DOI: 10.1590/1809-2950/18020425022018

ORIGINAL RESEARCH

Comparison of the neurological deficit severity in patients with acute ischemic stroke submitted or not to thrombolytic therapy

Comparação da severidade do déficit neurológico de pacientes com acidente vascular cerebral isquêmico agudo submetidos ou não à terapia trombolítica

Comparación de la severidad del déficit neurológico de pacientes con accidente cerebrovascular isquémico agudo sometidos o no a la terapia trombolítica

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Abstract | The stroke is responsible for high mortality rates and functional dependency in adults. The early intravenous thrombolytic therapy has been associated with a better functional prognosis. This study aimed to compare the neurological deficit severity in patients receiving or not thrombolytic therapy after stroke. Fifty-six patients were evaluated: eighteen who received thrombolytic therapy (TG group) and thirty-eight who did not receive it (NTG group). Individuals were assessed at the hospital admission and discharge (HD) regarding the severity of the deficit by the *National Institutes of Health Stroke Scale* (NIHSS). The sample average age was 65.9±11.4 years. GT patients showed significant improvement in NIHSS score between the admission and HD (p=0.004), as well as at the time of HD they showed less severe neurological deficit when compared with NTG group (p=0.028). The incidence of deficit varying from moderate to severe was lower in the TG (p<0.005), and 26.7% of patients did not show deficit at the DH. The patients receiving thrombolytic therapy showed better recovery of neurological deficits evaluated by NIHSS when compared with the group that did not receive thrombolytic therapy.

Keywords | Stroke; Neurologic Manifestations; Assessment.

Resumo | O acidente vascular cerebral é responsável por elevadas taxas de mortalidade e dependência funcional em adultos. A terapia precoce com trombolítico intravenoso tem sido associada a um melhor prognóstico funcional. O objetivo deste estudo foi comparar a severidade do déficit neurológico de pacientes que receberam ou não terapia trombolítica após AVC. Foram avaliados 56 pacientes, 18 que receberam trombolítico (Grupo GT) e 38 que não receberam a terapia trombolítica (GNT). Os indivíduos foram avaliados na internação e na alta hospitalar (AH) quanto a severidade do déficit pela *National Institutes of Health Stroke Scale* (NIHSS). A média de idade da amostra estudada foi de 65,9±11,4 anos. Os pacientes do GT apresentaram melhora significativa no escore da NIHSS entre a internação e a AH (p=0,004), além de no momento da AH apresentarem déficit neurológico menos severo quando comparado ao GNT (p=0,028). A incidência de déficit moderado a grave foi menor no GT (p<0,005), sendo que 26,7% dos pacientes estavam sem déficit no momento da AH. Conclui-se que os pacientes que receberam trombolítico apresentaram melhor recuperação dos déficits neurológicos avaliados pela NIHSS quando comparado ao grupo que não recebeu terapia trombolítica.

Descritores | Acidente Vascular Cerebral; Manifestações Neurológicas; Avaliação.

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Resumen | El Accidente Cerebrovascular es el responsable de altas tasas de mortalidad y dependencia funcional en adultos. La terapia precoz con trombolítico intravenoso se ha asociado con un mejor pronóstico funcional. El objetivo de este estudio fue comparar la severidad del déficit neurológico de pacientes que recibieron o no terapia trombolítica después de ACV. Se evaluaron 56 pacientes, 18 que recibieron el trombolítico (Grupo GT) y 38 que no recibieron la terapia trombolítica (GNT). Los individuos fueron evaluados en la hospitalización y en el alta hospitalaria (AH) en cuanto a la severidad del déficit por la *National Institutes of Health Stroke Scale* (NIHSS). La media de edad de la muestra estudiada fue de 65,9 ± 11,4 años. Los pacientes del GT presentaron una mejora significativa en el score de la NIHSS entre la hospitalización y la AH (p=0,004), además de en el momento de la AH presentar un déficit neurológico menos severo cuando comparado al GNT (p=0,028). La incidencia de déficit moderado a grave fue menor en el GT (p<0,005), considerando que el 26,7% de los pacientes estaban sin déficit en el momento de la AH. Se concluye que los pacientes que recibieron el trombolítico presentaron mejor recuperación de los déficits neurológicos evaluados por la NIHSS cuando comparado al grupo que no recibió la terapia trombolítica.

