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# Comparison of safety and efficacy outcomes of intravenous thrombolysis in posterior vs. anterior circulation stroke

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## *Abstract*

*Background & Objectives:* Most previous large clinical studies of intravenous thrombolysis (IVT) focused on anterior circulation stroke (ACS). However, the results from ACS studies cannot fully represent posterior circulation stroke (PCS) patients due to their differences in symptoms, signs and etiologies. This study aimed to compare whether there are differences in thrombolysis outcomes between ACS and PCS patients who underwent IVT alone, and to explore predictors of outcomes in PCS after IVT. *Methods:* We included acute ischemic stroke (AIS) patients who underwent IVT and divided them into ACS and PCS groups according to clinical symptoms and neuroimaging examinations. A series of baseline data were collected while symptomatic intracranial hemorrhage (sICH), hemorrhagic cerebral infarction (HI), parenchymal hemorrhage (PH), all intracranial hemorrhage (aICH), mortality and the modified Rankin Scale (mRS) score were employed to assess thrombolysis outcomes. *Results:* Among 321 IVT-treated AIS patients, 87 had PCS. The incidence of sICH (1.1% vs. 9.8%, $p$=0.007), PH (1.1% vs. 9.8%, $p$=0.007), and aICH (4.6% vs. 15.8%, $p$=0.008) were lower in PCS than in ACS. A higher proportion of PCS achieved an excellent recovery (56.3% vs. 43.6%, $p$=0.042) and functional independence (66.7% vs. 53.8%, $p$=0.039) at 3 months poststroke. Logistic regression analysis identified the National Institutes of Health Stroke Scale (NIHSS) score ($p$<0.001) and pre-event antiplatelet therapy ($p$=0.005) as significant predictors of excellent recovery and the NIHSS score ($p$<0.001) as a unique predictor of functional independence at 90 days in PCS.
*Conclusions:* PCS patients had a lower risk of intracranial hemorrhage complications and better functional outcomes after IVT alone.

*Keywords:* Posterior circulation stroke, intravenous thrombolysis, acute ischemic stroke, symptomatic intracranial hemorrhage, cerebral infarction

## INTRODUCTION

Acute ischemic stroke (AIS) is a disease with high disability and mortality[1] that seriously threatens the health of people worldwide and places a tremendous economic burden on families and society. Intravenous thrombolysis (IVT) is one of the most effective reperfusion therapies that can rescue ischemic penumbra tissue before irreversible neural damage occurs and has been widely used in AIS patients within 4.5 hours after symptom onset.[2] Intracranial hemorrhage (ICH) is one of the most serious complications following IVT and can lead to neurological deterioration with an incidence of 1%-8%.[3] Posterior circulation stroke (PCS) accounts for approximately 20%-30% of all AIS.[4] The common atypical symptoms of PCS patients, such as dizziness or nausea, tend to be misinterpreted or even ignored, prolonging the time to diagnosis and even reducing the rate of thrombolytic therapy. Most previous large clinical studies of IVT[5,6] have focused on anterior circulation stroke (ACS), and data on PCS patients are rare. However, there are significant differences in the symptoms, signs and etiologies[7] between ACS and PCS; therefore, the results of ACS studies cannot fully represent PCS patients. Our purpose was to determine whether there are differences in thrombolysis outcomes between ACS and PCS patients who underwent IVT alone and to explore outcome predictors after IVT in PCS patients.

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## METHODS

We retrospectively analyzed data from a prospective registry of consecutive AIS patients who received IVT in Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University from January 2019 to June 2022. Eligibility for IVT treatment was determined by the current guideline.[8] All patients were treated with a standard dose of 0.9 mg/kg alteplase within 4.5 hours of symptom onset, and everyone received urgent computed tomography (CT) scan prior to IVT. Patients who received additional endovascular treatment (EVT) were excluded to avoid the influence of EVT on prognosis.

CT or magnetic resonance imaging (MRI) was performed within 48 hours after IVT. The classification of the infarction region was determined by a professional neurologist in cooperation with a radiologist based on neuroimaging examinations and clinical presentation. ACS was described as symptomatic ischemia involving the territories of the internal carotid system. Moreover, PCS was defined as acute infarctions in the vascular territory of the vertebrobasilar system. Patients with no definite infarction detected on CT or MRI were classified according to clinical presentation. In addition, those patients whose infarction involved the vascular region of both the anterior and posterior circulation were excluded.

