

Factors affecting the occurrence of symptomatic intracerebral haemorrhage after intravenous thrombolysis depending on the haemorrhage definition

Czynniki wpływające na wystąpienie objawowego krwotoku śródmózgowego po dożylniej trombolizie w zależności od definicji krwawienia

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Abstract

Background and purpose: Symptomatic intracerebral haemorrhage (sICH) remains the most feared complication of systemic thrombolysis in patients with ischaemic stroke. The aim of the study was to analyze the impact of different factors on the occurrence of sICH, depending on definition used.

Material and methods: We retrospectively evaluated the influence of several factors on the occurrence of sICH (according to definitions used in ECASS2, SITS-MOST and NINDS studies) in 200 patients treated with systemic thrombolysis from 2006 to 2011. Multivariate analysis of impact of individual variables on the occurrence of haemorrhagic transformation (HT) and parenchymal haemorrhage type 2 (PH2) were performed.

Results: Haemorrhagic transformation occurred in 35 cases (17.5%). sICH was found in 10 cases according to ECASS2, in 7 cases according to SITS and in 13 cases according to NINDS. Older age was related to higher risk of sICH, regardless which definition was used (ECASS2: $p = 0.014$, SITS-MOST: $p = 0.048$, NINDS: $p = 0.008$), and female sex was related to higher risk of sICH according to NINDS and ECASS2 definition ($p = 0.002$ and $p = 0.04$, respectively). Blood glucose level and high NIHSS score (> 14 pts) were found as risk factor of sICH in ECASS2 definition ($p = 0.044$ and $p = 0.03$, respectively). In multivariate logistic regression higher NIHSS scores were associated with HT independent of age, gender and glucose level ($p = 0.012$). Multivariate analysis showed no impact of age, gender, severity of stroke and glucose level on presence of PH2.

Streszczenie

Wstęp i cel pracy: Objawowy krwotok wewnątrzmożgowy (*symptomatic intracerebral haemorrhage* – sICH) pozostaje najgroźniejszym powikłaniem systemowej trombolizy u chorych na ostry udar niedokrwienny mózgu. Celem pracy była ocena wpływu różnych czynników na występowanie sICH w zależności od zastosowanej definicji krwotoku.

Materiał i metody: Przeanalizowano retrospektywnie wpływ czynników epidemiologicznych i klinicznych na występowanie sICH (zgodnie z definicjami: ECASS2, SITS-MOST i NINDS) u chorych leczonych trombolitycznie od 2006 r. do 2011 r. Przeprowadzono analizę wieloczynnikową wpływu poszczególnych czynników na występowanie transformacji krwotocznej (HT) oraz krwawiaków śródmiaższowych typu 2 (PH2).

Wyniki: Transformacja krwotoczna wystąpiła w 35 przypadkach (17,5%), sICH stwierdzono w 10 przypadkach zgodnie z definicją ECASS2, w 7 wg SITS-MOST i 13 wg NINDS. Starszy wiek wiązał się z większym ryzykiem sICH niezależnie od zastosowanej definicji (ECASS2: $p = 0,014$, SITS-MOST: $p = 0,048$, NINDS: $p = 0,008$), a płeć żeńska zwiększała ryzyko sICH zgodnie z definicją NINDS i ECASS2 (odpowiednio $p = 0,002$ i $p = 0,04$). Stężenie glukozy we krwi i wysoka punktacja w skali NIHSS (> 14 pkt) były czynnikami ryzyka zgodnie z definicją ECASS2 (odpowiednio $p = 0,044$ i $p = 0,03$). W wieloczynnikowej regresji logistycznej wysoka punktacja w skali NIHSS wiązała się z występowaniem HT ($p = 0,012$). W analizie wieloczynni-

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Conclusions: Definition of sICH can determine variables that are related to a high risk of this complication. In our study most factors correlated with sICH using the ECASS2 definition.

Key words: stroke, thrombolytic therapy, definition of symptomatic intracranial haemorrhage.

Introduction

Acute ischaemic stroke remains one of the main causes of death and disability in our society [1]. The incidence of stroke in Poland is similar to that in other European countries (the incidence rate is 177/100 000 in males and 125/100 000 in females) [2,3]. According to the Ministry of Health, about 88 000 hospitalizations with a diagnosis of stroke were reported in Poland in 2007 (data may be underestimated by about 15%) [4].