Palabras clave | Accidente cerebrovascular; Manifestaciones neurológicas; Evaluación.

INTRODUCTION

Stroke is the leading death cause in Brazil for 20 years[1]. Stroke incidence and recurrence is high, with about 15 million new cases annually worldwide[2]. It represents the leading cause of neurological sequels and major motor and cognitive dysfunctions[3]. Approximately 90% of the survivors present some deficiency that results in limitations, disabilities or invalidity[4].

Studies show there is a relationship between stroke occurrence and potentially modifiable risk factors such as systemic arterial hypertension (SAH), smoking and dyslipidemias[5]. Its incidence could be reduced with treatment and prophylaxis of the risk factors[1,5].

The events from ischemic origin correspond to 85% of all the strokes[6]. Early treatment with thrombolytic agent acts on the dissolution of the clot blocking the artery, preventing the occurrence of irreversible tissue damage, and is the most indicated treatment for acute ischemic stroke (AIS)[6,7]. Strong evidences exist in the literature on the efficacy of intravenous recombinant tissue plasminogen activator (rtPA) associated with the reduction in neurological damages[6-8]. Over the years, several protocols were implemented to accelerate the reperfusion therapy and, thus, high expectation was raised regarding the resolution of the damages caused by stroke[7,8]. Recent studies question the risk-benefit of this intervention, which has been shown to be ineffective in the reperfusion of occlusive great vessels[9,10].

In this context, this study aimed to compare the neurological deficit severity in patients who were treated with rtPA after acute ischemic stroke with that of patients who did not receive thrombolytic therapy.

METHODOLOGY

This is a prospective cohort study, carried out between December 2015 and July 2016, at the Hospital Nossa Senhora da Conceição, in Porto Alegre, RS, Brazil. The research project was previously approved by the Ethics and Research Committee of the Grupo Hospitalar Conceição, under opinion No 1.361.832. All individuals included signed an Informed Consent Form or consented verbally to it, according to resolution 466/112 of the Brazilian National Health Council.

The sample was obtained for convenience, and all the patients who were admitted in the emergency room of the hospital were tracked daily, through the electronic medical record. Individuals over 18 years with a diagnosis of acute stroke were included in the study and individuals with previous stroke or other pathologies that resulted in impairment of functional capacity, hemodynamic instability that would prevent the assessment, changes in consciousness level and/or cognitive disabilities that would constrain the evaluation were excluded.

The patients were assessed at the hospital admission, emergency room and hospital discharge (HD), by the National Institutes of Health Stroke Scale (NIHSS), which is a scale whose scores range from zero to 42 points, representing the highest score a more severe neurological deficit[3]. The first assessment was performed

in the first 24 hours since the emergency admission, and the patients with medical indication for thrombolytic therapy (following protocols and evaluation of the staff of neurologists) were assessed before administration of the thrombolytic drug. The sociodemographic data and risk factors were collected through interviews with the patient or his/her family member and were confirmed by the evolutions and examinations registered in the patient records.

For data analysis, the patients were divided into two groups:

a) Thrombolytic Group (TG), composed of the patients receiving intravenous thrombolytic therapy;
b) Non-Thrombolytic Group (NTG), composed of the patients receiving intravenous thrombolytic therapy;

Statistical analysis: The quantitative variables were described using mean and standard deviation, or median and interquartile range. The qualitative variables were described using absolute and relative frequencies. For data distribution assessment, we used the Shapiro-Wilk test.

To compare the medians between groups, we used the Mann-Whitney test. To compare the proportions, Pearson's chi-square or Fisher's exact tests were applied. To compare the hospital admission and discharge, Wilcoxon test was used. The associations between continuous variables were evaluated by Spearman's rank correlation coefficient. The significance level adopted was 5% ($p<0.05$) and the analyses were performed in the software SPSS version 21.0.

