Clinical outcomes of ischemic stroke patients after thrombolytic therapy

Desfechos clínicos de pacientes com acidente vascular cerebral isquêmico após terapia trombolítica

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Abstract

Objective: To analyze outcomes and associated factors in ischemic stroke patients submitted to thrombolytic therapy.

Methods: This was a retrospective cohort study of ischemic stroke patients submitted to thrombolytic therapy. Comorbidities, neurologic deficits and time of thrombolysis were described. The chi-squared test was used to assess association among comorbidities, time of thrombolysis, and occurrence of hemorrhagic transformation.

Results: There was a high frequency of comorbidities. Mean neurological deficit score was 15 points. Mean time window was 98 minutes and needle-to-door time, 89.9 minutes. Hemorrhagic transformation was observed in 20 patients. Bivariate analysis revealed that hemorrhagic transformation was associated with greater neurologic deficit score, atrial fibrillation and heart disease. Neurologic deficit fell from 51% to 12.5% between admission and discharge.

Conclusion: Thrombolytic therapy presented positive outcomes, regardless of long thrombolysis time and high neurologic deficit scores.

Keywords
Stroke; Thrombolytic therapy; Tissue plasminogen activator

Descritores
Acidente vascular cerebral; Terapia trombolítica; Ativador de plasminogênio tecidual

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Introduction

Stroke and ischemic heart disease are the leading causes of premature death worldwide. Strokes are also one of the main events responsible for reducing functional capacity in activities of daily living. \(^{(1)}\)

The occurrence of strokes is related to risk factors, which are dependent on lifestyle habits that increase the probability of developing the disease. \(^{(2)}\)

There are two types of strokes, ischemic and hemorrhagic, depending on the determining ischemic mechanisms or predominant brain lesion topography. Approximately 80% of strokes are ischemic and, for the most part, involve the thromboembolic occlusion of the arterial territory corresponding to the neurologic manifestation, causing reduced cerebral perfusion pressure. \(^{(3)}\)

Stroke treatment promotes arterial rechanneling, dissolving occlusive thrombi or emboli through chemical (systemic or intra-arterial use of thrombolytic drugs) or mechanical thrombolysis (surgical removal of clots). These procedures restore cerebral blood flow to the region of ischemic penumbra, leading to functional recovery. \(^{(4)}\)

Since the early 2000s, the standard pharmacological treatment for acute ischemic stroke has been thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA). \(^{(5)}\)

The effectiveness of this therapy has been demonstrated; however, there are still challenges in the implementation of thrombolytic treatment protocols and few ischemic stroke patients benefit from this therapy. One of the main limiting factors is time. The shorter the time window between onset of stroke symptoms and drug infusion, greater the chances of a good prognosis. \(^{(6)}\)

The main clinical outcomes associated with this treatment are: significantly improved National Institute of Health Stroke Scale NIHSS score, hospital discharge, low occurrence of symptomatic hemorrhagic transformation, and low treatment-related deaths. \(^{(7,8)}\)

In Brazil, intravenous thrombolysis for ischemic stroke is conducted in several hospitals. However, there are few national reports on the demographic and clinical characteristics of patients submitted to this treatment. There is also little information on the frequency of complications due to this therapy, such as hemorrhagic transformation. More information is needed on how epidemiological and health system characteristics influence the treatment’s safety, considering ischemic stroke as an extensively undertreated event.

In this context, the objective of this study was to analyze outcomes and associated factors in ischemic stroke patients at a hospital after receiving rt-PA thrombolytic therapy.

Methods

This was a quantitative retrospective cohort study. It was approved by the ethics committee of the Federal University of Triângulo Mineiro, under resolution 1.040.479.

The investigation took place at a public teaching hospital that covers 27 municipalities in the south of the Minas Gerais Triangle Region, Brazil. This facility provides high-complexity care, exclusively via the Brazilian Unified Health System (SUS). It has 301 active beds, of which 25 belong to the emergency department. The hospital is a certified teaching hospital and meets the professional training demands of health undergraduate programs, medical, nursing and multiprofessional residencies, and graduate-level programs.

Between January 2012 and January 2015, 828 stroke patients diagnosed were admitted. Of these, 78 received rt-PA treatment. The chart numbers of patients submitted to thrombolysis during this period were obtained from the institution’s electronic system, requested at the medical archive service. Data were gathered using an instrument specifically designed to gather information on the variables of interest of this study.
This study included the medical charts of patients 18 years or older diagnosed with ischemic stroke and International Disease Classification IDC 10 (I 64.0) duly registered with the pharmacy and the medical archive service for intravenous thrombolytic treatment.

