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Sarikaya, H ; Arnold, M ; Engelter, S T ; Lyrer, P A ; Mattle, H P ; Georgiadis, D ; Bonati, L H ; Fluri, F ; Fischer, U ; Findling, O ; Ballinari, P ; Baumgartner, R W

Abstract: BACKGROUND AND PURPOSE: Intravenous thrombolysis is an approved treatment for anterior (ACS) and posterior (PCS) circulation stroke. However, no randomized controlled trial has investigated safety and efficacy of intravenous thrombolysis according to stroke territory, although PCS is assumed to differ from ACS in many ways. We aimed to compare the safety and clinical outcome of intravenous thrombolysis applied to patients with PCS and ACS. METHODS: Prospectively collected data of 883 consecutive patients with acute ischemic stroke (788 ACS, 95 PCS) treated with intravenous thrombolysis in 3 Swiss stroke centers were analyzed. Presenting characteristics, symptomatic intracranial hemorrhage, mortality, and favorable outcome (modified Rankin scale 0 or 1) at 3 months were compared between patients with PCS and ACS. RESULTS: As compared with patients with ACS, those with PCS were younger (mean age, 63 versus 67 years, P=0.012) and had a lower mean baseline National Institutes of Health Stroke Scale score (9 versus 12, P<0.001). Patients with PCS less often had symptomatic intracranial hemorrhage (0% versus 5%, P=0.026) and had more often a favorable outcome (66% versus 47%, P<0.001). Mortality was similar in the 2 groups (PCS, 9%; ACS, 13%; P=0.243). After multivariable adjustment, PCS was an independent predictor of lower symptomatic intracranial hemorrhage frequency (P=0.001), whereas stroke territory was not associated either with favorable outcome (P=0.177) or with mortality (P=0.251). CONCLUSIONS: Our study suggests that PCS is associated with a lower risk of symptomatic intracranial hemorrhage after intravenous thrombolysis as compared with ACS, whereas favorable outcome and mortality were similar in the 2 stroke territories.

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Outcomes of Intravenous Thrombolysis in Posterior Versus Anterior Circulation Stroke

H Sarikaya,MD[1], M Arnold,MD[2], ST Engelter,MD[3], PA Lyrer,MD[3], HP Mattle,MD[2], D Georgiadis,MD[1], LH Bonati,MD[3], F Fluri,MD[3], U Fischer,MD[2], O Findling,MD[2], P Ballinari,PhD[4], RW Baumgartner,MD[1]

Department of Neurology, University Hospital of Zurich, Switzerland[1]

Department of Neurology, University Hospital of Bern, Switzerland[2]

Department of Neurology, University Hospital of Basel, Switzerland[3]

Institute of Psychology, University of Bern, Switzerland[4]

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Corresponding author: Hakan Sarikaya, MD

Neurology Department

University Hospital of Zurich

8091 Zurich, Switzerland

Tel. +41 44 255 11 11

Fax +41 44 255 88 64

E-mail: hakan.sarikaya@usz.ch

Background and Purpose. Intravenous thrombolysis (IVT) is an approved treatment for anterior (ACS) and posterior (PCS) circulation stroke. However, no randomized-controlled trial has investigated safety and efficacy of IVT according to stroke territory, although PCS is assumed to differ from ACS in many ways. We aimed to compare the safety and clinical outcome of IVT applied to patients with PCS and ACS.

Methods. Prospectively collected data of 883 consecutive patients with acute ischemic stroke (788 ACS, 95 PCS) treated with IVT in three Swiss stroke centers were analyzed. Presenting characteristics, symptomatic intracranial hemorrhage (sICH), mortality and favorable outcome (modified Rankin scale 0 or 1) at 3 months were compared between patients with PCS and ACS.

Results. As compared to patients with ACS, those with PCS were younger (mean age 63 vs. 67 years, p=0.012) and had a lower mean baseline National Institutes of Health Stroke Scale score (9 vs. 12, p<0.001). Patients with PCS less often suffered sICH (0% vs. 5%, p=0.026) and had more often a favorable outcome (66% vs. 47%, p<0.001). Mortality was similar in the two groups (PCS, 9%; ACS, 13%; p=0.243). After multivariable adjustment, PCS was an independent predictor of lower sICH frequency (p=0.001), whereas stroke territory was associated neither with favorable outcome (p=0.177) nor with mortality (p=0.251).