This study was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province.

### *Data acquisition*

We collected the following variables: sex and age, risk factors associated with AIS (history of stroke and cancer, cigarette smoking, alcohol drinking, hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia), pre-event antiplatelet and anticoagulant medications, time from onset to treatment (OTT), baseline National Institutes of Health Stroke Scale (NIHSS) scores, systolic blood pressure (SBP) and diastolic blood pressure (DBP) prior to IVT, and laboratory data (blood glucose and platelets).

### *Outcome parameters*

We evaluated the safety outcomes of symptomatic intracranial hemorrhage (sICH), hemorrhagic cerebral infarction (HI), parenchymal hemorrhage (PH), all intracranial hemorrhage (aICH) and mortality within 3 months. ICH was divided into HI and PH by using the ECASS II definition. sICH was defined as any ICH associated with neurological deterioration according to the NINDS criteria.[9] aICH including HI, PH and subarachnoid hemorrhage.

Clinical outcomes were evaluated applying the modified Rankin Scale (mRS) score at 3 months poststroke, which was assessed by certified neurologists during follow-up outpatient visits or telephone interviews with the patients or their families. We defined mRS scores of 0 to 1 as excellent recovery and of 0 to 2 as functional independence.

### *Statistical analysis*

A comparison of baseline characteristics and outcome parameters between ACS and PCS patients was conducted. The Mann-Whitney U test was applied to compare continuous variables, while the Pearson chi-square test or Fisher's exact test were applied to compare categorical variables. Univariable regression was applied to explore the associations between potential risk factors and outcome variables, and then these filtered variables ($p<0.1$) were subjected to multivariate binary logistic regression. All analyses were performed using SPSS 26.0 (SPSS Inc., Chicago, IL, USA). A $p$ value $<0.05$ was considered statistically significant.

## RESULTS

During this study, 371 patients underwent IVT for AIS. Of those, 47 patients who received IVT bridging endovascular treatment and 3 patients with both vascular territories affected were excluded. Finally, 321 AIS patients were identified in our study. Among them, 234 (72.9%) had ACS, and 87 (27.1%) had PCS.

### *Baseline characteristics*

Age (median 72 vs. 68, $p=0.008$), baseline NIHSS scores (median 8 vs. 4, $p<0.001$), and the rate of atrial fibrillation (25.6% vs. 11.5%, $p=0.006$) were higher in ACS patients than in PCS patients (Table 1). There was no statistically significant difference in sex, hypertension, diabetes, hyperlipidemia, history of stroke and cancer, cigarette smoking and alcohol drinking, pre-event antiplatelet and anticoagulant medications, OTT, SBP or DBP prior to IVT, blood glucose, or platelets between the two groups (all $p>0.05$, Table 1).

**Table 1: Baseline characteristics and outcome parameters between the ACS and PCS groups**

| Variables | ACS(n=234) | PCS(n=87) | *P* |
|---|---|---|---|
| Age, Median, years | 72 | 68 | 0.008 |
| Male sex, n(%) | 133(56.8) | 53(60.9) | 0.51 |
| Hypertension, n(%) | 155(66.2) | 59(67.8) | 0.79 |
| Diabetes mellitus, n(%) | 45(19.2) | 13(14.9) | 0.375 |
| Atrial fibrillation, n(%) | 60(25.6) | 10(11.5) | 0.006 |
| Hyperlipidemia, n(%) | 103(44) | 33(37.9) | 0.327 |
| Cancer, n(%) | 9(3.8) | 2(2.3) | 0.733 |
| Cigarette smoking, n(%) | 74(31.6) | 37(42.5%) | 0.068 |
| Alcohol drinking, n(%) | 39(16.7) | 18(20.7) | 0.402 |
| Prior stroke, n(%) | 46(19.7) | 16(18.4) | 0.798 |
| Pre-event antiplatelet medication, n(%) | 32(13.7) | 12(13.8) | 0.978 |
| Pre-event anticoagulation, n(%) | 2(0.9) | 1(1.1) | 0.614 |
| Baseline NIHSS score, Median | 8 | 4 | <0.001 |
| OTT, Median, min | 153.5 | 154 | 0.621 |
| SBP prior to IVT, Median, mmHg | 157 | 166 | 0.066 |
| DBP prior to IVT, Median, mmHg | 86 | 83 | 0.213 |
| Blood glucose, Median, mmol/L | 6.86 | 7.35 | 0.377 |
| Platelet, Median, x10^9/L | 208.5 | 221 | 0.074 |
| sICH, n(%) | 23(9.8) | 1(1.1) | 0.007 |
| HI, n(%) | 11(4.7) | 3((3.4) | 0.766 |
| PH, n(%) | 23(9.8) | 1(1.1) | 0.007 |
| aICH, n(%) | 37(15.8) | 4(4.6) | 0.008 |
| Mortality within 90 days, n(%) | 33(14.1) | 6(6.9) | 0.079 |
| MRS score at 90 Days, Median | 2 | 1 | 0.006 |
| Functional independence at 90 days, n(%) | 126(53.8) | 58(66.7) | 0.039 |
| Excellent recovery at 90 days, n(%) | 102(43.6) | 49(56.3) | 0.042 |