Medical charts that were not found in the archive service’s registration system after five attempts and those that were incomplete in terms of research variables were excluded.

Seventy-nine patients were included in the initial sample; however, 14 charts were not found after five attempts with the hospital’s medical archive service. Thus, the sample comprised 64 medical charts that met the inclusion criteria.

The studied sociodemographic variables were: age, gender, ethnicity and origin, and comorbidities as recorded on the admission form or diagnosed during hospital stay. Tobacco use and alcohol consumption were considered as risk factors.

Etiology of ischemic stroke was classified as per Adams et al. (9) into large artery atherosclerosis, small artery atherosclerosis, heart embolism, undetermined, and other causes.

In this study, time window was defined as the time between stroke symptom onset and hospital admission, in minutes; door-to-needle time was understood as the time between hospital admission and intravenous thrombolysis, in minutes; time of thrombolysis was the time between onset of stroke symptoms and rt-PA infusion, in minutes; time of admission corresponded to time between admission and discharge, in days.

Hemorrhagic transformation due to hospital admission (pneumonia, urinary tract infection and pressure ulcers), discharge, and death comprised the clinical outcomes.

The NIHSS was used to assess stroke-related neurologic deficit. Minimum score is zero and maximum is 42, and, in general, the scale is used to estimate stroke severity, predict size of injury, patient evolution and prognosis. (10) Yaghi et al. (11) considers an NIHSS score less or equal to 7 as indicative of minor neurologic deficit, 8 to 14, as moderate deficit, and greater or equal to 15, severe deficit.

The data were inserted in an electronic spreadsheet using Excel® for Windows®, validated via dual data entry. Next, they were exported and processed using the Statistical Package for the Social Sciences (SPSS), version 22 for Windows 8®, for data processing and analysis.

Descriptive statistics were computed for quantitative variables using measures of central tendency (mean and median) and dispersion (standard deviation). The chi-square test was used to determine association between time of thrombolysis and NIHSS score after rt-PA infusion.

To assess statistical significance of NIHSS score improvement at the time of admission and discharge, scores were categorized into minor, moderate and severe. (11) After this procedure, the Wilcoxon test was applied.

Qualitative variables were analyzed according to descriptive statistics via simple univariate frequencies, and association measures via contingency tables.

Significance was set at 5% (p<0.05), with a 95% confidence interval.

Results

Between January 2012 and January 2015, 828 stroke patients were admitted; of these, 657 (79.4%) were ischemic and (11.8%) received rt-PA treatment. For this study, 64 patient charts were evaluated.

Of the analyzed charts (n=64), the age range of the study subjects was 39 to 85 years (mean 65.7 years, standard deviation 11.3)

The sociodemographic data revealed that most patients were men 34 (59.6%), white 31 (54.4%) and from the city of Uberaba 48 (84.2%).

The most prevalent comorbidities were systemic arterial hypertension (76.6%), atrial fibrillation (28.1%), heart disease (25%) and diabetes mellitus (17.2%).

The most prevalent etiology was large artery occlusion (50%), followed by heart embolism (28%), ischemic stroke (20%), cardioembolic stroke (15%) and other causes (7%).

The site of stroke for most patients (73.4%) was the middle cerebral artery. In terms of etiology, most of the events were caused by heart embolism (50%), followed by large artery occlusion (28%).
According to the NIHSS, neurologic deficit score at the time of admission varied between 6 and 30 points, with mean score 14.7 and median 15. At the time of admission, scores varied between zero and 25 points, with a mean and median of 7.7 and 15, respectively.

Level of severity of neurologic deficit as measured by the NIHSS at admission and discharge is demonstrated in table 1. There were improvements in scores by deficit category whose statistical significance was appraised via the Wilcoxon test, p<0.01.

The results of the time intervals involved in thrombolytic therapy were: mean time window of 98.4 minutes and standard deviation of 61.2. Door-to-needle time obtained a mean of 89.9 minutes and standard deviation of 39.8. Time of thrombolysis had a mean of 191.4 minutes and standard deviation 52.9.

Complications due to thrombolytic therapy and hospital admission were: symptomatic hemorrhagic transformation 20 (31%), pneumonia 13 (20.4%), urinary tract infection 5 (7.9%) and pressure ulcer 4 (6.3%).

