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Thrombolysis in Patients with Ischemic Stroke: Epidemiology, Deficits and Disability in Hospital Admission and Discharge

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Abstract:

OBJECTIVE: to evaluate epidemiological and neurological disabilities at hospital admission and discharge of patients with acute ischemic stroke who underwent intravenous thrombolysis.

METHODS: A longitudinal study conducted from January-August 2012 at the Cerebrovascular Accident Unit of the General Hospital of Fortaleza/Ceará. The National Institute of Health Stroke Scale and modified Rankin Scale were used at admission and discharge of patients treated with intravenous rt-PA.

RESULTS: In all, 38 patients aged 27-87 years (SD±14.1) participated. Most were men (60.5%); had low-medium education level (71.1%); hemiparesis (97.4%); lip deviation (71.1%); aphasia (42.1%) and impairment of the middle cerebral artery (89.5%). The mortality rate was 23.7% after three months. Aphasia had OR=7.8 for death, CI=1.3- 45.1. There was statistical significance in the NIHSS ($p<0.01$) and MRS ($p<0.01$) scores when compared between admission and discharge.

CONCLUSIONS: There was significant improvement concerning neurological severity and functional disability at admission, discharge and 90 days after thrombolysis.

Keywords: *Stroke; thrombolytic therapy; neurological severity; disability; epidemiology.*

1. INTRODUCTION

The Cerebrovascular Accident (CVA) remains a leading cause of disability and death worldwide. One in six people in the world will suffer a stroke in their lifetime. The disease affects 15 million people of all races and ethnicities and causes six million deaths every year[1]. Epidemiological data show that in Brazil, depending on the region, stroke is the first or second leading cause of death[2].

Stroke can cause motor and cognitive deficits depending on the injured area, the size of the affected area and the lack of collateral blood flow[3]. Individuals who suffer a stroke face a situation of disability, which makes them permanently dependent. This occurs because, in most cases, the motor sequelae affect the dominant hemisphere, which may cause a negative impact on work and family life[3,4].

According to Bamford[5], THE FOLLOWING SYNDROMES OF CEREBRAL CIRCULATION can be found IN ISCHEMIC STROKE, and THESE SYNDROMES CAN be extrapolated to hemorrhagic stroke: (1) TACS: total anterior circulation stroke syndromes. It is the most common stroke and usually causes altered level of consciousness and serious motor deficit; (2) PACS: partial anterior circulation syndromes, designated as a minor stroke which may or may not cause altered consciousness and a less intense motor deficit; (3) POCS: posterior circulation stroke syndrome. This stroke is limited to the vertebrobasilar system and causes visual disturbances (visual anopsia and agnosia); ocular motor abnormalities; bulbar muscular atrophy (swallowing); sensory, vestibular and motor deficits. (4) LACS: lacunar stroke syndromes. They are caused by strategic obstructions of small brain supply arteries and have an atherothrombotic origin.

The acute ischemic stroke (AIS) begins when the neuronal tissue presents a dysfunction caused by a reduction in cerebral blood flow. When cerebral ischemia occurs, it is possible to observe two defined areas in the brain: the ischemic core and its adjacent zone, called penumbra[6]. The ischemic penumbra represents an area of dysfunctional neuronal tissue with considerable recovery capacity when cerebral blood flow is restored within a therapeutic window in a suitable time, using intravenous thrombolytic therapy or thrombolysis[7].

Intravenous thrombolysis is the lysis or breakage of an intravascular thrombus with certain types of prescription drugs, which the main purpose is to unblock the artery before there is a degree of irreversible damage to the brain tissue[8].

In the acute phase of ischemic stroke, this therapy, which has extensive scientific evidence, can reduce mortality and disabling motor and cognitive sequelae resulting from the ictus (a localized neurological deficiency that appears acutely). Thrombolysis is performed using the recombinant tissue plasminogen activator (rt-PA) and offers 30% more chances of the patient evolve without functional disability after the ninetieth day of infusion as demonstrated by the THE NINDS RT-PA STUDY GROUP[9]. Thus, rt-PA for acute ischemic stroke has been recommended by leading international (since 1996)[10-13] and national (from 2001)[11-20] guidelines, with studies that continue to prove its efficacy[12-13].