RESULTS

During the study period, 443 individuals were admitted with suspected acute ischemic stroke, and the assessment of 56 patients could be concluded, as shown in the flowchart in Figure 1.

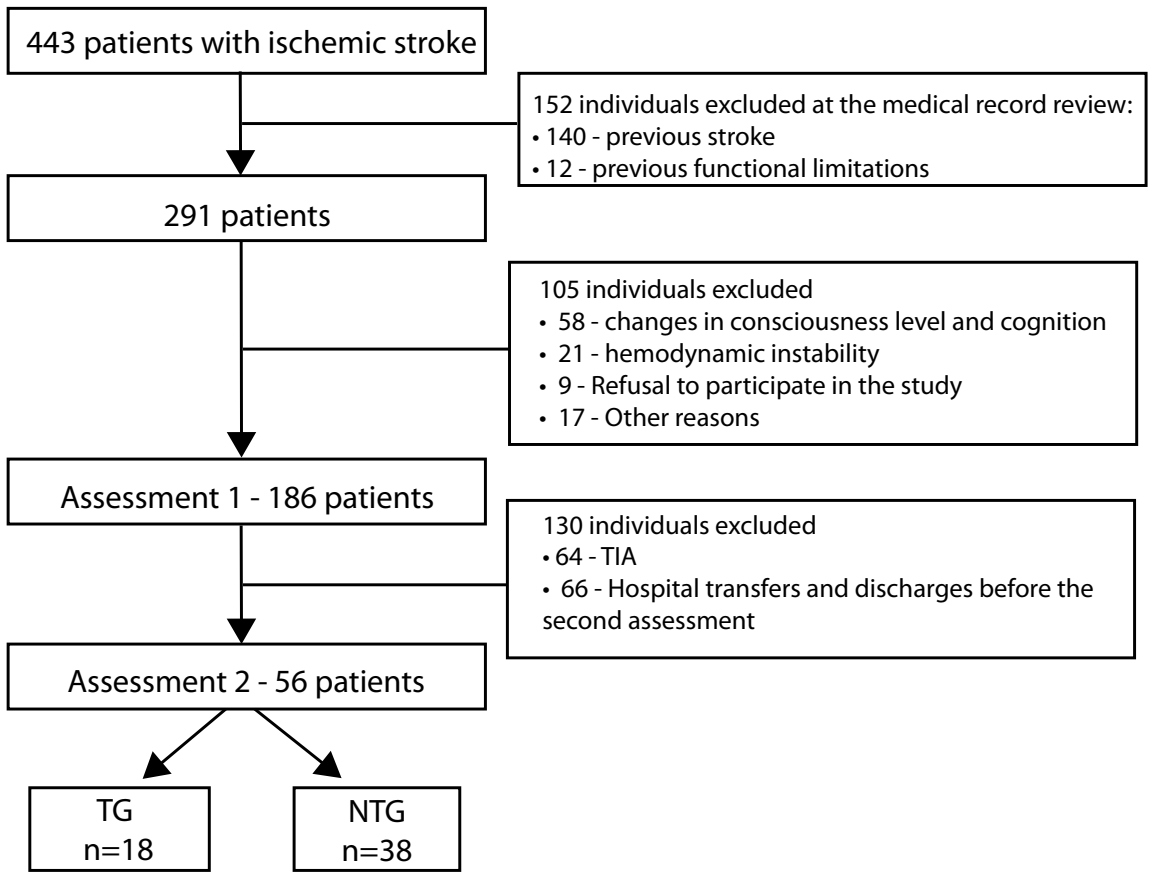

Figure 1. Flowchart of inclusion of patients

Source: Elaborated by the authors (2018)
TIA: transient ischemic attack; TG: thrombolytic group; NTG: non-thrombolytic group

The sample average age was 65.9 ± 11.4 years, being the most Caucasians (82.1%) and male (53.6%). The most prevalent risk factors were: SAH (83.9%), smoking (62.5%) and Dyslipidemia (62.5%). The characteristics of the individuals are described in Table 1.

