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Morbimortality and determinants of reperfusion in ischemic stroke

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SUMMARY

BACKGROUND: Cerebrovascular accident (or stroke) and ischemic heart disease are the the major causes of death in the world. It is estimated that about 85% of strokes are ischemic in origin. Reperfusion therapy in the acute phase of ischemic stroke with a recombinant human tissue plasminogen activator is effective, but some factors influence the success of this treatment.

OBJECTIVE: The aim of this study was to evaluate clinical aspects and possible determinants for reperfusion after venous thrombolysis.

METHODS: This is a retrospective, cross-sectional, observational study based on a review of hospital records of inpatients diagnosed with ischemic stroke treated with intravenous thrombolysis, the main outcome being reperfusion or not.

RESULTS: Data from this study revealed a predominance of females in the group of reperfused patients and males in the non-reperfused group, both maintaining moderate severity on the National Institutes of Health Stroke Scale and admission without statistical significance (p>0.18). In addition, the mean admission severity score was 13.2 for the group of reperfused patients and 14.2 for those not reperfused, and the mean ejection fraction of both groups was within normal functionality, with a mean of 0.50 for reperfused patients and 0.62 for non-reperfused patients.

CONCLUSION: We found an association between successful venous chemical thrombolysis reperfusion and lower mortality in patients with acute stroke.

KEYWORDS: Acute ischemic stroke. Acute ischemic stroke. Thrombolysis. Reperfusion.

INTRODUCTION

Cerebrovascular accidents (CVA or stroke) and ischemic heart diseases are the major causes of death worldwide, with over 2 million deaths since the year 2000 and almost 9 million in 2019. Apart from causing premature deaths, CVA is also one of the main diseases compromising the physical capacity of individuals in their daily activities. Data from the World Health Organization (WHO) demonstrate that the CVA is the second cause of death in adults around the world and the main cause in Brazil, being responsible for 10% of total amount of deaths, 32.6% of deaths of vascular origin, and 40% of early retirements[1,2].

The American Stroke Association describes the CVA as an acute focal injury of the central nervous system by a vascular cause or even with clinical evidence of symptoms persisting for over 24 h and exclusion of other etiologies. Accordingly, the CVA is characterized by the sudden loss of blood circulation (thrombotic or embolic arterial obstruction) in a determined area of the encephalon with corresponding symptoms of loss of focal or global brain functions, possibly leading to severe cases of coma or not[3]. It is estimated that around 85% of cerebrovascular accidents have ischemic origin (I-CVA) and 15% are hemorrhagic. I-CVA occurs due to thrombosis and is responsible for 30% of the cases of CVA, with high risk considered for individuals with arterial fibrillation, thrombi in the left ventricle, cardiac tumors, valve diseases, expanded myocardiopathy, and heart failure[4].

Thrombolytic treatment with recombinant tissue plasminogen activator (rtPA) during the acute phase of the I-CVA is evidence level 1A[5]. The venous use of the rtPA is time-dependent and decreases morbidity by 30% when applied within a period £4.5 h[6].

Treatment during the acute phase aims to re-establish the flow in the occluded vessel in the lowest possible timeframe and reduce oxygen consumption in the areas at risk. The therapeutic evolution of the disease follows similar steps for the treatment of acute myocardial infarction, initially adopting measures to protect the cells submitted to the Ischemia through a reduction in metabolic consumption, while taking measures to re-establish the flow[6,7]. Considering the high rates of individuals still afflicted by acute I-CVA and the effects resulting from the non-clearance of the interruption of the secondary

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blood flow to possible cardioembolic cardiac alterations, the object of this study was to assess the clinical aspects and possible determinants for reperfusion after venous thrombolysis in the I-CVA[7].

METHODS

This is a retrospective observational cross-sectional study, based on a review of hospital records of admitted patients with a diagnosis of ischemic CVA treated with intravenous thrombolysis, with the main outcome being the occurrence of reperfusion. Clinical and demographic variables, comorbidities, and findings of the transthoracic echocardiogram performed in post-thrombolysis were analyzed. The study was carried out in a large-sized public high-complexity hospital, certified by the Ministry of Health and Education as a teaching hospital and hospital of reference in neurological and neurosurgical emergencies, being the only public hospital available with open doors to venous thrombolysis in the state.

