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Original research article

Cerebral thrombolysis in patients with ischemic stroke and heart failure

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ABSTRACT

Background: Heart failure (HF) is common among patients with ischemic stroke (IS), however its impact on outcome after iv-thrombolysis has not been fully determined. Moreover, definition of HF has been recently modified, but majority of stroke studies classified patients regarding an old HF criteria. Thus, the aim of our study was to evaluate the relationship between both, newly and formerly defined HF and the long-term outcome, mortality and the presence of hemorrhagic complications in patients with acute IS treated with iv-thrombolysis.

Methods: We retrospectively evaluated data from 328 Caucasian patients with IS consecutively treated with iv-thrombolysis. HF was defined according to old and new definition; long-term outcome was assessed with modified Rankin Scale (mRS) score and mortality rate on 90th days after IS.

Results: The incidence of HF did not differ between patients with favorable (mRS 0–2) and unfavorable (mRS 3–6) functional outcome respectively for the old and for the new definition (10.4% vs. 15.5, $p = 0.17$; 17.4% vs. 18.1%, $p = 0.88$) and between those who survived and died within 90 days after IS (11.7% vs. 20.0%, $p = 0.27$; 17.2% vs. 25.0%, $p = 0.38$, respectively). Multivariate analysis showed no impact of HF diagnosis on outcome ($p = 0.94$) or mortality ($p = 0.64$).

Conclusion: The presence of systolic HF, defined according to an old and a new definition, does not determine safety and efficacy of cerebral iv-thrombolysis in patients with IS.

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1. Introduction

Heart failure (HF) is a risk factor for ischemic stroke (IS) that is present in approximately 1–2% of the population. Factors that predispose to thromboembolic events with HF include low cardiac output, with relative stasis of blood in dilated cardiac chambers, poor contractility, and regional wall motion abnormalities. The risk of stroke increases with decreasing left ventricular ejection fraction (LVEF), even after adjusting for other stroke risk factors [1–3]. HF is found in 10–24% of acute stroke patients and is associated with poor outcome and increased mortality in IS [4–7]. The most frequent causes of IS in patients with HF are: thrombus formation due to impaired left ventricular contractility and atrial fibrillation (AF), increased aggregation of thrombocytes and reduced fibrinolysis [8–10].

Intravenous cerebral thrombolysis (iv-thrombolysis) with rt-PA is effective medical therapy for acute IS, but its widespread implementation is limited by a high number of contraindications and relatively short time window [11]. Moreover, its safety and efficacy is influenced by the patient's age, severity of initial deficit, presence of hemorrhagic complications and a number of other factors [12–15].

A cardiogenic etiology, which is present in 22–39% of ischemic strokes, may determine the safety and efficacy of iv-thrombolysis [16,17]. Numerous reports have demonstrated the negative impact of atrial fibrillation (AF) on the long-term outcome of iv-thrombolysis [8,18,19]. Inversely, data on the outcome after cerebral thrombolysis in patients with HF are sparse. Moreover, available reports concern heterogeneous groups of patients, treated with both intra-arterial and iv-thrombolysis, within a wide range of time windows, and mostly do not include assessment of the left ventricular ejection fraction (LVEF) in the protocol [20,21]. A single study, based on the polish stroke patients, showed that low LVEF is an independent factor for death within 14 days after thrombolytic therapy [22]. Moreover, since the definition of HF has been modified in 2016, little studies concerned an impact of newly defined HF on stroke outcome. Thus, it still remains unclear if cerebral iv-thrombolysis is similarly safe and efficient in IS patients with HF as in IS patients without HF.

Therefore, we aimed to evaluate the relationship between the presence of systolic HF, diagnosed on the basis of the patient's history and echocardiographic parameters, and the safety and efficacy of iv-thrombolysis in routine practice.

2. Methods

2.1. Study design and patients

We retrospectively evaluated the demographic and clinical data of Caucasian patients with IS who were consecutively treated with iv-thrombolysis from January 2008 to January 2013 in the Department of Neurology and Stroke Unit of the Holy Spirit Specialist Hospital in Sandomierz, Poland. Patients' records were collected from the Pomeranian Stroke Register (PRUM), which is an open, multi-center, internet-based consecutive stroke register [23]. Data from patients treated >4.5 h from stroke onset, those with combination therapy (intravenous plus intra-arterial thrombolysis) were excluded.