Table 1. Sample characteristics

Variables	TG n=18	NTG n=38	p
Age (years)	66.4±10.7	65.7±11.8	0.812
Gender			1.000
Female	8 (44.4)	18 (47.4)	
Male	10 (55.6)	20 (52.6)	
Skin Color			0.217
Black	4 (22.2)	5 (13.2)	
White	13 (72.2)	33 (86.8)	
Education level (years)	6.5 (3.5 -11)	5 (4-8)	0.287
Family history of stroke	9 (50.0)	19 (50.0)	1.000
Diabetes mellitus	4 (22.2)	14 (36.8)	0.431
Systemic arterial hypertension	14 (77.8)	33 (86.8)	0.448
Dyslipidemia	9 (50.0)	26 (68.4)	0.301
Smoking	10 (55.6)	25 (65.8)	0.658
Alcoholism	5 (27.8)	13 (34.2)	0.861
Modifiable risk factors *			0.463
0	1 (5.6)	1 (2.6)	
1	3 (16.7)	4 (10.5)	
2	7 (38.9)	8 (21.1)	
3	3 (16.7)	12 (31.6)	
4	4 (22.2)	10 (26.3)	
5	0 (0.0)	3 (7.9)	

Source: Elaborated by the authors (2018). TG: thrombolytic group; NTG: non-thrombolytic group; *Modifiable risk factors: diabetes mellitus, hypertension, dyslipidemia, smoking and alcoholism (0-5: number of modifiable risk factors of the patient, being zero the absence of risk factors and 5 the presence of 5 out of the modifiable risk factors assessed). Values expressed in median (P=25–75=); mean±standard deviation, and n(%)

Table 2 shows the results of the neurological deficit severity assessment by NIHSS at the time of hospital admission and HD. Comparing the score in NIHSS scale of HD with that of the admission, significant neurological condition improvement was observed only for the TG. TG patients also showed fewer neurological deficit at the time of HD when compared with NTG patients.

Table 2. Comparison between the groups regarding the outcomes in study

Variables	TG (n=18)	NTG (n=38)	p
NIHSS			
Admission	9 (6-17)	7.5 (4-10)	0.060
Discharge	2 (0-5)	6 (2-10)	0.028
Variation (Δ)	5 (3-8)	1 (1-3)	<0.001
P	0.004	0.078	
Length of hospitalization	12 (6-14)	12 (10-22)	0.179
Death	3 (16.7)	6 (15.8)	1.000
Hemorrhagic transformation	2 (11.1)	5 (13.2)	1.000

Source: Elaborated by the authors (2018). NIHSS: *National Institutes of Health Stroke Scale*; TG: Thrombolytic Group; NTG: Non-Thrombolytic Group; Values expressed in median (P25-P75) and n(%)

When comparing both groups regarding the deficit severity, 26.7% of patients from TG did not have deficit at the moment of HD (p<0.005). The incidence of deficit varying from moderate to severe was significantly lower in TG at the hospital discharge when compared with the hospital admission (p<0,005), as described in Figure 2.

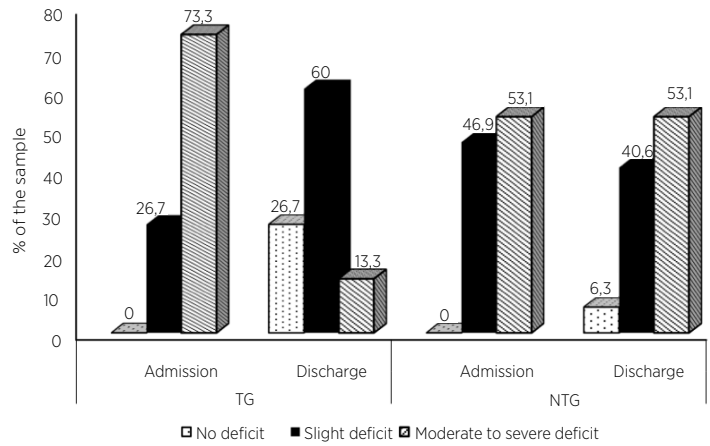

Figure 2. Comparison of the neurological deficit severity according to the NIHSS at the hospital admission and discharge