The selected patients were those hospitalized consecutively with the diagnosis of acute I-CVA and who were submitted to venous thrombolytic treatment at the CVA unit of reference and had met the inclusion criteria. The convenience sample was of the non-probabilistic type. Patients above the age of 18 years were included in I-CVA, diagnosed, and submitted to venous thrombolysis at the unit specialized in acute cerebrovascular diseases in the period between January 2015 and December 2018. Patients under the age of 18 years and over 80 years, as well as patients with coagulopathy, prior hemorrhagic CVA, I-CVA with prior hemorrhage, I-CVA with pre-thrombolysis hemorrhagic transformation, previous background of some form of intracranial hemorrhage or cerebral vascular malformation, or contraindication for thrombotic procedures, were excluded from this analysis.

DATA ANALYSIS AND ETHICAL ASPECTS

The collected data were processed using Statistics Program for Social Sciences (SPSS) version 21. The following descriptive measures were used: central tendency and dispersion, mean and median, chi-square, and calculation of single and relative frequencies. The level of significance was $P<0.05$. The research was approved by the Research Ethics Committee involving individuals at Hospital Geral Roberto Santos, registered under number 2.993.032/2018.

RESULTS

During the period from January 1, 2016 to December 31, 2018, 540 individuals were included in the research and 224 patients were excluded. From the total number assessed, 192 (60.7%) presented post-thrombolysis reperfusion of the I-CVA, 124 (39.2%) were not reperfused, and 12 (2.2%) did not present data consistent with reperfusion.

The analysis of the data prior to the thrombolytic procedure and after being afflicted by acute I-CVA revealed that 316 individuals met the criteria for participating in the research. After the treatment of the collected data, it was evidenced that there was a predominance of the female gender, with stratified ages between 60 and 79 years, corresponding to 47.7% (83 women) of the total number of individuals for this age group and 51.8% of the total of 160 women in the research. Described under Table 1 is

Table 1. Description of the distribution of comorbidities by age of the reperfused individuals.

Comorbidities	Stratified age groups											
	27–59 years				60–79 years				80 years			
	Reperfused patients				Reperfused patients				Reperfused patients			
	Yes (119)		No (49)		Yes (176)		No (104)		Yes (3)		No (12)	
	n	%	N	%	n	%	n	%	n	%	n	%
Systemic arterial hypertension	57	68.7	32	66.7	73	68.9	52	76.5	2	66.7	8	100.0
Diabetes mellitus	19	22.9	5	10.4	34	32.1	23	33.8	0	0.0	3	37.5
Tobacco use at present or in the past	19	22.9	3	6.3	21	19.8	12	17.6	0	0.0	1	12.5
Alcohol intake at present or in the past	10	12.0	1	2.1	21	19.8	10	14.7	0	0.0	0	0.0
Cardiopathy	9	10.8	5	10.4	13	12.3	4	5.9	1	33.3	0	0.0
High cholesterol	1	1.2	1	2.1	6	5.7	1	1.5	0	0.0	0	0.0
Pulmonary arterial hypertension	0	0.0	1	2.1	0	0.0	0	0.0	0	0.0	0	0.0
Chagas disease	4	4.8	1	2.1	8	7.5	2	2.9	0	0.0	0	0.0

the age distribution of reperfused individuals by comorbidity in the studied population.

In relation to the post-thrombolysis outcome, around 40 patients (12.6%) died after 24 h of the procedure, mostly of the male gender (52.5%) and of the age group between 50 and 70 years. In total, 10.7% of the total thrombolized individuals relevant for the study were transferred to the intensive care unit, and 78.9% were discharged from the CVA unit of reference to the unit of low complexity (wards or open units) and/or sent home.

The study revealed that the studied patients, whether reperfused or not, had different frequencies of comorbidities and cardiovascular risk factors, characterizing the studied population as heterogeneous and of high cardiovascular risk.

With reference to individuals submitted to the reperfusion procedure, the average age was 60.5 years, and for non-reperfused individuals, it was of 62.8 years. The data of this study reveal a predominance of the female gender in the group of reperfused patients and the male gender in the non-reperfused group; both groups maintain moderate severity in the National Institutes of Health Stroke Scale (NIHSS) of hospital discharge and admission without statistical significance (p>0.18). Moreover, the average score of severity was 13.2 for the group of reperfused patients and 14.2 for non-reperfused patients, and the mean ejection fraction of both groups was within normal functionality, with mean values of 0.50 for reperfused patients and 0.62 for non-reperfused patients, as outlined in Table 2.

Table 2. Reperfused patients and some stratified clinical parameters.

