhagic complications after IVT. These hemorrhagic complications include hemorrhagic transformation, gastrointestinal bleeding, urethral bleeding, skin and mucous membrane bleeding, and gum bleeding. Our study showed that the hemorrhagic complications rate was 9.4% after IVT, partially consistent with the results of previous studies.[17,19]

AF is an important cause of ACI, due to the occlusion of cerebral blood vessels. Hemorrhagic complications occurs in up to 71% of cardioembolic strokes.[20] The most commonly accepted explanation is that ACI is caused by the blockage of a large artery by the thrombus; this blockage then causes local vasospasm. The local vasospasm and fragmentation of the thrombus cause tissue ischemia, and damaged vessel walls and capillaries are exposed to reperfusion.[21] This is consistent with our findings.

In this study, we found that ALT was a protective factor of hemorrhagic complications. It is well known that liver dysfunction is related to hemorrhage, perhaps due to the decrease of blood coagulation factor and platelets.[22] According to previous studies, some liver function indicators play an important role in hemorrhagic complications.[23,24] For example, alkaline phosphatase, bilirubin and gamma glutamyl transpeptidase may play a harmful role in the prognosis of hemorrhagic complications through aggravating inflammation reaction, damaging cerebral vessels or enlarging edema after stroke.[23,25] However, other indicators such as ALT and aspartate aminotransferase were found to have neuroprotective effects and may improve the prognosis of hemorrhagic complications.[26,27] In our clinical practice, decompensated liver disease is a contraindication to

Table 2

Clinical and biochemical data of the patients in 2 groups.

Variables	Non-hemorrhagic complications (n = 354)	Hemorrhagic complications (n = 37)	P value
PT	12.80 (11.80–13.50)	13.10 (12.40–13.85)	.081[*]
APTT	33.60 (28.83–38.03)	33.20 (29.60–37.80)	.882
TT	17.10 (16.20–18.10)	17.25 (16.58–19.00)	.347
FIB	3.34 (2.81–3.95)	3.27 (2.97–3.94)	.931
PLT	221.50 (188.00–262.00)	216.00 (169.00–252.00)	.130
MPV	9.30 (8.70–10.00)	9.80 (8.85–10.45)	.058[*]
PDW	15.40 (10.70–15.90)	15.20 (12.45–16.00)	.645
P-LCR	20.40 (16.60–24.93)	22.60 (19.70–29.45)	.030[*]
LDH	202.20 (169.00–234.25)	222.50 (190.50–265.33)	.022[*]
Cre	76.10 (66.00–92.00)	75 (60.05–93.45)	.556
GLU	6.74 (5.74–8.25)	7.17 (6.29–9.85)	.127
GHb	5.80 (5.50–6.30)	5.75 (5.53–6.08)	.830
D-Dimer	404.00 (157.50–1011.00)	540.50 (230.25–1535.50)	.290
albumin	39.30 (35.68–42.21)	40.06 (35.90–42.75)	.866
DBIL	4.00 (3.00–5.70)	4.50 (3.10–7.70)	.247
I-Bil	8.50 (6.00–11.30)	9.20 (5.85–11.85)	.763
ALT	16.00 (12.40–23.10)	13.10 (8.75–20.10)	.065[*]
AST	21.80 (17.38–26.23)	22.80 (19.50–28.60)	.189
γ-GT	25.25 (19.00–39.00)	28.00 (20.60–40.00)	.766
TG	1.20 (0.90–1.69)	0.75 (0.57–1.20)	<.001[*]
TCHO	5.01 (4.19–5.92)	4.93 (3.97–5.55)	.438
HDL	1.18 (1.03–1.48)	1.47 (1.13–1.64)	.026[*]
LDL	3.00 (2.37–3.74)	2.81 (2.10–3.48)	.275
UA	346.80 (291.78–422.40)	344.30 (279.30–396.60)	.763
baseline NIHSS score	7 (4–10)	10 (7–16)	<.001[*]

Values are median (IQR). γ-GT = γ-glutamyl transpeptidase, ALT = alanine aminotransferase, APTT = acivated partial thromboplastin time, AST = aspartate aminotransferase, Cre = creatinine, DBIL = direct bilirubin, FIB = fibrinogen, GHb = glycated hemoglobin, GLU = blood glucose, HDL = high-density lipoprotein, I-Bil = indirect bilirubin, LDH = lactate dehydrogenase, LDL = low density lipoprotein, MPV = mean platelet volume, NIHSS = baseline National Institute of Health Stroke Scale, PDW = platelet distribution width, P-LCR = platelet -larger cell ratio, PLT = platelet, PT = prothrombin time, TCHO = total cholesterol, TG = triglyceride, TT = thrombin time, UA = uric acid.

[*] $P < .1$.

IVT. Therefore, for the patients with mild change of liver function, the liver may affect the prognosis of hemorrhagic complications through liver function indicators. Glutamate would accumulate after ACI, and ALT could protect cerebral tissue by decreasing glutamate.[26,27] Indeed, previous studies have demonstrated a beneficial relationship between ALT and outcome after ACI.[26,28] Moreover, glutamic-oxaloacetic transaminase 1 is involved in glutamate metabolism in AF condition.[29] These results suggest that we can reduce the risk of hemorrhagic complications by reducing glutamate.

In addition, we found that TG lower than 0.76 mmol/L was associated with hemorrhagic complications. Some studies have

Table 3

Logistic regression analysis of influencing factors of hemorrhagic complications.

Variables	OR	95% CI	P value
AF	2.91	1.06–7.99	.039[*]
PT ≥13.05	0.97	0.35–2.69	.959
MPV ≥ 9.55	1.47	0.39–5.49	.568
P-LCR ≥ 19.6	2.04	0.49–8.58	.329
LDH ≥ 180.5	1.78	0.51–6.23	.367
ALT≥12.75	0.27	0.10–0.72	.009[*]
TG ≥0.76	0.16	0.06–0.45	.000[*]
HDL ≥1.445	1.20	0.44–3.24	.725
baseline NIHSS score ≥6.5	2.27	0.77–6.73	.137

AF = atrial fibrillation, ALT = alanine aminotransferase, HDL = high-density lipoprotein, LDH = lactate dehydrogenase, MPV = mean platelet volume, NIHSS = baseline National Institute of Health Stroke Scale, P-LCR = platelet -larger cell ratio, PT = prothrombin time, TG = triglyceride.

[*] $P < .05$.

shown inconsonant relationship between triglyceride and hemorrhagic complications risk,[30,31] One recent study reported that low triglycerides levels were related to increased risk of hemorrhagic complications.[32] The mechanism by which low triglyceride levels promote hemorrhagic complications is unclear. In stroke-prone rats low serum cholesterol levels led to low cholesterol in erythrocyte membrane, and abnormal erythrocyte membrane fragility may cause arterial necrosis in endothelial cells.[33] Furthermore, low cholesterol could promote cerebro-vascular endothelium fragility.[34] The results of this study support these speculations.

This study has some limitations. First, this was a single-center retrospective study, the relatively small sample size might have caused some biases. Therefore, we should design prospective multi-center clinical trials with large sample size to confirm our results. Next, Urokinase used only in a few countries, it may cause racial bias. Third, we need explore the mechanisms by which these predictors cause hemorrhagic complications.

In conclusion, this study revealed some predictors of hemorrhagic transformation after IVT with Urokinase in ACI patients. In particular, patients with AF and lower levels of ALT or TG have increased risk of hemorrhagic complications after IVT with Urokinase. These patients should be given great attention during IVT treatment.

Author contributions

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