Clinical predictors of hemorrhagic transformation after thrombolytic therapy an Egyptian center experience

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Background: thrombolysis is the only approved pharmacological treatment for acute stroke. It acts as a mediator of recanalization and sometimes causes secondary hemorrhage depending on the size of the ischemic lesion, little is known about the efficacy and hemorrhagic complication of thrombolytic therapy, we aim to identify clinical predictors of hemorrhagic transformation.

Methods: a cross-sectional comparative study in Sohag University Hospital for 1226 acute ischemic stroke patient admitted to our department from 1st April 2019 till 31st March 2020, of the 21 patients treated with thrombolytic therapy further subdivided into two groups; (Group A): patients who didn’t complicate with hemorrhagic transformation and (group B) patients who developed hemorrhagic transformation after receiving intravenous thrombolysis, the correlation between hemorrhagic transformation and clinical characteristic, vascular risk factors, and demographic data is done.

Results: We found a small percentage (1.7%) of acute ischemic stroke patients receiving thrombolytic therapy. Old age, ischemic heart disease, high admission NIHSS on admission, and NIHSS 24h after admission are associated with hemorrhagic transformation with p-value (0.024), (0.048), (0.085), and (0.001) respectively. Patients treated with thrombolytic therapy have statistically significant improvement in NIHSS 24h after admission in comparison to the admission NIHSS with a p-value (< 0.001).

Conclusion: Elderly, high NIHSS on admission, and tachycardia are associated with hemorrhagic transformation following treatment with IV thrombolytic therapy, Despite the updated management of acute ischemic stroke only a small percentage (1.7%) of acute ischemic stroke patients receiving thrombolytic therapy, this in need of further investigations.

Keywords: thrombolytic therapy, stroke, Sohag, hemorrhagic transformation

List of abbreviation NIHSS; National Institute Of Health Stroke Scale, TOAST; trials of Org 10172 in acute stroke treatment, r-tPA; tissue plasminogen activator, AHA; the American Heart Association, ASAT; American Stroke Association, HI; Hemorrhagic Infarctions, HT; Hemorrhagic transformation, ECASS; European Cooperative Acute Stroke Study, PH; parenchymal hemorrhage, SICH; symptomatic intracranial hemorrhage

Introduction

The Middle East North Africa is made up of 17 countries and stretches from East Asia to Morocco in the West. In 2017 the area has an estimated 411 million people. In the absence of high-quality data from the area about stroke incidence and prevalence, it is difficult to establish the exact burden of this
devastating disease. But because these countries are undergoing epidemiological research, the burden of non-communicable diseases is increasing and an updated review of the literature available suggests an increase in the incidence of stroke and mortality in the region¹.

Unfortunately, stroke care in this area is still in its infancy and while alteplase was approved more than two decades ago, this therapy is supported by very few centers. Until 2012, there were less than 10 centers in this area that treated patients with intravenous thrombolysis for acute ischemic stroke and utilization of reperfusion therapies for stroke <1% in Egypt ²

updating guidelines and recommendations for assessing the consistency of the Stroke Survival Chain, in which remains < 1 percent. The American Heart Association / American Stroke Association (AHA / ASA) is constantly pre-hospital onset to arrival time (OAT) and intra-hospital to-needle time (DNT) do not exceed 35 and 60 min, respectively³. In developed countries, most hospitals are adjusting their programs to shorten the time for stroke patients to fit these guidelines in administrative procedures, clinical assessment, imagery, and laboratory investigation⁴.

Thus, stroke treatment protocols in developing countries face many difficulties among their stroke patients, including low stroke understanding, poor finances, and complicated administrative procedures with resulting in higher mortalities and greater disabilities⁵. Hemorrhagic transformations (HTs) were classified according to clinical and radiological criteria. HI1 was defined as small petechiae along the margins of the infarct; HI2, as confluent petechiae within the infarcted area, but no space-occupying effect; PH1, as blood clots in ≤30% of the infarcted area with some slight space-occupying effect; and PH2, as blood clots in >30% of the infarcted area with a substantial space-occupying effect⁷.