In Ceara, the Cerebrovascular Accident Unit (CVAU) was implemented, with a full multidisciplinary team, in 2009 at the General Hospital of Fortaleza to perform the thrombolytic treatment for those affected by stroke[14]. The CVAU of the general hospital of Fortaleza is the largest referral center in Brazil for the treatment of patients suffering from stroke within the Unified Health System (SUS). It was qualified by the Ministry of Health as level three for ensuring comprehensive care to patients from the emergency services up to the back-office services. It has 20 beds and a multidisciplinary health team composed of doctors, physiotherapists, occupational therapists, psychologists and nursing staff.

However, there are few epidemiological and clinical data on patients enrolled in this unit. Thus, this study aims to evaluate epidemiological aspects, neurological severity and functional disability in patients with AIS who underwent thrombolytic therapy with intravenous rt-PA at admission and discharge in the CVAU of the general hospital of Fortaleza.

2. METHODS

This is a quantitative, longitudinal, descriptive and analytical study. The study population consisted of patients who were selected among victims of acute ischemic stroke and had to perform thrombolytic therapy. The study was conducted from January to August 2012 in the CVAU of the HGF located in Fortaleza city, Ceara, Brazil.

Patients aged 18 and older who suffered an acute ischemic stroke and underwent thrombolytic treatment were included in the population. Patients with AIS who were not treated with the thrombolytic therapy, patients with hemorrhagic stroke, neurologic diagnoses other than ischemic stroke, patients with visual disturbances and severe motor and/or cognitive sequelae installed prior to the ischemic event were excluded.

The research began with the collection of demographic data (age, sex, race, marital status, education, income, occupation, origin, sedentary lifestyle, smoking and drinking) and epidemiological data (obesity, diabetes, dyslipidemia, hypertension, cardiopathies) and hemorrhagic complications, among others, in the patients' records. These were produced based on the literature and placed in a structured form. The data was collected at the time of admission of patients.

In a second step, patients were assessed at admission and discharge, through two nationally validated neurological scales: the National Institute of Health Stroke Scale (NIHSS) which provides a quantitative measure of stroke-related neurologic deficit[15] and the Modified Rankin Scale - mRS, which measures the patient's degree of functional disability[16].

The NIHSS is an instrument used to measure the degree of neurologic impairment in patients who suffered an AIS. With the result of this scale, it is possible to estimate whether the patient can make intra-arterial or venous thrombolysis, or mechanical thrombectomy[15].

The mRS is an instrument used for measuring the degree of functional disability, revealing the impact of treatments for stroke patients[17]. It can also be applied via telephone, as a structured interview, and its result is similar to the face-to-face interview[18].

Assessments through the scales were done twice. The first one occurred at patient's admission to the CVAU of the HGF and the second before discharge. The average time to apply the first assessment was five hours after admission to the unit, with SD± 2 hours. This time was set due to the vulnerable condition of the patient, who was evaluated by members of the multidisciplinary team during the thrombolytic procedure. Thus, due to patient's instability and with the purpose to protect him/her from various evaluations conducted concurrently, the NIHSS and mRS assessments were conducted after the multidisciplinary team approach.

After ninety days of thrombolytic infusion, a second assessment was performed by using the mRS only. This assessment was conducted with discharged patients or one of their family members through a telephone call. The purpose of this assessment was to verify the results of functional disability three months after treatment with rt-PA and compare it with the results of the international protocol (SITS-MOST)[19] and national protocol[20].

The dependent variables in this study were: NIHSS; mRS and Death. The dependent or predictor variables were: risk factors and co-morbidities; clinical and functional signs and symptoms. The same variables underwent descriptive analysis in order to determine their distribution and also inferential analysis to determine the association between them.

First, a test was performed to verify the normality of the data through the Shapiro-Wilk Test. Pearson's chi-squared test, linear trend test and Fisher's exact test (when the dependent variables were categorized) were used to assess the association between the independent variables and the mRS, the NIHSS and Death.

For testing, the NIHSS was dichotomized into mild Deficit and moderate/severe Deficit, and mRS was dichotomized into: Without disability x mild/severe Disability.

Spearman's rank correlation coefficient was used in the comparison of results of the scales. Student's t-test was used to compare means of the quantitative dependent variables. All tests were performed with a significance level of 0.05. Data was processed, tabulated and analyzed in the Statistical Package for Social Sciences - SPSS, version 19 (SPSS Inc., Chicago, IL, USA).

Without any conflicts of interest, the project was approved by the Research Ethics Committee of the General Hospital of Fortaleza under protocol No. 290206/12 ensuring the autonomy of individuals, non-malfeasance, beneficence and righteousness expressed in the survey.