ACS: anterior circulation stroke; PCS: posterior circulation stroke; NIHSS: National Institutes of Health Stroke Scale; OTT: time from onset to treatment; SBP: systolic blood pressure; IVT: Intravenous thrombolysis; DBP: diastolic blood pressure; sICH: symptomatic intracranial hemorrhage; HI: hemorrhagic cerebral infarction; PH: parenchymal hemorrhage; aICH: all intracranial hemorrhage; MRS: modified Rankin Scale.

*Outcome parameters*

The incidence rates of sICH (1.1% vs. 9.8%, $p$=0.007), PH (1.1% vs. 9.8%, $p$=0.007), aICH (4.6% vs. 15.8%, $p$=0.008) were lower in the PCS group than in the ACS group (Table 1). The overall MRS scores (median 1 vs. 2, $p$=0.006) of PCS patients were lower than in ACS group at 3 months (Table 1). PCS patients were more likely to achieve functional independence at 3 months (66.7% vs. 53.8%, $p$=0.039) and excellent recovery at 3 months (56.3% vs. 43.6%, $p$=0.042) than ACS patients, but no significant difference in 90-day mortality (6.9% vs. 14.1%, $p$=0.079) was discovered (Table 1).

*Logistic regression analysis*

For all AIS patients, logistic regression analysis after adjustment for the covariates identified the baseline NIHSS score ($p$<0.001), prior stroke ($p$=0.006) and hypertension ($p$=0.013) as independent predictors of sICH; the NIHSS score ($p$<0.001), prior stroke ($p$=0.005), hypertension ($p$=0.007) and atrial fibrillation ($p$=0.006) were shown to be independently associated with aICH; age ($p$=0.001), prior stroke ($p$=0.011), and the NIHSS score ($p$<0.001) were independent predictors of mortality (Table 2).

For PCS patients, multivariate logistic

**Table 2: Multivariate logistic regression depicting the associations of variables and the respective outcomes**

| Outcomes | Variables | OR | 95%CI | *P* |
|---|---|---|---|---|
| sICH in all AIS | NIHSS score | 1.189 | 1.119-1.264 | <0.001 |
| | Prior stroke | 4.499 | 1.535-13.185 | 0.006 |
| | Hypertension | 0.285 | 0.106-0.766 | 0.013 |
| aICH in all AIS | NIHSS score | 1.114 | 1.061-1.171 | <0.001 |
| | Prior stroke | 3.328 | 1.443-7.671 | 0.005 |
| | Hypertension | 0.353 | 0.165-0.755 | 0.007 |
| | Atrial fibrillation | 2.972 | 1.375-6.427 | 0.006 |
| Mortality in all AIS | Age | 1.076 | 1.030-1.125 | 0.001 |
| | Prior stroke | 3.353 | 1.320-8.518 | 0.011 |
| | NIHSS score | 1.221 | 1.139-1.310 | <0.001 |
| Excellent recovery in PCS | NIHSS score | 0.608 | 0.481-0.770 | <0.001 |
| | Pre-event antiplatelet therapy | 0.058 | 0.008-0.430 | 0.005 |
| Functional independence in PCS | NIHSS score | 0.668 | 0.548-0.814 | <0.001 |

AIS: anterior circulation stroke.

regression analysis identified the NIHSS score ($p$<0.001) and pre-event antiplatelet therapy ($p$=0.005) as significant predictors of excellent recovery at 90 days; the NIHSS score was a unique predictor of functional independence at 3 months in the PCS group (Table 2).