Conclusion. Our study suggests that PCS is associated with a lower risk of sICH after IVT as compared with ACS, while favorable outcome and mortality were similar in the two stroke territories.

INTRODUCTION

Intravenous thrombolysis (IVT) is an approved treatment of acute ischemic stroke in anterior (ACS) and posterior (PCS) cerebral circulation. However, PCS differs from ACS in stroke etiology and outcome, as PCS is more often due to atherosclerosis,[1-2] and prognosis is assumed to be worse with a higher morbidity and mortality,[3] the latter reaching up to 54% after basilar artery occlusion.[4] In spite of these presumed differences, knowledge about safety and efficacy of IVT in PCS is sparse for several reasons: (1) no randomized, controlled trial or phase IV study has investigated safety and efficacy of IVT according to stroke territory;[5-10] (2) just 5% of patients from the National Institutes of Neurological Diseases and Stroke (NINDS) study had PCS, although approximately 20-25% of all ischemic strokes are localized in the posterior circulation;[5, 11-12] (3) The European Cooperative Acute Stroke Study (ECASS) I and II trials included only patients with hemispheric stroke syndromes,[6-7] whereas the Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) and the ECASS III trials did not report on the number of patients with PCS.[8-9, 13]

We undertook this multicenter, observational study to compare safety and clinical outcome of IVT according to stroke territory.

PATIENTS AND METHODS

We studied prospectively collected data of consecutive patients with acute ischemic stroke who underwent IVT with alteplase, but no other or additional thrombolytic treatment in the stroke centers of the University Hospitals Basel, Bern and Zurich from June 1998 to December 2008. Baseline investigations included neurologic and physical examination, assessment of stroke severity by using the National Institutes of Health Stroke Scale (NIHSS),[14] routine blood analysis, 12-lead electrocardiography (ECG), brain computed tomography (CT) and/or magnetic resonance imaging (MRI). The following variables were ascertained: age, gender, baseline NIHSS score, vascular risk factors according to predefined criteria,[15] atrial fibrillation, history for coronary artery disease, antithrombotic medication, time to treatment, stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria,[16] blood pressure and blood glucose values. Thrombolysis was applied according to current guidelines by using intravenous alteplase 0.9 mg/kg to a maximum of 90 mg, ten percent of the total dose given as a bolus and the remaining dose in the next hour.[17] Prestroke modified Rankin Scale (mRS) score >1 was no reason for exclusion. All patients treated with IVT were admitted to intermediate or intensive care units for at least 24 hours. The centers Basel and Zurich treated patients primarily with IVT, whereas the center Bern performed more intra-arterial and/or mechanical thrombolyses, especially in patients with basilar artery occlusion. All centers used the 3-hour time window for IVT. The investigators in Zurich extended the time window to 4.5 hours from March 2002 onwards, while this was the case in Bern and Basel from October 2008 onwards. The rationale was the pooled analysis by Hacke and colleagues presented at the 27th International Stroke Conference in February 2002 (San Antonio, Texas) and the ECASS III trial published in September 2008, respectively.[13, 18]

Classification of PCS and ACS

PCS was defined as a symptomatic infarct in the territory of the vertebral, the cerebellar or the posterior cerebral arteries or the basilar artery.[1] ACS was defined as a symptomatic infarct in the territory of the middle or anterior cerebral artery or both. Lesions that were asymptomatic or not congruous with the clinical presentation were not considered. The classification of stroke territory was performed by one experienced senior stroke physician in each center (Basel, STE; Bern, MA; Zurich, RWB) by using both clinical and radiological findings.

Outcome parameters

All intracranial hemorrhages (ICH) were ascertained on follow-up CT or MRI obtained within 48 hours after IVT and additional scans in case of clinical deterioration. Symptomatic intracranial hemorrhage (sICH) was defined as any intracranial bleed temporally related to a neurological deterioration (NINDS criteria).[5] In addition, we also used the more conservative definition from the ECASS II trial.[7] Clinical outcomes were all-cause mortality and the level of independence measured by mRS score at 3 months, with favorable outcome defined as a score of 0-1, and unfavorable as a score of 2-6. The mRS scores were assessed by certified neurologists by clinical examination or structured telephone interview with the patient or caregiver.