3. RESULTS

Of all 319 patients who were hospitalized due to AIS from January to August 2012 in the CVAU of the General Hospital of Fortaleza, 38 could make intravenous thrombolytic therapy. The average hospital stay at the unit was 14 days.

Sociodemographic data on the group showed that most of patients were men [23 (60.5%)], had low to medium levels of education [27 (71.1%)], received one to two minimum wages [31 (81.6%)] and were originally from the Capital [29 (76,3%)]. Patients' ages ranged from 27 to 87 years (mean 65 years SD±14.1).

Regarding occupation, most of patients were retired [14 (36.8%)] and independent workers [06 (15.8%)] and six (15.8%) were unemployed. There was a predominance of mixed ethnicity [33 (86.8%)], followed by White [4 (10.5%)]. There were 10 illiterate people (26.3%), and only one (2.6%) patient had a higher education level.

The most prevalent risk factors and comorbidities were: sedentary lifestyle (n=34, 89.5%); hypertension (n=32, 84.2%); old age (n=26. 68.4%); dyslipidemia (n=16. 42.1%) and diabetes (n=15, 39.5%).

The most prevalent clinical and functional signs and symptoms at admission were sudden numbness or weakness on one side of body [37 (97.4%)], walking [37 (97.4%)] and talking [35 (92.1%)] difficulties, deviation of labial commissure [27 (71.1%)] and aphasia [16 (42.1%)].

Regarding the stroke extension, there was prevalence of the total anterior circulation syndrome - TACS [15 cases (39.5%)], and concerning the affected vascular territory, most 34 (89.5%) had injured the middle cerebral artery - MCA.

Table 1 shows the degree of neurological deficit defined by the NIHSS at admission and discharge. There was significant improvement in the range of stroke severity scale of the NIHSS when compared at admission and discharge of thrombolized patients (p<0.01). The median NIHSS score was 12 at admission and classified as moderate deficit. At discharge, the median NIHSS score was four, classified as mild deficit.

Table1. *NIH Stroke Scale at hospital admission and discharge.*

Scale score	Admission		Discharge		p value
	N	%	N	%	
Minor Deficit (0 -7)	07	18.4	22	66.7	<0.001
Moderate Deficit (8 - 14)	13	34.2	05	15.2	
Severe Deficit (>=15)	18	47.4	06	18.2	
Total	38	100.0	33*	100.0	

Note: *Fisher's test. *Excluded death cases (5)*

Source: *Developed by authors based on the assessment of the NIHSS*

Table 2 shows the degree of functional disability defined by the Modified Rankin Scale (mRS) at hospital admission and discharge. There was significant improvement in the levels of the mRS when comparing the results at admission and discharge of thrombolized patients (p<0.01). At discharge, according to the results of the mRS, 48.6% of patients left without disability or mild disability. The scale score was ≤ 2.

Table2. *Modified Rankin Scale at hospital admission and discharge*

Scale Score	Admission		Discharge		p value
	N	%	N	%	
No Symptoms (0)	0	0.0	02	6.1	
No Significant Disability (1)	0	0.0	09	27.3	
Slight Disability (2)	01	2.6	05	15.2	
Moderate Disability (3)	07	18.4	09	27.3	<0.001
Moderate Severe Disability (4)	28	73.7	06	18.2	
Severe Disability (5)	02	5.3	02	6.1	
Total	38	100.0	33*	100.0	

Note: *Fisher's test.* 5 death cases were excluded.*

Source: *Developed by the author based on the assessment of the Rankin scale.*

Table 3 shows the degree of functional disability defined by the mRS comparing the results between hospital admission and the ninetieth day after thrombolysis, when there were four more deaths. Even with the occurrence of deaths, there was significant improvement (p<0.01) in the mRS bands, showing, in patients who survived after the ninetieth day of thrombolysis treatment, a score ≤ 2 in 55% of the group.

Table3. *Modified Rankin Scale at admission and 90th day after thrombolysis*

Scale	Admission		90 days after thrombolysis		
	N	%	N	%	p value
No Symptoms (0)	0	0.0	01	3.6	
No Significant Disability (1)	0	0.0	06	21.4	
Slight Disability (2)	01	2.6	14	50.0	< 0.001
Moderate Disability (3)	07	8.4	02	7.1	
Moderate Severe Disability (4)	28	73.7	02	7.1	
Severe Disability (5)	02	5.3	03	10.7	
Total	38	100.0	28*	100.0	

Note: *Fisher's test. * Intra-hospital death cases, deaths after discharge and a non-notified death case after 90 days from discharge were excluded.*

Source: *Developed by authors based on the assessment of the Rankin Scale.*

Table 4 shows the correlation between the group mortality and the variables: clinical and functional signs/symptoms; risk factors and comorbidities identified at admission. Patients with aphasia on admission (42%) had an odds ratio of 7.8 (CI=1.3 - 45.1, p=0.01) while diabetes was associated with

the occurrence of death (p=0.01). There was association between hemorrhagic complications and death (p =001).