Cerebral systemic thrombolysis (intravenous thrombolysis) with recombinant tissue plasminogen activator (rt-PA), initiated within 4.5 hours after the onset of symptoms, is the most effective medical therapy for acute ischaemic stroke [5]. The results of several trials confirmed the efficacy, but some complications of these therapy have been revealed [6-8]. Intracerebral haemorrhage (ICH) is the most serious of them. Only some of them are associated with the worsening of the patient's status, of which sICH is the most important.

Currently, several definitions of sICH exist. The definition used in the National Institute of Neurological Disorders and Stroke (NINDS) trial considers sICH in any case of deterioration in the National Institutes for Health Stroke Scale (NIHSS) score within 7 days in presence of any type of ICH in the control computed tomography (CT) scan [9]. In the European Cooperative Acute Stroke Study 2 (ECASS2) protocol, investigators defined sICH as an intracerebral haemorrhage if the patient had clinical deterioration causing an increase in NIHSS score by 4 points, and if the haemorrhage was likely to be the cause of the clinical deterioration [7,8]. According to the Safe Implementation of Thrombolysis in Stroke – Monitoring Study (SITS-MOST) definition, sICH is defined as clinical deterioration in NIHSS score by 4 points within 24 hours and with the occurrence of intracerebral haemorrhage type 2 in the 22 to 36 hours follow-up imaging scans after the start of thrombolysis treatment [10].

kowej nie stwierdzono wpływu wieku, płci, nasilenia udaru w punktacji NIHSS ani stężenia glukozy na wystąpienie PH2.

Wnioski: Definicja sICH może określić zmienne, które są związane z dużym ryzykiem tego powikłania. W badanej grupie chorych najczęściej czynników wiązało się z sICH definiowanym zgodnie z ECASS2.

Słowa kluczowe: udar, leczenie trombolityczne, definicje objawowego krwawienia wewnątrzczaszkowego.

Therefore we aimed to evaluate the relationship between several factors and the presence of sICH according to different definitions, by what we tried to determine which definition is most sensitive in this respect.

Material and methods

We retrospectively evaluated the influence of epidemiological and clinical factors on the occurrence of sICH, according to ECASS2, SITS-MOST and NINDS definitions in 200 consecutive Caucasian patients treated with intravenous thrombolysis between September 2006 and March 2011, in stroke unit in Sandomierz. Our study center was recognized as a stroke unit according to the Polish national criteria and was equipped with the proper monitoring and diagnostic facilities [11]. All patients were examined at the time of admission by a stroke physician, and the severity of stroke symptoms was assessed using the NIHSS [12]. Cerebral thrombolysis with the intravenous infusion of rt-PA was administered according to the current guidelines [13]. Because the Polish guidelines changed in June 2010, patients treated within the 4.5-hour time window and patients over 80 years of age were included in the study [14]. All patients had CT of the brain performed prior to treatment, 22-36 hours after the start of treatment and on the seventh day, as well as in case of deterioration of the neurological status. All our patients received standard care, typical of a stroke unit, including rehabilitation, psychological and speech therapy as well. We used the ECASS2 classification based on CT image and radiological features of haemorrhagic transformation [8,15].

The study protocol was accepted by the Ethics Committee of Regional Chamber of Physicians in Kielce (Consent No. 8/2011). All personal data of the analyzed patients were treated confidentially.

Statistical methods

Statistical analysis was performed with Statistica 6.0. Univariate analyses were performed and χ^2 tests with appropriate corrections (Yates correction, Fisher exact test) for sample size and expected counts and nonparametric Mann-Whitney U -tests were used because of skewed distribution. The multivariate analysis was performed with the use of multiple logistic regression. Calculations were not always mathematically possible due to the limited number of observations, therefore the multivariate analysis was performed for haemor-

rhagic transformation and parenchymal haematoma type 2. The results of the logistic regression models were presented as odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). The level of significance was set at $p < 0.05$.

Results

General characteristics of the group of patients are shown in Table 1. Patients with heart disease, especially with atrial fibrillation, were abundant in our study population.

Table 1. Characteristics of group of patients

Variable	
Gender	
Female	88 (44%)
Male	112 (56%)
Age (years) [mean \pm SD, (range)]	69.07 \pm 10.57 (41-92)
Arterial hypertension	134 (67%)
Diabetes mellitus	25 (12.5%)
Dyslipidemia	154 (77.0%)
Atrial fibrillation	68 (34.0%)
Previous stroke	33 (16.5%)
Coronary disease	105 (52.5%)
Previous smoker	36 (18%)
Current smoker	40 (20.0%)
Dose of rt-PA (mg) [mean \pm SD, (range)]	64.2 \pm 12.8 (50-80)
Onset-to-needle time (min.) [mean \pm SD, (range)]	150.5 \pm 41.2 (45-290)
Door-to-needle time (min.) [mean \pm SD, (range)]	63.7 \pm 28.8 (10-190)
Clinical stroke syndrome (OSCP)	
Total anterior circulation infarct	54 (27.0%)
Partial anterior circulation infarct	102 (51.0%)
Lacunar infarct	43 (21.5%)
Posterior circulation infarct	1 (0.5%)
Baseline NIHSS score, mean \pm SD	12.3 \pm 5.0
Patients with the following NIHSS scores:	
0-7	43 (21.5%)
8-14	90 (45.0%)
≥ 15	67 (33.5%)