Parameters		Reperfused										
		Yes					No					p-value
		n	%	Mean	95%CI		n	%	Mean	95%CI		
					Inferior	Superior				Inferior	Superior	
Death	Yes	14	7.3				26	21.0				<0.001
	No	178	92.7				98	79.0				
Stratified age	27–59 years	83	43.2				48	38.7				0.40
	60–69 years	58	30.2				38	30.6				
	70 years and over	51	26.6				38	30.6				
Gender	Male	89	46.4				67	54.0				0.18
	Female	103	53.6				57	46.0				
NIHSS admission	No stroke symptoms	0	0.0				0	0.0				0.04
	Minor stroke	2	1.3				6	5.8				
	Moderate stroke	98	64.5				51	49.5				
	Moderate-to-severe stroke	32	21.1				30	29.1				
	Severe stroke	20	13.2				16	15.5				
NIHSS discharge	No stroke symptoms	4	2.6				0	0.0				<0,01
	Minor stroke	35	22.9				23	22.1				
	Moderate stroke	81	52.9				40	38.5				
	Moderate-to-severe stroke	23	15.0				23	22.1				
	Severe stroke	10	6.5				18	17.3				
Dysfunction of the left ventricle	Yes	45	23.4				32	25.8				
	No	147	76.6				92	74.2				
Age				60.5	58.8	62.3			62.8	60.7	64.9	
Pumping force of the blood				0.59	0.56	0.61			0.62	0.59	0.65	
Severity scale upon hospital admission				13.2	12.3	14.0			14.1	12.9	15.3	
Severity scale upon hospital discharge				7.47	6.30	8.64			11.36	9.68	13.04	

The effectiveness of the applicability of the NIHSS on hospital admission and discharge is possible to observe in the data analysis. The categorization in intervals is considered, as per the previously described Table 1, and the results obtained are compared. Hospital admission and discharge NIHSS had minimum scores of 1 and maximum scores of 29 points. A higher score was observed for patients in the age group of 60–79 years, with an average score of 14.1 and a mean value of 14, above the younger age groups, where the average reached 12.7 for individuals under the age of 59 years and a mean value of 12 with a p-value of 0.04, described in Table 3.

There was a predominance in the NIHSS admission interval of 5 to 15 with approximately 58.4% (149 individuals), corresponding to patients in the symptom group with moderate sequelae, followed by moderate to severe levels of NIHSS admission 16–20 with 28.7% (62 individuals). To have a more reliable record of hospital discharge registers and a better understanding of the clinical status of patients, the NIHSS upon discharge was observed. These results indicate that approximately 79.7% (138 individuals) of the total NIHSS hospital discharge had scores of 1 to 15 points, considered light to moderate CVA, suggesting symptoms of minor to moderate intensity, as represented in Table 2. A loss of 19.3% (61 individuals) should be observed in the NIHSS admission data and 44.3% (140 individuals) of NIHSS discharge due to the fact that these were not registered in the physical records.

DISCUSSION

An association was observed between the I-CVA and prior cardiopathies and echocardiographic alterations with alteration to the left atrium and low ejection fraction common remodeling pathways due to an increase in cardiac cavities in advanced cardiopathies <40%. Effectively, various studies confirm the

Table 3. Distribution of the initial National Institutes of Health Stroke Scale and discharge of the studied population.

	Scores				% in stratified age			
	Stratified age			Total	Stratified age			Total
	27–59 years	60–79 years	80 years		27–59 years	60–79 years	80 years	
NIHSS admission								
Minor stroke	5	2	1	8	4.5	1.5	14.3	3.1
Moderate stroke	74	73	2	149	66.1	53.7	28.6	58.4
Moderate-to-severe stroke	22	39	1	62	19.6	28.7	14.3	24.3
Severe stroke	11	22	3	36	9.8	16.2	42.9	14.1
Total	112	136	7	255	100	100	100	100
NIHSS discharge								
No stroke Symptoms	3	1	0	4	2.7	0.7	0.0	1.6
Minor stroke	31	26	1	58	27.7	18.8	14.3	22.6
Moderate stroke	53	66	2	121	47.3	47.8	28.6	47.1
Moderate-to-severe stroke	17	27	2	46	15.2	19.6	28.6	17.9
Severe stroke	8	18	2	28	7.1	13.0	28.6	10.9
Total	112	138	7	257	100	100	100	100

NIHSS		N	Average	95%CI		Percentage			p-value
				Inferior limit	Superior limit	25	Median	75	
Severity scale upon admission	27–59 years	112	12.7	11.7	13.7	8,0	12,0	17,0	0.04
	60–79 years	136	14.1	13.2	15.1	9.0	14.0	18.0	
	80 years	7	16.6	9.5	23.6	15.0	18.0	22.0	
Severity scale upon discharge	27–59 years	77	8.3	6.7	9.8	3.0	6.0	14.0	0,31
	60–79 years	94	9.9	8.5	11.2	4.0	8.0	14.3	
	80 years	5	10.6	–0.4	21.6	3.5	6.0	20.0	

greater individual association of CVA in patients with reduced EF (<40%).