Source: Elaborated by the authors (2018)

NIHSS: *National Institute of Health Stroke Scale*; 0: no deficit; 1-5: slight deficit; 6-42 moderate to severe deficit

Comparison between the groups – Admission: p=0.259; Discharge: p=0.017 (P<0.05 in the categories "no deficit" and "moderate to severe deficit"); Comparison between admission and discharge in each group – NTG: p=0.480 e TG: p=0.004

The average time of the therapeutic window (onset of symptoms until administration of thrombolytic drug) was 3.24±0.71 hours. Door-to-needle time (DNT), which is the time elapsed between the arrival at the emergency department and the beginning of the thrombolytic drug administration, was 80.3±28.2 minutes.

No significant difference between the length of hospitalization, the mortality rate and the rate of hemorrhagic transformation were observed between the treated groups, as can be seen in Table 2.

DISCUSSION

In Brazil, stroke is responsible for high mortality rates, disability and functional dependency in adults[11]. Several authors point out the stroke as a disease neglected due to the low investment in its prevention and treatment[1,11,12]. The population of low socioeconomic status and schooling is more affected, which may be related to lack of information and lack of awareness of the risk factors, leading to the increased incidence and recurrence of stroke[1,11,12].

The average schooling of our sample was 5 years and, among the 443 patients, 140 (31.56%) had already had one or more previous stroke. This high recurrence rate was equal to that reported in the Laloux's study[13]. These findings reinforce the importance of doubling the care after the first stroke to reduce the possibility of new events[13].

Regarding the risk factors, most of the patients studied (96%) showed more than one risk factor associated, corroborating the Laloux's[13] study, which identified that 84% of the recurrent stroke patients had more than one risk factor associated[13]. Another case-control study investigated patients from 32 countries and associated 10 potentially modifiable risk factors with about 90% of the stroke events. This study pointed out the need for multiple risk factors acting together and mentioned that a reduction of at least one risk factor for individual would already decrease the occurrence of stroke[5].

The literature points out SAH as the primary risk factor for stroke, and the most important target for its prevention[5,13,14]. Laloux points SAH as the most prevalent risk factor (79%), followed by dyslipidemia (43%), smoking (25%), atrial fibrillation (24%) and diabetes mellitus (22%)[13]. In our sample, the prevalence of these risk factors was even greater: SAH (84%), diabetes mellitus (32%), atrial fibrillation (16%), smoking and dyslipidemia (62.5%, both). This high rate of risk factors, especially SAH and dyslipidemia, may be related to the lifestyle of the population studied. As already known, people from Rio Grande do Sul, Brazil, consume a large amount of barbecue, a high-fat diet and excess salt[15].

For the length of hospitalization, the median in this study was twelve days in both groups. The patients with prolonged hospitalization showed some complications related to infection or needed diagnostic investigation or surgical treatment, such as carotid endarterectomy or decompressive craniectomy. Studies affirm that the hospitalization length is directly related to the number of complications, neurological impairment severity, age, as well as to the hospital organization[16,17].

The neurological improvement observed in this study was similar to that cited in the literature and in the pioneering study by National Institute of Neurological Disorders and Stroke (NINDS)[16-18]. TG showed a seven-point improvement in NIHSS, from the admission to the HD, which resulted in a significantly better neurological condition at the time of HD in comparison with NTG. Although patients from TG had been admitted showing greater damage, they were discharged showing a better neurological condition, and 26.7% of patients did not show deficit at the HD.

The most important study evaluating thrombolytics role in stroke showed improvement of at least four points in NIHSS 24 hours after the onset of the symptoms[18]. The positive results of such study prompted the adoption of the thrombolytic agent alteplase (rtPA) in June 1996[6]. The protocol used in the NINDS is recommended in several countries[18]. However, the use of the drug arouse controversies, mainly for more serious strokes, in older patients and when the treatment starts late[9,10].