Statistical analysis

Normally distributed data were expressed as mean ± standard deviation (SD) and compared using t-test. The two groups (IVT treatment in anterior versus IVT treatment in posterior circulation stroke) were compared using the Mann-Whitney test for continuous variables and the chi-square or Fisher exact test (the latter if some expected counts in the two-by-two table were too low) for dichotomous variables.

Multiple logistic regression analyses were performed to assess the joint effects of the affected territory (anterior versus posterior) and the other predictors on the outcome parameters sICH, mortality and favorable outcome. In a first step, the influence of every single potential predictor on the outcome parameters was evaluated using univariate logistic regression analysis. The parameters examined were age, admission NIHSS score, time to treatment, systolic and diastolic blood pressure, blood glucose levels on admission (continuous variables), patients gender, arterial hypertension, smoking status, diabetes mellitus, hypercholesterolemia, coronary artery disease, atrial fibrillation, diabetes mellitus and medication with antiplatelets or anticoagulants at stroke onset (categorical variables). In a second step, a multivariate logistic regression analysis was performed, including all potential predictors with a p-value < 0.2 from univariate analyses into the model. The parameter stroke territory (ACS or PCS) was forced in both models. For evaluating the association of stroke territory with sICH in logistic regression model, we used 1000 Bootstrap samples to estimate the standard error of the regression coefficients. Significance was declared at $p<0.05$ level. IBM SPSS Statistics 18.0 was used for all analyses.

RESULTS

Study population

Between June 1998 to December 2008, 892 consecutive patients at three centers underwent IVT for acute ischemic stroke (Basel, n=359; Berne, n=116; Zurich, n=468). Nine of the 892 patients were excluded, because the affected vascular territory remained unclear (n=9). Of the 883 patients included, 95 (11%) suffered PCS and 788 (89%) ACS. No patient showed combined clinical and radiological findings of both ACS and PCS. Baseline characteristics, stroke severity and etiology of the two groups are shown in Table 1. Patients with PCS were younger (63 vs. 67 years, p=0.012) and had

lower mean NIHSS scores (9 vs. 12, p<0.001), whereas the other characteristics did not differ between the two groups. Basilar artery occlusion was diagnosed in 10 of 95 (11%) patients with PCS.

Outcomes

At 3 months, clinical outcome was available in 878 (99%) and sICH classification in 877 (99%) of the included 883 patients. Five (<1%) patients were lost to follow-up, one with PCS and 4 with ACS.

Using the NINDS criteria, a total of 36 (4%) patients suffered a sICH, and 10 of these were fatal. Symptomatic ICH occurred in 5% of patients with ACS, but in none of patients with PCS (p=0.026) (Table 2). Multivariate logistic regression analyses identified atrial fibrillation (p=0.019), antiplatelet medication (p=0.025) and diastolic blood pressure (p=0.029) as independent predictors of sICH. With respect to the lack of sICH in PCS, we applied the bootstrap method for estimating the standard error of the regression coefficients. When assessing the joint effects of stroke territory, atrial fibrillation, antiplatelet medication and diastolic blood pressure on sICH, we identified a strong association between stroke territory and sICH (p=0.001) independent from the other predictors (Table 2). Applying the ECASS II criteria, sICH was observed in 26 of 883 (3%) patients, all of which occurred in ACS. The statistical difference was less pronounced (p=0.049), but still significant in logistic regression analysis by using the bootstrap method (p=0.001).

A total of 108 (12%) patients died during the three month follow-up period. Mortality did not significantly differ between the two groups (PCS, 9%; ACS, 13%; p=0.243) (Table 2). Multivariate logistic regression analyses identified age (p<0.001), NIHSS score (p<0.001) and blood glucose (p=0.001) as independent predictors of mortality.

No association between stroke territory and mortality was observed after adjusting for these predictors (p=0.251) (Table 2).