The Department of Neurology and Stroke Unit of the Holy Spirit Specialist Hospital in Sandomierz is recognized as a stroke unit according to the Polish national criteria and is equipped with appropriate monitoring and diagnostic facilities [24]. The stroke unit provides a 24-h stroke service 7 days a week. All patients were examined at the time of admission by a stroke physician, and the severity of stroke symptoms was assessed using the National Institutes of Health Stroke Scale (NIHSS) [25]. Stroke was diagnosed on the basis of the ICD 10 criteria and was confirmed on discharge by clinical evaluation and neuroimaging. Cerebral thrombolysis with the intravenous infusion of recombinant tissue plasminogen activator (rt-PA) was administered according to current guidelines [11, 27,28].

All blood samples were routinely taken at the time of admission and the results of biochemical analyses were obtained before starting iv-thrombolysis. Brain computed tomography (CT) scans were performed in all patients upon admission to hospital and between 22–36 h after iv-thrombolysis. In selected cases, especially in the case of hemorrhagic complications, additional CT scans were performed according to the patient's status and clinical indications. Brain magnetic resonance imaging (MRI) was not routinely performed.

The 90-day stroke outcomes were measured using the modified Rankin scale (mRS) [26]. A favorable outcome was defined as mRS score ≤2 points, while an unfavorable outcome was defined as an mRS of 3–6 points. Hemorrhagic transformation (HT) and symptomatic intra-cerebral hemorrhage (SICH) rates were assessed according to the European Cooperative Acute Stroke Study (ECASS) II criteria [29].

2.2. Cardiovascular assessment

A basic cardiological assessment was performed in all patients treated with iv-thrombolysis including electrocardiography (ECG) on admission, 3-day continuous ECG monitoring and blood pressure and transthoracic echocardiography (TTE) performed during the first day of hospitalization. TTE was performed according to guidelines applicable until 2013 [30]. Systolic heart failure was recognized according both, to the old criteria when patients' complaints were categorized as class II–IV according to the New York Heart Association functional classification (NYHA) [31] before hospitalization and concomitant reduction of the LVEF below 45% was detected by TTE (LVEF moderately and severely abnormal) [30] or based on previous diagnosis in medical records and according to the new criteria in which, apart from additional factors, HF with preserved, mid-range and reduced ejection fraction was diagnosed [32].

The ethics committee approved all data analyses (Ethics Committee of Świętokrzyska Medical Chamber), and all patients treated with iv-thrombolysis were reported to the SITS registry.

2.3. Statistical methods

This study was based on a retrospective data analysis. Univariate analysis and logistic regression was performed with STATISTICA v. 9.1. All continuous variables were tested for a normal distribution and equality of variance. Because of the non-normality of the variables, non-parametric Mann–Whitney *U* tests were used to perform the univariate analysis of the continuous variables. Categorical data were compared using chi square tests. *p* values <0.05 were considered statistically significant. The multivariate analysis was performed using multiple logistic regression models. Factors identified in univariate analysis with a *p* value <0.01 were included in the multivariate model. Age and sex were also included in the analysis. The results of the logistic regression models were presented as odds ratios (ORs) and the corresponding 95% confidence intervals (CIs).

3. Results

Total number of stroke patients with acute stroke admitted to the Stroke Unit in Sandomierz between January 2008 and January 2013 was 1491, including 328 (22%) treated with iv-thrombolysis. The mean age of patients treated with rt-PA was 69.84 ± 11.51 years; 19.2% of patients were older than 80 years; 55.5% were males. HF, defined according to old was diagnosed in 12.2% of and according to new definition in 17.7% of patients. A previous history of hypertension was detected in 68.6% of patients, coronary heart disease in 63.1%, past myocardial infarction in 14.9%, AF (chronic or paroxysmal) in 38.4%; 54.9% of patients were on antiplatelet and 12.8% on anticoagulant therapy. Additionally, concomitant myocardial infarction was detected on admission in 1.2% of patients. A favorable outcome after iv-thrombolysis

Table 1 – The clinical characteristics of the subgroups of stroke patients with a favorable and an unfavorable outcome and of patients who alive and dead after iv-thrombolysis.

