CLINICAL SCIENCE

Frequency and predictors of symptomatic intracranial hemorrhage after intravenous thrombolysis for acute ischemic stroke in a Brazilian public hospital

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OBJECTIVE: Scarce data are available on the occurrence of symptomatic intracranial hemorrhage related to intravenous thrombolysis for acute stroke in South America. We aimed to address the frequency and clinical predictors of symptomatic intracranial hemorrhage after stroke thrombolysis at our tertiary emergency unit in Brazil.

METHOD: We reviewed the clinical and radiological data of 117 consecutive acute ischemic stroke patients treated with intravenous thrombolysis in our hospital between May 2001 and April 2010. We compared our results with those of the Safe Implementation of Thrombolysis in Stroke registry. Univariate and multiple regression analyses were performed to identify factors associated with symptomatic intracranial transformation.

RESULTS: In total, 113 cases from the initial sample were analyzed. The median National Institutes of Health Stroke Scale score was 16 (interquartile range: 10-20). The median onset-to-treatment time was 188 minutes (interquartile range: 155-227). There were seven symptomatic intracranial hemorrhages (6.2%; Safe Implementation of Thrombolysis in Stroke registry: 4.9%; $p = 0.505$). In the univariate analysis, current statin treatment and elevated National Institute of Health Stroke Scale scores were related to symptomatic intracranial hemorrhage. After the multivariate analysis, current statin treatment was the only factor independently associated with symptomatic intracranial hemorrhage.

CONCLUSIONS: In this series of Brazilian patients with severe strokes treated with intravenous thrombolysis in a public university hospital at a late treatment window, we found no increase in the rate of symptomatic intracranial hemorrhage. Additional studies are necessary to clarify the possible association between statins and the risk of symptomatic intracranial hemorrhage after stroke thrombolysis.

KEYWORDS: Acute Stroke; Thrombolytic Therapy; Brain Hemorrhage; Statins; Tissue Plasminogen Activator.

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INTRODUCTION

Acute ischemic stroke is one of the leading causes of mortality and disability worldwide and represents a life-changing and ominous event for many patients (1). Currently, intravenous thrombolysis with tissue plasminogen activator (TPA) is the only approved medical therapy for acute ischemic stroke aimed at arterial recanalization. However, the use of such therapy has been relatively low, partially due to its narrow therapeutic window but also because of concerns about the risk of symptomatic intracranial hemorrhagic transformation (SIH), which may be associated with clinical deterioration and death (2-4).

Reliable predictors of SIH are still under debate. In a systematic review that included 12 studies, there was considerable variance between results, and no predictor of SIH was common to all studies (5). Defining the accurate risk factors for SIH could increase the safety of TPA treatment for stroke and should eventually reduce the unnecessary concerns about its risks.

No potential conflict of interest was reported.

Stroke is the main cause of death in Brazil, which has a higher age-adjusted mortality rate related to this condition than other South American countries (6-8). Little information exists on the safety of thrombolysis and the occurrence of SIH in South America (9-11). Recent studies found alarming results on public stroke awareness, delays in hospital admission and high stroke-related in-hospital mortality in Brazil (12,13). Nevertheless, there are few data about the safety of IV TPA for stroke in the country. SIH may be more common among more severe stroke patients (14), and the impact of late admission and, consequently, of late onset-to-needle time on the safety of IV TPA is also a matter of concern.

In this study, we aimed to determine the frequency of SIH and the factors associated with its occurrence among patients with an acute ischemic stroke treated with IV TPA at our public tertiary emergency unit in Brazil.

PATIENTS AND METHODS

We reviewed our institutional prospective stroke registry to identify all patients treated with IV TPA at the emergency unit of our hospital from May 2001 to April 2010. This prospective registry and this study were approved by the local institutional review board. Demographic data, cerebrovascular risk factors, prior medical history and medical therapy, clinical data, and relevant laboratory data were collected from this prospective registry by the investigators. Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS) and assessed by certified medical staff from the institution (15). The exclusion criteria were predefined as the lack of data for onset-to-treatment time, admission NIHSS score or neuroimaging scans.