A favorable outcome was observed in 426 (49%) patients. Favorable outcome occurred more often in patients with PCS (66%) as compared to those with ACS (47%, p<0.001) (Table 2). Multivariate logistic regression analyses showed NIHSS score (p<0.001), blood glucose (p<0.001), age (p=0.006), antiplatelet medication (p=0.008), and anticoagulation (p=0.022) to be independently associated with favorable outcome. Stroke territory no longer predicted favorable outcome after adjustment for these predictors (p=0.177) (Table 2).

DISCUSSION

To our best knowledge, this is the largest series assessing the safety and clinical outcome of IVT for PCS in comparison to ACS. Few studies have examined IVT in patients with PCS; most of them had a small sample size (range of 9 to 12 patients)[19-21] or were restricted to patients with basilar artery occlusion.[4, 22]

The rate of patients with PCS (11%) was lower than reported in other studies, which may be explained by the following reason: our study excluded patients with PCS who received endovascular treatment or conservative therapy only, the latter being the case in 31% of patients in the BASICS registry.[4] Furthermore, patients with PCS might have more (relative) contraindications for IVT such as National Institute of Health (NIHSS) score ≤4 points or fluctuating stroke symptoms.[5, 23-24]

The main finding of the present study was the lack of sICH in patients with PCS; after multivariable adjustment, PCS was associated with a lower sICH risk. In line with our findings, a previous study reported a significantly lower rate of hemorrhagic transformations after IVT for basilar artery occlusions as compared to middle cerebral artery occlusions and no sICH in basilar artery occlusions.[25] Older age, history of diabetes, aspirin pre-treatment, high NIHSS score at baseline, high systolic blood pressure at presentation and high baseline blood glucose have been described as independent predictors of sICH following IVT.[26] In the present study, the frequency of diabetes mellitus and baseline blood glucose levels were similar in patients with PCS and ACS. Patients with PCS had significantly lower baseline NIHSS scores as compared to those with ACS in the present study. A similar difference in NIHSS baseline scores was reported in two other studies.[23-24] This may partly be explained by the fact that the NIHSS has limitations in the assessment of stroke severity in PCS, as it is highly weighted toward deficits in ACS such as aphasia and hemiparesis, whereas signs of PCS including bulbar deficits and ataxia receive fewer points.[27] Furthermore,

NIHSS in PCS does not correlate with volume of ischemic lesion and lesion volume in PCS does not predict outcome,[28-29] which is in contrast to ACS.[30] Thus, we believe that the observed differences in NIHSS scores between patients with PCS and ACS may rather be related to shortcomings of the NIHSS. The age difference between the two patient groups was statistically significant but unlikely to account for such a pronounced discrepancy in the sICH rates between stroke territories. Smaller infarct volumes may be a reason for lower sICH rates in PCS; however, the reason for this remains hypothetical and we do not have any data about the ischemic or infarct volumes in both territories. From anatomical point of view, one argument might be the difference in vessel calibers as especially the brainstem is nourished by small endarteries. Collateral flow through the posterior communicating or the cerebellar arteries may lead to a slower evolution of irreversible ischemia in PCS with proximal artery occlusion.[31] However, there are currently no anatomic nor clinical-epidemiological studies to support that collateral supply is better in posterior circulation, thus this argument remains rather hypothetical.

In our study, mortality between PCS and ACS did not differ significantly in univariate and multivariate analyses. Favorable clinical outcome following IVT was more frequent in patients with PCS as compared to those with ACS in univariate analysis ($p<0.001$). The association of favorable outcome with PCS was no longer significant after multivariable adjustment, however ($p=0.177$). We are not aware of other studies that assessed the outcome after IVT according to stroke territory, thus no comparisons to existing literature can be undertaken.