Variables	Functional outcome at 90 days			Mortality at 90 days		
	Favorable outcome (mRS 0–2)	Unfavorable outcome (mRS 3–6)	*p*	Alive	Dead	*p*
n(%) 328	212(64.63)	116(35.37)	–	308(93.90)	20(6.10)	–
Age (mean; SD)	68.30 ± 11.95	72.66 ± 10.13	***0.002***	69.38 ± 11.55	76.85 ± 8.47	***0.01***
Gender (male)	120(56.60)	62(53.45)	0.58	175(56.82)	7(35.00)	0.06
Baseline NIHSS (median; IQR)	9.0(6.0–12.0)	15.0(10.0–18.0)	***<0.001***	10.0(7.0–15.0)	17.0(13.0–20.5.0)	***<0.001***
Independent prior stroke (mRS 0–2)	191(90.09)	110(94.83)	0.14	282(91.56)	19(95.00)	0.59
Onset to treatment time (median; IQR)	160.0(134.5–190.0)	160.0(132.0–180.0)	0.93	160.0(134.5–190.0	152.0(130.0–72.5)	0.55
MAP (median; IQR)	103.0(97.0–114.0)	111.0(100.0–120.0)	***<0.001***	107.0(97.0–117.0)	111.0(101.5–117.0)	0.15
DBP (median; IQR)	80.0(78.0–90.0)	87.5(80.0–97.0)	0.05	80.0(80.0–90.0)	80.0(80.0–92.5)	0.53
SBP (median; IQR)	148.5(130.0–164.0)	160.0(146.5–170.0)	***<0.001***	150.0(137.0–170.0)	160.0(147.5–170.0)	0.09
Dyslipidemia	152(71.70)	88(75.86)	0.42	227(73.70)	13(65.00)	0.40
Smoking (current)	48(22.64)	18(15.52)	0.12	65(21.10)	1(5.00)	0.08
Hypertension	141(66.51)	84(72.41)	0.27	209(67.86)	16(80.00)	0.26
Heart rate (median; IQR)	72.0(64.0–80.0)	75.0(68.0–80.0)	0.04	75.0(64.0–80.0)	76.0(66.0–100.0)	0.17
Coronary heart disease	134(63.21)	73(62.93)	0.96	193(62.66)	14(70.00)	0.51
Heart infarct on admission	1(0.47)	3(2.59)	0.10	4(1.30)	0(0.00)	0.10
First abnormal ECG	134(63.21)	77(66.38)	0.57	196(63.64)	15(75.00)	0.30
Chronic atrial fibrillation	42(19.81)	24(20.69)	0.85	61(19.81)	5(25.00)	0.57
Paroxysmal atrial fibrillation	31(14.62)	29(25.00)	***0.02***	54(17.53)	6(30.00)	0.16
PSVT	43(20.28)	23(19.83)	0.92	63(20.45)	3(15.00)	0.56
Antiplatelet therapy before stroke	118(55.66)	62(53.45)	0.70	168(54.55)	12(60.00)	0.64
Anticoagulant therapy before stroke	25(11.79)	17(14.66)	0.46	40(12.99)	2(10.00)	0.70
HT (*n*, %)	24(11.32)	21(18.10)	0.09	40(12.99)	5(25.00)	0.13
SICH[a] (*n*, %)	0	4(3.45)	***<0.01***	2(0.65)	2(10.00)	***<0.001***
NYHA (median; IQR)	0(0–1)	1(0–2)	0.08	0(0–2)	1(0–3)	0.07
NYHA II–IV	71(33.49)	52(44.83)	***0.04***	112(36.36)	11(55.00)	0.10
Ejection fraction, %						
EF (median; IQR) (old definition)	55(50–60)	55(50–60)	0.76	55(50–60)	55(52.5–60)	0.35
EF <45% (*n*, %)	20(9.43)	15(12.93)	0.33	34(11.04)	1(5.00)	0.4
EF <40% (*n*, %)	15(7.08)	13(11.21)	0.20	27(8.77)	1(5.00)	0.56
EF 40–49% (*n*, %)	29(13.68)	15(12.93)	0.85	41(13.31)	3(15.00)	0.83
EF ≥50% (*n*, %)	168(79.25)	88(75.86)	0.48	240(77.92)	16(80.00)	0.83
Heart failure						
Old definition (*n*, %)	22(10.38)	18(15.52)	0.17	36(11.69)	4(20.00)	0.27
New definition (*n*, %)	37(17.45)	21(18.10)	0.88	53(17.21)	5(25.00)	0.38