Intravenous thrombolysis was administered in accordance with an institutional protocol, which was based on the National Institute of Neurological Disorders and Stroke (NINDS) trial and the European Cooperative Acute Stroke Study-3 (ECASS-3) trial (16,17). Informed consent was obtained from all patients or their proxy. NIHSS was assessed every 15 minutes during infusion, every hour during the first 6 hours, and every 6 hours during the first 48 hours after treatment. The monitoring and control of blood pressure were performed according to the Brazilian Consensus for the Thrombolysis in Acute Ischemic Stroke, which uses the same monitoring strategy and blood pressure thresholds for intervention as the NINDS trial protocol and the American Stroke Association guidelines for the early management of adults with acute stroke (18,16,19). The Brazilian protocol includes sodium nitroprusside and metoprolol as optional drugs for blood pressure control because labetalol, intravenous nicardipine, and nitropaste are not widely available in Brazil. In our hospital, sodium nitroprusside and metoprolol were used for blood pressure control. A control brain computed tomography scan was obtained 24 to 48 hours after treatment or immediately for neurological deterioration. All protocol violations were reviewed and registered by the main investigators. The results from our institution were compared with those of the Safe Implementation of Thrombolysis in Stroke – International Stroke Thrombolysis Registry (SITS-ISTR), which was published after the ECASS-3 trial and included patients within the 4.5-hour window of treatment (20).

Image review

All of the images were independently reviewed by the main investigators (PTC, BLS, and FAD). When present, intracranial hemorrhages were categorized according to the ECASS classification system (hemorrhagic infarction (HI) type 1, HI type 2, parenchymal hematoma (PH) type 1, and PH type 2) (21). In the event of disagreement between investigators, images were further reviewed by an experienced stroke neurologist (OMP) for consensus. SIH was defined as any intracranial hemorrhage associated with an increase of 4 points or more on the NIHSS score or death, according to the criteria applied in the ECASS-2 trial (22).

Statistical analysis

In the univariate analysis, Fisher's exact test was used for categorical data, and Wilcoxon's rank-sum test was used for quantitative data. A forward stepwise logistic regression analysis was used to identify the independent predictors of SIH among the variables with a p-value<0.1 in the univariate analysis. The Spearman correlation coefficient (rs) was used to evaluate the correlations between quantitative variables. All of the statistical analyses were performed with the SPSS package (version 15.0 for Windows; Chicago, Illinois, USA).

RESULTS

Between May 2001 and April 2010, 117 consecutive patients with acute ischemic stroke were treated with IV TPA in the emergency department of our institution. Four patients were excluded from the current analysis because relevant data regarding treatment were unavailable. None of those patients had SIH. The mean age in the remaining sample was 63 ± 12.8 years old. The median onset-to-treatment time was 188 minutes [interquartile range (IR) = 155-227]. This median onset-to-treatment time was higher than the SITS-ISTR <3 h cohort [140 (IR = 114-165); $p<0.001$] and lower than the 3-4.5 h cohort [205 (IR = 190-229); $p = 0.048$]. Five (4.4%) patients received IV TPA within 90 minutes, 47 (41.6%) from 91-180 minutes, 51 (45.1%) from 181-270 minutes, and 10 (8.8%) after 270 minutes. The median admission NIHSS score was 16 (IR = 10-20). Our sample had more severe strokes than the SITS-ISTR in both treatment cohorts [<3 h cohort: 12 (IR = 7-17), $p<0.001$; 3-4.5 h cohort: 10 (IR = 6-15), $p<0.001$]. Twenty-eight (24.8%) patients had an NIHSS score equal to or less than 10, 60 (53.1%) from 11-20, 19 (16.8%) from 21-30, and six (5.3%) scored greater than 30. The demographic characteristics and clinical and laboratory data at the time of admission are shown in Table 1. Our sample had more prior stroke events and concurrent comorbidities and higher admission blood pressure than the SITS-ISTR. SIH occurred in 7 patients (6.2%), which were categorized as 2 PH-1 and 5 PH-2. SIH was related to in-hospital death ($p = 0.005$). Using the same ECASS-2 definition for SIH, we did not observe more hemorrhages compared with the SITS-ISTR (6.2% vs. 4.9%; $p = 0.505$).