Data are shown as number (%) if not otherwise stated

OSCP – Oxford Community Stroke Project, NIHSS – National Institutes of Health Stroke Scale

Table 2. Haemorrhagic transformation in analyzed group of patients

Type of intracerebral haemorrhage	N (%)
Any intracerebral haemorrhage	35 (17.5)
Haemorrhagic infarct type 1	7 (3.6)
Haemorrhagic infarct type 2	8 (4.0)
Parenchymal haematoma type 1	8 (4.0)
Parenchymal haematoma type 2	8 (4.0)
Symptomatic intracerebral haemorrhage – ECASS	10 (5.0)
Symptomatic intracerebral haemorrhage – SITS-MOST	7 (3.5)
Symptomatic intracerebral haemorrhage – NINDS	13 (6.5)
Parenchymal haematoma remote type 1	4 (2.0)
Parenchymal haematoma remote type 2	0

ECASS – European Cooperative Acute Stroke Study, SITS-MOST – Safe Implementation of Thrombolysis in Stroke – Monitoring Study, NINDS – National Institute of Neurological Disorders and Stroke

Haemorrhagic transformation occurred in 17.5% of cases. Symptomatic ICH was found in 5% of cases (according to ECASS2), 3.5% (SITS-MOST) or in 6.5% (NINDS), depending on definition (Table 2).

Older age was related to higher risk of sICH, regardless which definition was used (ECASS2, $p = 0.014$; SITS-MOST, $p = 0.048$; NINDS, $p = 0.008$). Female sex was related to higher risk of sICH according to NINDS and ECASS2 definition ($p = 0.002$ and $p = 0.04$, respectively). Blood glucose level and high NIHSS score (> 14 pts) were risk factors of sICH in ECASS2 definition ($p = 0.044$ and $p = 0.03$, respectively) (Table 3).

In multivariate logistic regression, higher NIHSS scores were associated with haemorrhagic transformation independent of age, gender and glucose level ($p = 0.012$). Multivariate analysis showed no impact of age, gender, severity of stroke according to NIHSS score and glucose level on presence of parenchymal haematoma type 2 (Table 4).

Discussion

Haemorrhagic transformation is the most serious complication of thrombolytic therapy. In fact, it is a group of haemorrhagic changes in the brain, with different pathogenesis and clinical significance [16]. Some of haemorrhagic transformations seem to be natural course of the ischaemic injury, which probably would

appear even without thrombolytic treatment [17,18]. Only a fraction of haemorrhagic transformations is related to deterioration of the patient's status and are defined as sICH. Analysis of these cases is difficult because of the multiplicity of definitions of sICH. The influence of different factors on the occurrence of sICH differed depending on the use of one out of three definitions.

Mazya *et al.* [19] analyzed data from 31 627 patients treated with intravenous alteplase enrolled in the SITS International Stroke Thrombolysis Register. The outcome measure was sICH per the SITS-MOST definition. The authors identified 9 independent risk factors for sICH: baseline NIHSS score, serum glucose, systolic blood pressure, age, body weight, stroke onset to treatment time, aspirin or combined aspirin and clopidogrel, and history of hypertension.

In our study, older age was related to sICH regardless which definition was used. Older age was defined as independent risk factor for sICH in several previous studies [7,8,10,20] but another studies did not confirm this association [21,22]. In most studies of thrombolytic therapy, patients under 80 were included and only in some of trials treatment of elderly patients with rt-PA was allowed. Recently published results of the Third International Stroke Trial IST-3 show survival benefits of rt-PA in elderly stroke patients [23].

Gender differences in coagulation and fibrinolytic factors have been reported in acute ischaemic stroke [24]. Meseguer *et al.* collected efficacy and safety outcomes for patients treated with rt-PA in their center and they also performed a systemic PubMed literature search for previous 16 studies that evaluated the gender effect among intravenous rt-PA-treated patients. None of these studies supported a gender difference in favourable outcome, and one suggested an increased risk of mortality in men. In unadjusted partial meta-analysis in all patients from these studies, the authors found a trend toward a lower risk of sICH in women [25]. In our population, female sex was correlated with higher risk of sICH according to NINDS and ECASS2 definitions.