Our results corroborate venous thrombolysis as therapy for reperfusion in patients with I-CVA, reducing hospital morbimortality. Cardiovascular risk factors, prior cardiopathy, and advanced age are predominant in the studied population. These data reinforce the fact that with advanced age there is an increase in the risk for CVA, different from the younger age groups, where hereditary conditions, such as malformation, thrombophilia, and the use of medications and illicit drugs, may exist[8]. Despite the recognized relationship between age, cerebral Ischemia, and female gender for greater life expectation in this group, no positive association was found in this study.

Venous thrombolysis for arterial reperfusion is the main treatment behavior at present for ischemic CVA. Our results demonstrate the significant difference in mortality in patients submitted to the intervention. Our data on mortality and ischemic CVA are not correlated to the presence of systemic arterial hypertension (SAH) and diabetes, possibly due to the high level of comorbidities in the groups, CVA being a common complication of DM, both in young insulin-dependent individuals as in the elderly with type 2 DM. DM favors atherosclerotic disease of small and large vessels in the brain[9], and hyperglycemia occurs in over half of patients in the acute phase of the CVA, even those with a prior background of normoglycemia, and is associated with increased morbidity and mortality, independently of the age group, ischemic CVA mechanism, or extension of the ischemic lesion[10].

With respect to the CVA outcome, in this study, among the various risk factors studied, the relationship with alcohol intake was outlined. Alcohol intake is also associated with increased cardiopathy risks, such as systemic hypertension, atrial fibrillation, and dilated cardiomyopathy[10]. These conditions are juxtaposed, increasing even further the risk of CVA for alcohol-user patients. The low number of deaths, as well as the high number of discharges from the CVA sector to low-complexity units, suggests a trend for reference centers and early treatment in acute I-CVA, a trained team, and the quality of the service rendered by the institution.

Embolism of a cardiac origin is responsible for around 20 to 30% of all CVAs, and atrial fibrillation (AF) is the main cardiogenic cause[11]. AF increases between five and eight times the risk of CVA, being a significant risk factor for I-CVA; accordingly, it must be duly approached since these patients could benefit from prophylactic anticoagulation[12]. The findings of the study revealed that, among the prior factors and risks, AF appeared in only 8.2% (26 individuals). Of these, 61.5% (16 individuals) of the individuals with a successful outcome in venous reperfusion belonged to the female group, 76.9% had risk factors such as hypertension, and all of them were previously diagnosed with coronary diseases.

When associated with reperfusion and the severity score upon admission and discharge, most of the reperfused patients had moderate scores, suggesting that reperfusion had a low impact on the severity of the condition. Early treatment with a thrombolytic agent acts to dissolve the clots that obstruct the artery before irreversible tissue damage occurs and is the most indicated treatment for acute I-CVA.

There is strong evidence in the literature on the effectiveness of intravenous rtPA in reducing neurological damage[13]. The most important study assessing the role of thrombolytics in the I-CVA revealed improvement in at least four NIHSS scores after 24 h of the beginning of the symptoms. The favorable results of this study triggered the approval of the thrombolytic agent Alteplase (rtPA) in June 1996. However, there is some controversy about the use of the medication, especially in more extensive CVAs, for patients of advanced age and when there is a delay in the treatment[14].

CONCLUSION

An association was found between successful reperfusion by venous chemical thrombolysis and lower mortality in patients with acute I-CVA. Risk classifications predict favorable results for arterial reperfusion. The presence of cardiopathies with reduced ejection fraction in the echocardiogram was significant and associated with the severity of the I-CVA in the studied population. New studies could better establish these variables and their correlation with severity.

AUTHORS' CONTRIBUTIONS

ARO: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **PAPJ:** Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization. **FVB:** Formal Analysis, Supervision. **EMN:** Formal Analysis, Methodology, Supervision, Validation, Visualization. **JOF:** Data curation, Formal Analysis, Methodology, Project administration, Supervision, Validation, Visualization. **LR:** Supervision, Validation, Visualization. **ACIC:** Formal Analysis, Supervision, Validation, Visualization, Writing – review & editing. **RA:** Formal Analysis, Methodology, Project administration, Supervision, Validation, Visualization.

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