## DISCUSSION

Our study investigated the outcome differences between ACS and PCS patients treated with IVT alone and explored the predictors of favorable outcomes in the PCS group. The major findings in this study indicated that the incidence rate of ICH, including sICH, PH and aICH, among PCS patients was significantly lower than that among ACS patients after IVT. For PCS patients, the baseline NIHSS score and pre-event antiplatelet therapy were identified as predictors of excellent recovery, while the NIHSS score was identified as a unique predictor of functional independence at 90 days.

Regarding the comparison of thrombolytic outcomes in PCS and ACS patients, some earlier studies showed no significant difference between them. After excluding patients with PCS in the infratentorial region, Breuer L *et al*.[10] found that there was no substantial difference between patients with AIS involving the supratentorial posterior cerebral artery (PCA) territory and those with ACS. Forster A *et al*.[11] compared PCS (n=30) and ACS (n=198) patients who underwent IVT within 3 h after onset and found that the risk of ICH was the same in both groups. In recent years, several multicenter observational studies found that PCS patients had a lower frequency of ICH.[12,13] Keselman B *et al*.[12] included 753 PCS patients, and an additional meta-analysis found that the risk of ICH complications after IVT in PCS was significantly lower than that in ACS, which was consistent with our results. Moreover, we observed a higher proportion of functional independence and excellent recovery at 90 days in PCS patients, probably because those who received bridging EVT were excluded. To our knowledge, basilar artery occlusion stroke is one of the most devastating forms of AIS, with a high rate of dependency or death despite timely reperfusion therapy.[14] In addition, for common symptoms of PCS such as vertigo and ataxia, obvious neurological deficits are less likely to remain after rehabilitation. Overall, the lower risk of ICH and favorable functional outcomes in PCS patients suggested that the benefit of IVT in PCS may be greater, even beyond 4.5 h, and that the benefit probably outweigh the potential risk.

The mechanism underlying the lower risk of ICH in PCS has not been clarified. Currently, age, stroke severity, atrial fibrillation, blood glucose and

pre-event antiplatelet therapy are well-established predictors of ICH in AIS.[15] Our study showed that there were some differences in baseline data between the two groups: patients with PCS were younger, had a lower proportion of atrial fibrillation and had lower NIHSS scores. Similar differences in age[12,16], atrial fibrillation[12,13,16] and the NIHSS score[12,17] were reported in several studies, which potentially affect the incidence of ICH, although it is well known that the NIHSS has limitations to assess stroke severity in PCS patients. There are several possible hypotheses. Previous studies have shown that good collateral circulation was associated with a favorable prognosis and a reduced risk of ICH[18]; therefore, strokes of the posterior circulation may be less susceptible to hemorrhagic transformation due to better collateral circulation[19] and lower infarct volume[20] than ACS. Furthermore, white matter, which is more abundant in the brain stem than in other parts of the brain, might increase ischemia tolerance. Unfortunately, owing to the low incidence of ICH in PCS patients, logistic regression analysis of predictors of ICH was undermined in most prevenient published studies.[13,17,21] Dornak T *et al*.[22] included 158 PCS and identified atrial fibrillation, the NIHSS score, occlusion of the basilar artery or PCA and additional EVT as predictors of ICH in PCS. However, for patients who receive IVT alone, the data are lacking, and studies with larger samples are needed in the future. For predictors of favorable outcomes in PCS, we identified the baseline NIHSS score as the unique predictor of functional independence at 90 days, which was consistent with a recent report.[23] This means that the NIHSS can be used to assess the prognosis of PCS, despite its validity in evaluating stroke severity in PCS, which might be discounted. We considered that infarct volume probable be a better parameter to assess PCS patients compared with the NIHSS score. Regrettably, we lacked relevant data, further studies to explore whether infarct volume is a specific thrombolysis outcome predictor in PCS patients are valuable.

In conclusion, this study showed that PCS patients had a lower risk of ICH complications and better functional outcomes after IVT alone. Therefore, appropriately extending the time window with PCS can be considered. Further prospective multicenter studies are needed to establish the results of our study.

There were several limitations of our study. First, we did not assess the presence of a fetal-type posterior cerebral artery. Second, unknown factors may have influenced follow-up outcomes due to different treatment procedures for discharged patients. Third, the sample size was relatively small, and caution should be taken when interpreting the results.

## DISCLOSURE

Conflict of interest: None.

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