In the USA, the alteplase commercialization has not been authorized for use after 3 hours of the vascular ictus. In some European countries, the authorization restricts the use of alteplase to patients aged 80 years or more. Europe and Australia warn against the use of this drug in case of a serious or slight ischemic stroke[19].

In Brazil, the Ministry of Health published, in 2013, the Manual of Routines for Attention to Cerebrovascular Accident, which indicates the use of rtPA when it is possible to start the thrombolytic drug infusion within 4.5 hours of the onset of the symptoms[20]. Such recommendations are followed at the Center where we conducted this study.

Several authors question the limited effectiveness of rtPA in occlusions of the great vessels and highlight the benefit of the endovascular treatment in these cases[9,10,19]. Some authors defend the thrombolytic treatment, regardless the patient age or the stroke severity[19], whereas others show a proportional increase in the hemorrhagic transformation[9]. However, a consensus was not reached on the importance of early treatment as indispensable for obtaining any benefit[6-9,19,21,22].

In this analysis, significant difference in the hemorrhagic transformation rate between both groups was not observed. The patients who have had hemorrhagic transformation were between 77 and 83 years and showed the highest NIHSS score at the hospital admission. A study conducted in Porto Alegre showed an eight-point improvement in NIHSS, from the arrival to the HD, in thrombolytic therapy patients. The hemorrhagic transformation rate was only 6.3%. The early treatment with a short therapeutic window of only 2.5 hours and the fact that the most severe cases of thrombolytic treatment were excluded may have contributed to these positive results[21]. Gouveia[22] investigated 14 patients under treatment with thrombolytic therapeutic window of 3 hours and observed reduction in more than five points in the NIHSS, without any occurrence of cerebral hemorrhage. The hemorrhagic transformation seems to be related to ages over 80 years, to the stroke severity and to SAH above the levels of 185/110 in the first 24 hours after the thrombolysis[23]. The fact is that several studies associate the early alteplase infusion with the reduction in hemorrhages, the effective reduction in disabilities and the good functional results[6-9,18,21,22].

Protocols to accelerate the infusion of the thrombolytic drug were deployed, such as *Manchester Triage System*, which evaluates the severity and determines the priority of care through colors, being the stroke classified into the red category with zero waiting time[8,24]. The DNT, ideal until 1 hour, measures the time from the moment the patient arrive at the emergency room to the time he receives the rtPA and is a performance indicator used for avoiding delays in the treatment[7,8]. Dishoeck reported a reduction in the average time of DNT from 75 to 45 minutes, between 2006 and 2012, in Netherland[8]. In Berlin, an experiment using ambulances, achieved DNT below 60 minutes in 32% of patients. Finland and Australia have even better DNT results, averaging between 20 and 30 minutes[7].

In this research, the DNT was, on average, 80.3±28-twenty minutes above the time established, achieving, however, a good average time (3.24±0. 71 hours) of therapeutic window. Adopting simple steps, such as measuring the staff performance by the DNT and reporting these results to all the professionals, can keep them stimulated and focused on the DNT improvement, including patients in thrombolytic therapy. The absence of a neurologist on the emergency staff and the need to call this professional when a stroke patient arrives may influence directly on the DNT.

Our study presents some limitations: we had great sample loss due to hospital transfers and unplanned hospital discharges, especially on weekends. We did not evaluate the obesity risk factor, because many patients had no anthropometric information available in the chart.

It is suggested to carry out new studies that can evaluate the long-term evolution of stroke patients undergoing thrombolytic therapy or not.

CONCLUSION

The results of this study confirm the benefits of thrombolytic therapy for patients with acute ischemic stroke. The patients who received rtPA showed higher neurological recovery when compared with the group of patients who did not receive rtPA. Simple measures to shorten the DNT and optimize the thrombolytic therapy are important to reduce the functional disability and mortality. In addition, it is essential to work on preventing modifiable risk factors to reduce stroke.

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