Regarding clinical outcomes (discharge and death), most of the investigated patients (90.6%) were discharged to home, 4.7% died from other causes, 3.1% were discharged to another hospital, and 1.6% died from thrombolysis.

Length of hospital stay ranged between 3 and 31 days, with a mean of 11.7 days.

Results of the association test between age and NIHSS score at time of admission did not find any association between age and NIHSS score (chi square with p>0.05).

There was no association between time window, divided into two categories (zero to 180 minutes and >180 minutes) and NIHSS score subdivided into categories zero to 14 points and 15 to 42 points (chi square with p>0.05).

Table 2 shows the correlation between the occurrence of hemorrhagic transformation according to the studied variables. Patients with NIHSS >15 were 2.8 times more likely to develop hemorrhaging after the procedure when compared to those with a score <15 points (p=0.01). There was no statistical significance between the occurrence of hemorrhages and age, door-to-needle time, and thrombolysis time.

Patients who presented atrial fibrillation had two times the risk to develop symptomatic hemorrhagic transformation; those with heart disease were two and half times more likely to suffer hemorrhagic transformation in comparison to individuals who did not present these diseases. These associations are shown in table 3.

### Table 1. National Institute Health Stroke Scale (NIHSS) scores on hospital admission and discharge of investigated patients (n=64)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Admission</th>
<th>Discharge</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor (0-7)</td>
<td>5 (7.8)</td>
<td>34 (53.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Moderate (8-14)</td>
<td>26 (40.6)</td>
<td>18 (28.3)</td>
<td></td>
</tr>
<tr>
<td>Severe (≥15)</td>
<td>33 (51.6)</td>
<td>6 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>-</td>
<td>4 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>64 (100)</td>
<td>64 (100)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Association between age, National Institute Health Stroke Scale (NIHSS) score, door-to-needle time and thrombolysis time; and occurrence of hemorrhagic transformation in selected patients (n=64)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>RR (95%CI)</th>
<th>OR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>18-60</td>
<td>4 (17.4)</td>
<td>19 (82.6)</td>
<td>0.4 (0.2-1.2)</td>
<td>0.3 (0.1-1.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>16 (39.0)</td>
<td>25 (61.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS, score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>0-14</td>
<td>5 (16.1)</td>
<td>26 (83.9)</td>
<td>0.4 (0.1-0.7)</td>
<td>0.2 (0.1-0.9)</td>
<td></td>
</tr>
<tr>
<td>15-42</td>
<td>15 (45.5)</td>
<td>18 (55.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Door-to-needle, minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>&lt;60</td>
<td>5 (26.3)</td>
<td>14 (73.7)</td>
<td>0.8 (0.3-1.9)</td>
<td>0.7 (0.2-2.4)</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>15 (33.3)</td>
<td>30 (66.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis, hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>&lt;3</td>
<td>9 (32.1)</td>
<td>19 (67.9)</td>
<td>1.1 (0.5-2.2)</td>
<td>1.1 (0.4-3.2)</td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>11 (30.6)</td>
<td>25 (69.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR - relative risk; 95%CI - 95% confidence interval
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Discussion

In this study, only 78 (11.8%) of the patients admitted underwent thrombolytic therapy, being that a frequency above 20% is considered adequate.\(^{(12)}\)

The main events that explain such low rates of thrombolysis for stroke patients are: lack of public awareness about stroke symptoms to activate emergency medical services; lack of training for prehospital transportation professionals; patients’ referrals to hospitals that do not perform thrombolysis; inefficient screening at emergency services to identify stroke cases; and lack of protocols that integrate all health professionals to avoid delays in patient presentation.\(^{(12,13)}\)

In this investigation, most patients were male and white, similar to other studies.\(^{(14,15)}\) There was no association between skin color and gender and rt-PA treatment outcomes.\(^{(14)}\)

Mean patient age was 65.7 years, close to that reported by the literature,\(^{(2,12)}\) and was not associated with patient severity on the NIHSS neither to the occurrence of hemorrhagic transformation. The benefits of thrombolysis do not depend on patient age or NIHSS score.\(^{(8)}\)

The selected cases presented high frequency of comorbidities. Arterial hypertension was the most prevalent risk factor, followed by heart disease, atrial fibrillation, and diabetes, data similar to those of other studies about rt-PA infusion.\(^{(2)}\) In this investigation, patients with atrial fibrillation and heart disease presented greater risk for hemorrhagic transformation. Saposnik et al.\(^{(16)}\) described the presence of atrial fibrillation as associated with greater risk for hemorrhagic transformation and higher death rates after intravenous thrombolysis.