Table4. *Correlation between death occurrence, and clinical and functional signs/symptoms, risk factors/comorbidities*

Clinical signs and symptoms and risk factors/co-morbidities at admission.	Death (N)	%	No Death (N)	%	P value
Aphasia at admission	07	77.8	09	31.0	*0.01
Convulsions	00	0.0	02	6.9	0.42
Extremely intense headachae	03	33.3	04	13.8	0.19
Sudden Numbness or weakness in one side of the body	09	100.0	28	96.6	0.57
Difficulty in walking	09	100.0	28	96.6	0.57
Dizziness	04	44.4	11	37.9	0.73
Incordination	04	44.4	07	24.1	0.24
Difficulty in seeing in one or both eyes	01	11.1	07	24.1	0.40
Confusion	01	11.1	06	20.7	0.51
Difficulty in speaking	08	88.9	27	93.1	0.68
Difficulty in understanding	04	44.4	07	24.1	0.24
Obesity	04	44.4	06	20.7	0.16
Diabetes	08	88.9	07	24.1	*0.01
Dyslipidemia	03	33.3	13	44.8	0.54
HAS	08	88.9	24	82.8	0.66
Tobacco Smoking	02	22.2	10	34.5	0.36
Alcoholism	01	11.1	12	41.4	0.09
Cardiopathies	05	55.6	12	41.4	0.45
Old age	07	77.8	19	65.5	0.26
Sedentarism	08	88.9	26	89.7	0.94
Hemorrhagic complications	02	67.0	01	33.0	*0.001

Note: *Pearson's test. *Significan variables. OR=7.8; CI=1.3-45.1 for aphasia.*

Source: *Developed by authors based on the data from records of january-august and neurological assessment / 2012. CVAU/HGF.*

Table 5 shows an overall mortality rate of 23.7%. In this rate, 13.2% (n=5) of deaths occurred in hospital and 10.5% (n=4) after the ninetieth day of the thrombolytic infusion.

Tabela5. *Intra-hospital mortality and deaths after the 90th day thrombolytic infusion*

Death	N patients	%
(Yes) intra-hospital	05	13.2
(Yes) After the 90th of thrombolytic infusion	04	10.5
(No)	28	73.7
Information not found	01	2.6
Total	38	100.0

Source: *Developed by authors based on the data from records of january - august / 2012. CVAU/HGF, and through telephone.*

4. DISCUSSION

Despite the importance of the CVAU of the HGF in the health care of patients with CVA in SUS, there is scarcity of epidemiological data about it. This information is important for the organization of the service, the creation/adjustment of care protocols for these patients, and also for the understanding of how this disease affects people's quality of life.

In eight months there were 319 hospitalizations due to AIS in the CVAU of the HGF and of all these patients, only 38 (11.9%) met the criteria to be treated with thrombolytic therapy. There are many reasons for the non-completion of thrombolytic therapy in the other patients, but the delay in reaching the hospital – time frame (time between the onset of symptoms of stroke and hospital arrival) is the main obstacle, given that national and international protocols describe a maximum time frame between 65 and 270 minutes[19]. Thus, the way the health system is organized is directly related to the patient`s chance to undergo thrombolysis.

Understanding that urgency and emergency systems (e.g. Mobile Emergency Service – SAMU and Emergency Care Units – UPAs), small hospitals and basic health units are, in most cases, the first reference to patients suffering from AIS, the rapid identification and referral/transfer of these patients to a CVAU is essential to the completion of thrombolysis. To do so, practitioners of these units must be able to recognize the signs and symptoms of ischemic stroke, and the organization of these services should be efficient and coordinated with the rest of the health care network, something that, unfortunately, is not really done in all Brazilian municipalities. Furthermore, the population should also be aware of the symptomatology and severity of this disease through continuing education programs for professionals and health education programs for the population, as well as an organized and efficient health care network that may contribute to a higher rate of thrombolysis performed in patients with AIS, improving prognosis and reducing disability[9-13].