The present study has several limitations. First, comparisons of stroke severity between PCS and ACS by using the NIHSS may not be quite accurate, as discussed above. Still, this drawback is currently inevitable in the absence of an alternative established evaluation tool. Second, a bias in patient selection is probable in view of a

multi-center study with different treatment preferences. A total of 631 patients with ischemic stroke underwent intra-arterial and/or mechanical thrombolysis during the study period at the three centers. Of these 631 patients, 116 had PCS and 515 ACS. Some patients with severe basilar artery occlusion may have been excluded due to endovascular treatment. On the other hand, this bias might be counterbalanced by the exclusion of severe ACS with middle cerebral artery occlusion, either due to treatment with intraarterial thrombolysis or ultrasound enhanced IVT. Third, we were not able to assess early recanalization rates and infarct volumes, which might have additionally influenced the sICH risk. The number of patients with PCS was small precluding definite conclusions on outcome differences between both stroke territories. Number of patients with prestroke mRS >1 would be valuable for interpretation of the results with respect to clinical outcome, the latter defined as mRS score 0-1 at 3 months. Unfortunately, we did not systematically evaluate the prestroke mRS in this study. Finally, we did not assess the presence of carotid blood supply to posterior cerebral circulation.

In conclusion, our study suggests that PCS is associated with a lower risk of sICH after IVT as compared with ACS, while favorable outcome and mortality were similar in the two stroke territories.

Table 1. Baseline Characteristics of 95 Patients with Posterior Circulation Stroke and 788 Patients with Anterior Circulation Stroke.

	Posterior circulation stroke (n=95)	Anterior circulation stroke (n=788)	*P* Value
Male sex [%]	62.1	62.8	0.892
Mean age ± SD [years]	62.9 ± 15.1	66.9 ± 14.3	0.012*
Hypertension [%]	62.1	63.1	0.854
Current smoking [%]	25.3	24.8	0.918
Diabetes mellitus [%]	16.0	13.6	0.528
Hypercholesterolemia [%]	46.4	38.7	0.171
Antiplatelet medication at stroke onset [%]	38.9	36.1	0.584
Anticoagulation at stroke onset [%]	1.1	2.4	0.714†
Coronary artery disease [%]	19.1	18.0	0.793
Atrial fibrillation [%]	17.0	24.6	0.102
Mean NIHSS score ± SD	9.3 ± 7.9	12.2 ± 5.9	<0.001*
Time to treatment ± SD	169.0 ± 54.5	160.0 ± 40.0	0.243*
Mean systolic blood pressure ± SD [mm Hg]	152.8 ± 24.7	155.6 ± 24.9	0.211*
Mean diastolic blood pressure ± SD [mm Hg]	85.9 ± 14.7	88.1 ± 16.4	0.210*
Mean blood glucose ± SD [mmol/L]	6.9 ± 2.6	6.9 ± 2.4	0.890*
Cause of stroke			
Large artery atherosclerosis [%]	15.2	12.9	
Cardiac embolism [%]	43.5	47.8	
Small artery disease [%]	8.7	4.3	0.331
Other determined etiology [%]	6.5	9.2	
Undetermined etiology [%]	26.1	25.9	

NIHSS denotes National Institutes of Stroke Scale, IVT intravenous thrombolysis, and SD standard deviation

P-values apply to chi-square tests unless otherwise indicated.

* Mann-Whitney test, † Fisher exact test

Table 2. Symptomatic Intracranial Hemorrhage, Mortality and Favorable Outcome in Patients with Posterior vs. Anterior Circulation Stroke Treated With Intravenous Thrombolysis.

	Symptomatic ICH			Mortality			Favorable outcome		
	[n/N (%)]	*P* Value Unadjusted	*P* Value Adjusted	[n/N (%)]	*P* Value Unadjusted	*P* Value Adjusted	[n/N (%)]	*P* Value Unadjusted	*P* Value Adjusted
Posterior Circulation Stroke	0/93 (0)			8/94 (9)			62/94 (66)		
		0.026*	0.001†		0.243	0.251‡		<0.001	0.177§
Anterior Circulation Stroke	36/784 (5)			100/784 (13)			364/784 (46)		

Symptomatic intracranial hemorrhage (ICH) refers to NINDS criteria. *P*-values apply to chi-square tests unless otherwise indicated.

* Fisher exact test

† adjusted for atrial fibrillation, antiplatelet medication and diastolic blood pressure in logistic regression analysis (bootstrap method)

‡ adjusted for age, NIHSS score and blood glucose in logistic regression analysis

§ adjusted for NIHSS score, blood glucose, age, antiplatelet medication, and anticoagulation in logistic regression analysis

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