mRS – modified Rankin Scale; NIHSS – National Institutes of Health Stroke Scale; SBP – systolic blood pressure; DBP – diastolic blood pressure; PSVT – paroxysmal supraventricular tachycardia; ECG – electrocardiography; HT – hemorrhagic transformation; SICH – Symptomatic Intracerebral Hemorrhage; EF – ejection fraction; NYHA – New York Heart Association; SD – standard deviation; IQR – interquartile range (Q_1–Q_3); bold and italics letters – results statistically significant.

[a] According to the ECASS III definition.

Table 2 – Multivariate logistic regression models showing factors associated with 90 days outcome and mortality.

Variables	Favorable outcome (mRS 0–2)			Mortality		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Heart infarct on admission	0.15	0.01–1.64	0.12	–	–	–
Heart rate (stepwise increase of 10 beats)	0.90	0.76–1.06	0.19	–	–	–
SBP (stepwise increase of 10 mmHg)	–	–	–	1.12	0.90–1.40	0.31
MAP (stepwise increase of 10 mmHg)	**0.80**	**0.67–0.96**	**0.02**	–	–	–
Age	**0.97**	**0.95–0.99**	**0.01**	**1.08**	**1.02–1.14**	**0.005**
Paroxysmal atrial fibrillation	0.62	0.31–1.21	0.16	–	–	–
NIHSS score on admission (each point)	**0.86**	**0.82–0.91**	**<0.0001**	**1.12**	**1.05–1.20**	**<0.001**
HF (new definition)	1.47	0.72–2.97	0.28	1.25	0.40–3.92	0.70
SICH[a]	8.71	0.001–1148	0.997	**16.08**	**1.70–152.21**	**0.015**

SBP – systolic blood pressure; mRS – modified Rankin Scale; NIHSS – National Institutes of Health Stroke Scale; NYHA – New York Heart Association; EF – ejection fraction; SICH – Symptomatic Intracerebral Hemorrhage; ECASS – European Cooperative Acute Stroke Study; bold and italics letters – results statistically significant.

[a] According to the ECASS III definition.

was found in 64.6% of patients and an unfavorable outcome in 35.4% of patients; 6.1% of patients died within 90 days of stroke onset.

We found no differences regarding the presence of HF or LVEF value between subgroups of patients with a favorable and unfavorable outcome, nor between subgroups of patients who died and those who survived within 90 days of stroke onset. Patients with an unfavorable outcome were characterized by older age and higher NIHSS score, mean (MAP) and systolic (SBP) blood pressures measured on admission and higher incidence of paroxysmal AF than patients with a favorable outcome. They were also characterized by more frequent incidence of Symptomatic Intracerebral Hemorrhage (SICH) and diagnosis of stage II–IV of HF according to NYHA than patients with a favorable outcome. The NIHSS score, MAP and SBP measured on admission and higher incidence of SICH were also higher in patients who died within 3 months from the stroke onset than in survivors (Table 1).

A multivariate analysis showed an impact of MAP, age and initial NIHSS score on the 3-month functional outcome and an impact of age, NIHSS and presence of SICH on 3-month mortality. No impact of HF on both, 3-month functional outcome and mortality were not found (Table 2).

4. Discussion

Our study showed no impact of heart failure, classified with respect to both, a new and an old HF criteria, on the safety and efficacy of iv-thrombolysis in routine treatment of patients with IS.

To the best of our knowledge, our study is the first to show that long-time outcome after iv-thrombolysis is not influenced by the presence of HF with LVEF impairment. The only studies that supported our results regarding the long-time outcome was presented by Paciaroni et al., but it was based only on patient's history, without echocardiographic assessment [33]. An interesting study of Lasek-Bal et al. showed that reduced EF predicts unfavorable short-term prognosis in patients treated with intravenous thrombolysis [22]. This may indicate that presence of HF may influence rather early than late outcome after cerebral thrombolysis.