Some patients received IV TPA despite having protocol violations: nine patients (8.0%) were older than 80 years old; ten (8.8%) patients received IV TPA after 270 minutes; and six (5.3%) patients had glycemia levels equal to or greater than 400 mg/dL. None of the patients above 80 years old suffered an SIH. One of the six patients with glycemia levels above 400 mg/dL suffered an SIH (16.6%; SIH in patients with glycemia $\leq$400 mg/dL: 5.4%; $p = 0.325$). Five patients with NIHSS scores between 11-20, two patients with scores between 21 and 30, and none of the patients with scores

Table 1 - A comparative analysis of patient demographic, medical history, and clinical and laboratory data.

	Present study	SITS-ISTR	*p*-value
Female sex	47.8%	39.7%	0.083
Hypertension	80.5%	59.2%	0.007
Diabetes mellitus	31.9%	16.0%	<0.001
Hyperlipidemia	21.2%	35.1%	0.002
Obesity	23.9%	NA	-
Smoking	28.3%	25.6%	0.517
Alcohol abuse	17.7%	NA	-
Atrial fibrillation	16.8%	22.9%	0.144
Congestive heart failure	15.0%	7.6%	0.007
Ischemic heart disease	16.8%	NA	-
Prior stroke	18.6%	10.3%	0.003
Chagas' disease	5.3%	NA	-
Current aspirin use	29.2%	29.4%	0.999
Current warfarin use	6.2%	NA	-
Current statin use	8.8%	NA	-
SBP (mmHg)	156 (140-180)	<3 h = 150 (136-165)	$p = 0.007$
		3-4.5 h = 150 (136-166)	
DBP (mmHg)	90 (80-104)	<3 h = 81 (74-90)	$p<0.001$
		3-4.5 h = 80 (74-90)	$p<0.001$
NIHSS	16 (10-20)	<3 h = 12 (7-17)	$p<0.001$
		3-4.5 h = 10 (6-15)	$p<0.001$
Glycemia (mg/dL)	114 (101-162)	<3 h = 117 (102-140)	$p = 0.011$
		3-4.5 h = 117 (103-142)	$p = 0.011$

SITS-ISTR: Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Registry. NA: not available. SBP: systolic blood pressure at the time of admission. DBP: diastolic blood pressure at the time of admission. NIHSS: National Institutes of Health Stroke Scale. Categorical variables are shown as relative frequencies (%). Numerical variables are shown as medians (interquartile range).

Table 2 - Univariate analysis.

	No SIH (n = 106)	SIH (n = 7)	*p*-value
Male sex	55 (51.9%)	4 (57.1%)	0.999
Age	63.0 ± 13.1	62.9 ± 7.6	0.979
NIHSS*	**15 (10-20)**	**19 (16-22)**	**0.083**
Onset-to-treatment*	185 (155-227)	190 (100-227)	0.560
Hypertension	85 (80.2%)	6 (85.7%)	0.999
Diabetes	35 (33.0%)	1 (14.3%)	0.428
High cholesterol	21 (19.8%)	3 (42.9%)	0.164
Smoking	31 (29.2%)	1 (14.3%)	0.671
Alcohol abuse	20 (18.9%)	Zero	0.350
Prior stroke	20 (18.9%)	1 (14.9%)	0.999
Atrial fibrillation	18 (17.0%)	1 (14.9%)	0.999
Chagas' disease	6 (5.7%)	Zero	0.999
Congestive heart failure	16 (15.1%)	1 (14.9%)	0.999
Ischemic heart disease	19 (17.9%)	Zero	0.599
Obesity	26 (24.5%)	1 (14.9%)	0.999
Aspirin use	32 (30.2%)	1 (14.9%)	0.671
Warfarin use	7 (6.6%)	Zero	0.999
Statin use	**7 (6.6%)**	**3 (42.9%)**	**0.015**
SBP (mmHg)	160.5 ± 34.2	157.1 ± 27.3	0.800
DBP (mmHg)	91.2 ± 22.8	97.0 ± 18.0	0.543
Glycemia (mg/dL)	142.9 ± 64.3	101.3 ± 35.3	0.121