High blood glucose level is a well-recognized risk factor of sICH [9,10,26,27]. In patients with acute ischaemic stroke from both parts of NINDS trial, higher admission glucose levels were associated with significantly lower odds for desirable clinical outcomes and significantly higher odds for sICH, regardless of rt-PA treatment [28]. High blood glucose was significantly higher in the group of patients with sICH in the

Table 3. The occurrence of symptomatic intracerebral haemorrhage by the definition chosen according to the main outcome variables

Baseline characteristics	Occurrence of symptomatic intracerebral haemorrhage								
	SITS-MOST definition			NINDS definition			ECASS definition		
	No	Yes	p-value OR (95% CI)	No	Yes	p-value OR (95% CI)	No	Yes	p-value OR (95% CI)
Age [years]; mean	68.8	77.1	0.048	68.5	77.2	0.008	68.6	77.9	0.014
Sex [no. of men]	111	1	0.061 8.12 (0.96-68.8)	110	2	0.002 7.86 (1.69-36.45)	110	2	0.043 5.5 (1.14-26.60)
Hypertension	131	3	0.33 0.36 (0.08-1.64)	127	7	0.461 0.55 (0.18-1.71)	129	5	0.408 0.47 (0.13-1.70)
Diabetes mellitus	23	2	0.467 2.96 (0.54-16.13)	22	3	0.448 2.25 (0.58-8.81)	22	3	0.220 3.27 (0.79-13.59)
Hyperlipidaemia	76	5	0.192 3.85 (0.73-20.35)	73	8	0.111 2.50 (0.79-7.93)	74	7	0.106 3.66 (0.92-14.60)
Dyslipidaemia	148	6	0.919 1.82 (0.21-15.55)	144	10	0.738 0.99 (0.26-3.78)	146	8	0.878 1.21 (0.25-5.89)
Atrial fibrillation	65	3	0.922 1.48 (0.32-6.80)	62	6	0.513 1.73 (0.56-5.36)	63	5	0.451 2.02 (0.56-7.22)
Coronary heart disease	104	1	0.094 0.14 (0.02-1.21)	99	6	0.636 0.76 (0.25-2.35)	101	4	0.626 0.59 (0.16-2.15)
Previous stroke	33	0	0.497	33	0	0.204	33	0	0.315
Current smoker	39	1	0.923 0.66 (0.08-5.63)	39	1	0.43 0.32 (0.04-2.51)	39	1	0.685 0.43 (0.05-3.50)
Previous smoker	35	1	0.81 0.75 (0.09-6.45)	35	1	0.53 0.36 (0.05-2.88)	35	1	0.80 0.49 (0.06-4.01)
Aspirin or other antiplatelet at stroke onset	112	4	0.732 0.96 (0.21-4.43)	108	8	0.79 1.17 (0.37-3.71)	110	6	0.844 1.09 (0.30-3.99)
Oral anticoagulant at stroke onset	31	0	0.534	30	1	0.683	30	1	0.964
Blood glucose [mmol/L]	6.88	8.10	0.32	6.84	8.1	0.055	6.84	8.51	0.044
Body weight [kg]	78.2	82.6	0.54	77.9	84.8	0.729	77.8	89.3	0.34

Table 3. Cont.

Baseline characteristics	Occurrence of symptomatic intracerebral haemorrhage							
	SITS-MOST definition			NINDS definition			ECASS definition	
	No	Yes	p-value OR (95% CI)	No	Yes	p-value OR (95% CI)	No	Yes
Systolic blood pressure > 160 mm Hg	71	3	0.94 1.29 (0.28-5.92)	68	6	0.68 1.50 (0.48-4.65)	69	5
Diastolic blood pressure > 90 mm Hg	47	4	0.130 4.14 (0.89-19.18)	46	5	0.436 1.92 (0.60-6.15)	46	5
NIHSS score								
< 7 pts	42	1	0.996 0.60 (0.07-5.12)	40	3	0.837 1.10 (0.29-4.20)	42	1
7-14 pts	88	2	0.615 0.48 (0.09-2.52)	87	3	0.101 0.35 (0.09-1.29)	88	2
> 14 pts	63	4	0.346 2.75 (0.60-12.67)	60	7	0.19 2.47 (0.80-7.67)	60	7
Onset-to-needle time								
< 90 min.	15	1	0.932 1.98 (0.22-17.53)	15	1	0.627 0.96 (0.12-7.86)	15	1
90-180 min.	158	5	0.839 0.55 (0.10-2.97)	153	10	0.944 0.74 (0.19-2.84)	156	7
181-270 min.	18	1	0.829 1.62 (0.19-14.22)	17	2	0.796 1.82 (0.37-8.89)	17	2
Baseline CT								
Signs of old stroke	68	5	0.120 4.60 (0.87-24.32)	65	8	0.101 3.00 (0.94-9.55)	67	6
Signs of current stroke	51	4	0.175 3.71 (0.80-17.17)	48	7	0.060 3.38 (1.08-10.55)	50	5