Evaluation of association between both, newly and formerly defined HF long-term outcome after cerebral thrombolysis is me be also considered as an advantage of our study. It has not been already explained if results of former studies basing on an old HF criteria may be extrapolated to patients with HF diagnosed according to its new definition, established with lower EF reduction thresholds.

Our findings conflict with other reports showing negative impact of heart failure on outcome after iv-thrombolysis in IS. A recently published paper by Palumbo et al. revealed that a clinical diagnosis of HF, based on both history and EF measurement, predicts mortality in acute IS patients undergoing iv-thrombolysis. However, the population evaluated by Palumbo et al. was relatively small, and included patients undergoing different schemes of thrombolytic treatment pooled together in the analysis (both systemic and endovascular, over a wide range of onset to needle times) [20]. Indeed, other reports concerning big cohorts of IS patients collected in VISTA and SITS archives either showed that history of HF was a predictor of higher mortality and unfavorable outcome by day 90 after iv-thrombolysis, however EF evaluation in acute phase if IS was not involved into the study protocols [21,34]. Therefore, our negative findings can be explained, both by the use of echocardiography and exclusion of off-label procedures.

Our results may also suggest that the high thrombolytic potential of rt-PA may additionally bring benefit for IS patients with HF, because it compensates increased aggregation of thrombocytes and reduced endogenous fibrinolysis occurring in course of HF [9,10]. Such mechanism may explain why we have found no association between the worse outcome and HF, which frequently exists in IS patients who are not treated with iv-thrombolysis [2–5,35].

Numerous studies have shown that an unfavorable iv-thrombolysis outcome is associated with older age, a higher NIHSS score and blood pressures at stroke onset [21,22,29,36–39]. Similarly, we found that an unfavorable outcome in 3 months after stroke onset was related to older age and a higher NIHSS score and the MAP at the time of admission. However, inversely to other authors we have not observed that preexisting disability contribute to outcome after iv-thrombolysis [40]. The results of the previous study conducted on Polish population also showed, that pre-stroke use of antiplatelets increased odds for being alive and independent at discharge and decreased odds for in-hospital mortality, however we have not found such relationship [41]. Similarly, inversely to Lasek-Bal et al. we have found no impact of AF on patient's outcome [22].

Our study has some limitations. Our study was a single center study. The study group was not large, but was larger than previous populations of stroke patients treated with cerebral thrombolysis assessed with respect to both patient history and echocardiographic findings. Although data collection was conducted in a prospective study, the analysis was retrospective. The role of diastolic heart failure was not investigated. We did not use the Boston scale for cardiovascular assessment, and history taking was based only on the NYHA classification. However, the incidence of HF in our study group did not differ from that reported for other populations of stroke patients [2,4]. The study analysis was based on the diagnosis of HF not on the status of cardiac hemodynamics during the index IS. The tendency to worse functional status expressed by higher NYHA class in patients with unfavorable outcome and in non-survivors suggest that functional decompensation of heart function may affect the outcome but not the diagnosis of HF or LVEF.

We realize that the lack of association between HF and an unfavorable outcome revealed in a retrospective study does not definitively confirm that patients with left ventricular heart dysfunction may benefit from the iv-thrombolysis similar to patients without HF. However, we believe that our negative results may dispel some safety concerns regarding IS patients being qualified for cerebral thrombolysis. Thus, we believe that, despite some limitations, our findings support the widespread use of cerebral thrombolysis.

5. Conclusion

Based on our results, the diagnosis of both, newly and formerly defined HF has no impact on the safety and effectiveness of iv-thrombolysis in patients with acute IS treated accordingly to current guidelines. However, this clinical problem requires further investigation.

Author contributions

Piotr Sobolewski: concept/design, data analysis/interpretation, drafting article, approval of article, data collection; Grzegorz Kozera: concept/design, data analysis/interpretation, critical revision of article, approval of article, data collection; Wiktor Szczuchniak: data analysis/interpretation, approval of article, Statistics, data collection; Anna Sobota: data collection, approval of article; Kamil Chwojnicki: data analysis/interpretation, Statistics, approval of article; Marcin Gruchała: critical revision of article, approval of article; Walenty M. Nyka: critical revision of article, approval of article.

Conflict of interest

None declared.

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