The most common etiology for ischemic stroke was heart embolism, corroborating the findings of other studies.\(^{(17,18)}\) Ischemic strokes caused by heart embolism represent approximately one-fourth of ischemic stroke cases, with worse symptomology and greater risk of developing hemorrhagic transformation.\(^{(19)}\)

The researched patients presented severe neurologic deficit on hospital admission as scored by the NIHSS, with a mean of 15 points, i.e., higher than those found in other retrospective studies. A study in the United States developed with 7,193 patients found a mean NIHSS score of 11.\(^{(15)}\) Al-Khaled et al.\(^{(20)}\) obtained a mean score of 11.6 in a study with 1,007 patients. Patients with symptomatic hemorrhagic transformation obtained NIHSS scores higher than 15 points on admission, with statistical significance (p<0.01), corroborating the data presented in the literature.\(^{(15,21)}\)

When compared with the literature,\(^{(8,18)}\) this study found a higher percentage of patients with 15 points or more on the NIHSS. The percentage fell after thrombolytic treatment, dropping from 56% to 12.5%, a statistically significant difference

### Table 3. Association between comorbidities and occurrence of hemorrhagic transformation in investigated patients (n= 64)

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Yes n(%)</th>
<th>No n(%)</th>
<th>RR (95%CI)</th>
<th>OR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAH</td>
<td>14(28.6)</td>
<td>35(71.4)</td>
<td>0.7(0.3-1.5)</td>
<td>0.6(0.2-2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5(45.5)</td>
<td>6(54.5)</td>
<td>1.6(0.7-3.4)</td>
<td>2.1(0.6-8)</td>
<td>0.3</td>
</tr>
<tr>
<td>AF</td>
<td>9(50)</td>
<td>9(50)</td>
<td>2(1-4)</td>
<td>3.2 (1-10)</td>
<td>0.04</td>
</tr>
<tr>
<td>Heart disease</td>
<td>9(53.8)</td>
<td>7(46.4)</td>
<td>2.5(1.3-4.8)</td>
<td>4.3(1.3-14.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2(18.2)</td>
<td>9(81.8)</td>
<td>0.5(0.102)</td>
<td>0.4(0.1-2)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

RR - relative risk; 95%CI - 95% confidence interval; SAH - systemic arterial hypertension; AF - atrial fibrillation
Treatment with intravenous rt-PA for ischemic stroke resulted in lower NIHSS scores at the time of hospital discharge. It is worth noting the occurrence of hospital pneumonia following rt-PA treatment diverges in the literature. Hoffmeister et al. found 23.6% patients with pneumonia. Bruening and Al-Khaled obtained 22.7%, while Gumbinger et al. registered 8% of patients with hospital-acquired pneumonia. Hospital-acquired pneumonia following ischemic stroke treatment is considered a potentially avoidable complication, associated with high NIHSS scores and prolonged hospital stay. This can explain the occurrence of the complication in the present study, as the patients presented higher NIHSS scores and longer hospital stays than in other studies.

Over 90% of the patients were discharged to home, and 6% died during the hospital stay. The death rate in this study was similar to that found by Schmidt et al., Al-Khaled et al., Ganesh et al. and Tong et al., with 6%, 8.2%, and 7.2%, respectively. In clinical practice, ischemic stroke patients treated with rt-PA present better outcomes when compared to those who do not receive rt-PA. This points to the need to increase treatment availability, with actions aimed at improving therapy, prevention measures and recognition of the disease.

Limitations of this study include its retrospective nature and the inclusion of only one specialized center. Incomplete data on patient charts limited the sample size, but did not compromise reaching the goals established by the researchers.

The results of this study can contribute to increasing the effectiveness of thrombolysis protocols for ischemic stroke patients and help support public policies in favor of more effective treatment in the healthcare system, resulting in improved neurologic recovery and quality of life for patients and family members.

Conclusion

Treatment with intravenous rt-PA for ischemic stroke resulted in lower NIHSS scores at the time of hospital discharge.
ference of symptomatic hemorrhagic transformation and the data obtained from a sample with a high frequency of comorbidities, severe neurologic deficits, and prolonged therapeutic windows.

**Collaborations**

Nascimento KG, Chavaglia SRR, Pires PS, Ribeiro SBF and Barbosa MH contributed with the project’s conception, data analysis and interpretation, relevant critical review of its intellectual content and final approval of the version for publication.

**References**