SIH: symptomatic intracranial hemorrhage. NIHSS: National Institutes of Health Stroke Scale. SBP: systolic blood pressure at the time of admission. DBP: diastolic blood pressure at the time of admission. Categorical variables are expressed as events (percentage). Numerical variables are expressed as the mean ± standard deviation. *Expressed as median (interquartile range).

greater than 30 or less than 11 experienced an SIH. Three patients with an onset-to-needle time between 91 and 180 minutes and four patients with an onset-to-needle time between 181 and 270 minutes had an SIH. SIH did not occur among patients treated within 90 minutes or after 270 minutes.

Ten patients were taking statins at the time of admission, and three of the ten patients suffered an SIH. Patients currently using statins were more likely to have hyperlipidemia ($p<0.001$) and congestive heart failure ($p = 0.042$). In the univariate analysis, prior statin use was associated with SIH, and there was a trend toward an association between greater stroke severity and SIH (Table 2). After the multivariate analysis, the prior use of statins was the only factor independently associated with SIH (OR = 3.8; 95% confidence interval: 2.5-8.2; $p<0.001$).

DISCUSSION

In this series of acute ischemic stroke patients treated with IV TPA in a single public university hospital of Brazil, we observed no increase in the SIH occurrence compared with the more recent data from the SITS-ISTR. Our patients had severe neurological deficits and a late onset-to-needle time. Patients with SIH had greater NIHSS scores at the time of admission, although this difference did not reach statistical significance. We found no association between SIH and age greater than 80 years old or onset-to-treatment time. Prior use of statins was the only factor independently associated with SIH.

A large pooled analysis of the main trials of IV TPA in acute ischemic stroke did not show a correlation between onset-to-needle time and SIH occurrence (23). In the NINDS trial, elevated NIHSS scores predicted SIH (14), but the ECASS-2 results did not confirm this association (4). Although IV TPA seems to remain equally safe for ischemic stroke treatment throughout the 4.5-hour treatment window, its functional benefit decreases with prolonged onset-to-needle time (23-25). More than half of our sample was treated after 3 hours of symptom onset, and few patients received IV TPA in the first 'golden hour'. In the last decade, a hierarchical network between emergency units has been implemented in the Brazilian emergency care systems. However, this referral network was not specifically designed for acute stroke care, and there were no unified multi-institutional protocols. We believe that this lack may have contributed to delays in acute stroke recognition and referral to our hospital in the first years of implementation of this emergency network. More recently, there has been an important endeavor (with major input from stroke neurologists) to improve pre-hospital care and organize regional stroke networks in Brazil (26).

Although we may conclude that acute stroke thrombolysis can be safely performed, even in severe patients treated within a rather late treatment window, the true efficacy of IV TPA in this setting is most likely less beneficial. There are striking demographic disparities among Brazilian regions, and nationwide clinical registries are necessary to address this issue (27). Fortunately, the Safe Implementation of Thrombolysis in Stroke – Iberoamerican Cerebrovascular Diseases Society (SITS-SIECV) Stroke Registry has been recently created and will show broader results about the safety and efficacy of IV TPA use for stroke treatment in Latin America.