SITS-MOST – Safe Implementation of Thrombolysis in Stroke – Monitoring Study; NINDS – National Institute of Neurological Disorders and Stroke; ECASS – European Cooperative Acute Stroke Study; NIHSS – National Institutes of Health Stroke Scale; CT – Computed Tomography

Table 4. Multivariate logistic regression analysis showing factors associated with a haemorrhagic transformation and parenchymal haematoma

Variables	Haemorrhagic transformation		Parenchymal haematoma type 2	
	OR	95% CI	OR	95% CI
Age (each year)	0.968	0.932-1.007	0.967	0.896-1.043
Male gender	0.815	0.370-1.796	0.547	0.108-2.773
Stroke severity according to NIHSS score (each point)	1.101	1.020-1.187	0.893	0.775-1.030
Glucose level (stepwise increase of 1 mmol/L)	0.909	0.778-1.062	0.908	0.684-1.205

OR – odds ratio, CI – confidence interval, NIHSS – National Institutes of Health Stroke Scale

ECASS2 trial [8]. In our study, high level of glucose was associated with sICH according to the ECASS2 protocol definition only.

Higher NIHSS score was estimated as an independent risk factor of sICH in several previous studies [7,9,29-32]. We also found this association in our patients but only according to ECASS2 definition.

There are no consistent data that chronic use of aspirin or other antiplatelet agents prior to treatment with rt-PA increases risk of sICH. Several studies have indicated that prior antiplatelet therapy increases the risk of ICH [10,27,29,33]. Only one study shows that prior anticoagulant therapy is an independent predictor of ICH [34]. We did not find influence of chronic use of antiplatelet or anticoagulant drugs prior to thrombolytic therapy on occurrence of sICH.

The presence of early ischaemic changes in baseline CT was indicated as significant predictor of sICH after thrombolysis in several previous studies [6,20]. We did not find such relationship in our patients. We did not find any association between sICH and old ischaemic changes in baseline CT either.

Direct comparison of sICH rates in different studies evaluating safety of systemic cerebral thrombolysis is complicated by the variability of definitions of sICH. A few studies comparing the definitions of sICH were published. In most of them, clinical usefulness of these definitions was analysed, on the base of evaluation of long-term outcome and mortality within 90 days [35, 36]. Gumbinger *et al.* [37] compared four definitions of sICH: NINDS, ECASS2, SITS and ECASS3 in terms of mortality, poor and good outcome after 90 days in group of 314 patients treated with intravenous rt-PA. None of these definitions featured an optimal combination of prediction of mortality and outcome.

The analysis of 6483 patients treated with alteplase from SITS-MOST registry showed that systolic blood pressure, atrial fibrillation, and body weight were pre-

dictors of sICH and current smokers had a lower rate of sICH [10]. The analysis of Polish stroke patients treated with intravenous thrombolysis entered into the SITS registry showed that certain group of patients was treated not fully adhering to the European license in Poland. Those patients, however, were not at increased risk of sICH or death [38]. To determine the role of various factors on the occurrence of sICH, the data from the Helsinki Stroke Thrombolysis Registry suggest that the most suitable definition of postthrombolytic sICH would be the ECASS2. Impact of the ECASS2-defined sICH differed only slightly from the NINDS. The occurrence of sICH according to these definitions was independently associated (or showed a trend) with similar parameters: age, baseline NIHSS score, baseline glucose level, presence of hyperdense artery sign and early infarct signs on admission imaging, and statin use. The frequencies of SITS-defined sICH in various thrombolysis cohorts were lower compared with other definitions [36]. Also in our study, most factors were related to sICH using the ECASS2 definition.

Conclusions

Definition of sICH can determine variables that are related to a high risk of this complication. In our study, the highest number of factors i.e. older age, female sex, blood glucose level and high NIHSS score (> 14 pts) was associated with sICH using the ECASS2 definition.

Disclosure

Authors report no conflict of interest.

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