Assessing the evolution of neurological deficit by the NIHSS at admission and discharge showed a significant improvement in neurological severity level ($p=<0.01$) of patients who underwent thrombolysis and is corroborated by researches[21,22] that demonstrated a reduction in NIHSS after the use of thrombolysis. Regarding the mRS, assessing the degree of functional disability at hospital admission and discharge showed a significant improvement in the degree of functional disability ($p<0.01$) that is similar to the results of a research conducted with more than 800 patients[23]. The mRS identified a positive significant evolution of functional disability ($p=<0.01$) in more than half of the patients who survived after the ninetieth day of thrombolytic infusion.

Knowing that the NIHSS assesses the degree of neurological deficit of the patient and that the mRS assesses the degree of functional disability, it is easy to see that a person with good scores in these tests has better conditions to carry out daily activities, interact with social environment (instrumental activities of daily living) and therefore has a better quality of life after ischemic stroke.

The findings of this study are consonant with historical meta-analyses that evaluated the benefit of thrombolytic therapy in ischemic stroke, such as NINDS, ECASS and ECSS II[9,10]. After the ninetieth day of treatment, a score ≤ 2 in the mRS could be observed in more than half percent of patients, and there was a death rate of 22.4%, approximately the mortality rate of the studied group[10]. The results of NINDS, ECASS I, II, and III, ATLANTIS and IST-3 show that patients with AIS who received rt-PA after the onset of symptoms were more likely to have minimal or no disability than patients who received placebo[9,10,24].

When correlating the mortality rate of the group with clinical and functional signs/symptoms and risk factors/co-morbidities, little less than half of patients presented motor aphasia, confirming that patients who had aphasia at admission were 7.8 times more likely to die than patients without aphasia, showing that it is predictive of severity and mortality, which is corroborated by authors[25] who considered aphasia a risk factor for death in the acute phase of stroke. Concerning risk factors, only diabetes was associated with death. Authors unanimously state that Diabetes Mellitus is associated with high mortality rates[26-29].

It can be observed, that pre-thrombolysis clinical situation affects the results of thrombolytic intervention (probably related to the location and size of the ischemic core and penumbra zone). Thus, when they are located in more critical areas (e.g., areas related to speech) or in a much more extensive area, the improvement caused by thrombolysis is less evident than when the magnitude and location of the ischemic strokes are smaller. The systemic situation (e.g., diabetes) may lessen the effects of thrombolysis, for it affects the body's recovery ability[29].

It was found that the mortality rate of the group increased after the ninetieth day of thrombolytic infusion, getting close to the results of other relevant studies conducted with patients treated with rt-PA[27]. This increase in mortality after 90 days of thrombolysis is probably due to post-ischemic stroke existing morbidities, which affect the functioning of the body, weakening it and contributing to the fatal outcome[21].

Of all the patients who were treated with thrombolytic therapy and died, 78% were 70 years old or older. In the USA, older age was significantly associated with increased mortality among thrombolized patients[29]. However, in the Third International Stroke Trial conducted with about 3000 people and half of them over the age of 80 years, authors concluded that thrombolysis can also be an effective treatment for this age group, once the mortality rate was the same as the one of the control group after six months[24].

Given the advances in thrombolytic therapy in ischemic stroke, the current issue is no longer on the efficacy of thrombolysis, but how to achieve the goal of treating patients eligible for this procedure, since, even with evidence of good results, this procedure is still not much used. The reasons are probably related to the non-recognition of the symptoms of stroke and urgency nature of *ictus* by the population and also due to lack of public educational activities and unavailability of proper professional care in these services. According to the WHO, all the people are vulnerable to stroke and it can be worsened by the neglect and indifference of authorities[1].

Therefore, it is recommended 20 that public and private hospitals adapt their structure to the emergency care, providing neurological care and quick access to cranial CT scan.

5. CONCLUSION

The neurological severity and functional disability in patients with AIS who underwent intravenous thrombolysis had significant improvement when quantified by the NIHSS and mRS at hospital admission and discharge.

The thrombolytic treatment leads to the reduction in functional disability of patients with stroke and decreases mortality, minimizing the negative impact on the performance of daily activities.

The results require greater emphasis by current public policies aimed at installation of thrombolytic therapy for a more comprehensive care network in the SUS.

AUTHORS' CONTRIBUTION

AMSB and MVLS devised the research project, performed data collection, literature review and analysis and composed the letter. APGFV helped developing the data analysis and final revision of the manuscript.

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