We observed a high frequency of baseline comorbidities in our sample. Indeed, our patients were more likely to have arterial hypertension, diabetes, dyslipidemia, heart disease

and higher blood pressure at the time of admission compared with the patients in the SITS-ISTR. Nevertheless, this profile was not related to a more frequent SIH occurrence in this study. Prior diabetes and congestive heart failure have been associated with SIH in some studies, but this association has not been consistently confirmed by others (5). The presence of severe comorbidities may be a surrogate marker for more critical underlying strokes and also suggests an important opportunity to reduce stroke recurrence.

The effect of prior statin use on SIH occurrence in acute ischemic stroke patients treated with recanalization therapies is controversial. The prolonged use of statins and low cholesterol levels have been associated with an increased risk of spontaneous hemorrhagic stroke, although a clear explanation for such an association has not been fully established (28). This relationship may be due to non-lipid-related effects. In clinical and experimental studies, statins have been observed to have anti-thrombotic and pro-fibrinolytic effects (29,30). HMG-CoA reductase inhibitors decrease platelet aggregation and reduce fibrinogen and prothrombin levels and their conversion to active forms (31,32). A positive relationship between prior statin use and SIH in intra-arterial thrombolysis-treated patients has been reported (33). However, there was no relationship between prior statin use and SIH or good functional outcome in a large prospective cohort of acute ischemic stroke patients treated with IV TPA (34). One study including patients treated with IV TPA, intra-arterial thrombolysis and endovascular embolectomy found that lower admission low-density lipoprotein levels but not prior statin use were related to SIH (35). Recently, a large pooled analysis found that statin users had more ECASS2-defined SIH, although this positive association was no longer significant after a multivariate analysis and adjustment for imbalances between the groups of statin users and non-statin users (36). These conflicting results could be related to ethnic disparities between the populations of these studies. In fact, it has been shown that ethnicity may have striking effects on statin pharmacokinetics (37). We believe that further studies would be necessary to answer this controversy.

The main limitations of our study include its small sample size and its single-center and retrospective design. The fact that variables such as age and stroke severity were not significantly related to SIH may be due to low study power because there were only seven hemorrhages. Larger studies are required before conclusions on the relationships between clinical variables and SIH can be drawn. Additionally, the blood pressure values during the first 48 hours after treatment were not assessed, and an imbalance of adequate blood pressure control between the subgroups is possible. We were also not able to retrieve cholesterol levels before or during the acute phase of stroke in many patients, and this precluded the analysis of the relationship between cholesterol levels and SIH. Furthermore, it is probable that our results may not reflect the acute stroke treatment conditions in other regions of Brazil.

Intravenous thrombolysis remains one of the few medical therapies for acute ischemic stroke. Nevertheless, few patients admitted to emergency departments receive thrombolytic treatment in developing countries. Scarce lay knowledge about stroke symptoms, ineffective health coverage and non-organized stroke care are contributing to this scenario (2,7,12). In fact, only recently has alteplase been reimbursed in the public health system in Brazil. Nevertheless, important efforts for the promotion of public stroke awareness and the organization of national and regional stroke networks in Brazil have already shown positive and promising results, with a reduction in stroke rate and mortality (38).

In this study, we found that, despite the increased severity of strokes and delayed admissions, acute stroke treatment with IV TPA can be safely performed in Brazil without an increased risk of SIH. In severe, late-treated patients with acute stroke, statin use may be associated with the occurrence of SIH. However, further studies are necessary to clarify this association.

AUTHOR CONTRIBUTIONS

Cougo-Pinto PT contributed to the methodological planning, data collection and analysis, image review, critical review of the results, and manuscript development and review. Santos BL and Dias FA contributed to the data collection, image review, and manuscript review. Fabio SR, Werneck IV and Camilo MR contributed to the data collection and manuscript review. Abud DG and Leite JP participated in the critical review of the results and manuscript development and review. Pontes-Neto OM contributed to the methodological planning, image review, data analysis, critical review of the results, and manuscript development and review.

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