Patients and methods

Study design and patients

We conducted a cross-sectional retrospective cohort study enrolling patient hospitalized for acute ischemic stroke at the Department of Neurology, Sohag University Hospital; data were collected between 1st April 2019 and 31st March 2020. One thousand two hundred twenty-six patients with acute ischemic stroke have been admitted during the period of the study however one thousand one hundred ninety-two patients were excluded as they presented to the hospital after the time window for thrombolysis and eight patients had been excluded due to missed data, transfer or had contradictions for thrombolysis. So only twenty-one patients received thrombolytic therapy, furtherly subdivided into two groups according to treatment response: nineteen patients didn’t develop hemorrhagic transformation (group A) and two patients developed hemorrhagic transformation (group B) flow chart is shown in Figure1

Ethical consideration

The study was approved by the local Ethics committee of the Sohag Faculty of Medicine. all patients signed written consent.

Variable definitions

Strokes were tested and verified if neurological defects lasted longer than 24 hours and/or focal ischemic damage suggested by cranial computed tomography or magnetic resonance imaging was detected ⁶ Intracranial hemorrhages was identified as symptomatic (SICH) if the patient experienced clinical deterioration causing a 4-point increase in the National Institutes for Health Stroke Scale (NIHSS) score and the hemorrhage was likely to cause clinical deterioration⁷.
For the whole participants, we analyzed medical and socio-economic variables, including age, sex, cerebrovascular risk factors, current smoking, stroke intensity (as assessed by the National Institutes of Health Stroke Scale) on admission and 24 after admission, and the subtype of stroke according to the TOAST criteria.

**Data analysis**

Descriptive statistics of patients presented using frequencies and percentages for categorical variables, and the median range for continuous variables, using the \( \chi^2 \) test or Fisher's exact test for categorical variables. Mann-Whitney U test was used for continuous variables. Both analyses were conducted using SPSS for version 19.0 of Windows (SPSS Inc., Chicago, Illinois) and Graph Pad Prism 8.0 (Graph Pad Software Inc., La Jolla, California, USA). A P value < 0.05 has been regarded as statistically significant.

Results of the study

The mean age of our study population was around 59 ±12.1 years. Males are slightly more than females (62% versus 38%). Most cases were from rural regions (77%), and all of them were married (100%). All cases were right-handed (100%). Hypertension was found in more than one-third of our cases (38%). Diabetes mellitus was found in 9.5% of our cases and more than half of the patients were nonsmokers (81%). Regarding cardiac diseases, RHD is the most common heart disease found (38%) followed by IHD (24%), then AF (4.8%), and lastly CHF only 4.8%. As regard, clinical stroke scales the mean admission NIHSS was 11±5, and the median NIHSS 24 h after admission was 6 and the range was 22.

Regarding etiology of ischemic stroke small vessel disease "S" was the most common TOAST classification, the subtype is seen in 28.6% of cases, and cardioembolic “C” in 28.6% then large artery atherosclerosis "L" 23.8% and stroke of undetermined etiology “U” in 19%, Cerebral hemorrhage followed treatment was found in 9.5% of our population (Table 1).
The age is significantly higher in group B compared to group A with a p-value (0.024), patient in group B has higher admission NIHSS compared to group A but the p-value is not statistically significant (0.085). NIHSS 24 hours after admission was statistically significantly lower in group A in comparison to group B with a p-value (0.001). Tachycardia on admission and the history of IHD is significantly higher in the group compared to group A with p-value (0.025), and (0.048) respectively, CHF is relatively higher in group B compared to group A but the p-value not statistically significant (0.09) (Table 2).

There was a statistically significant difference between admission and 24h NIHSS p value was (< 0.001) figure 2.
Discussion

To the best of our knowledge, this is the first study to identify clinical characteristics and complications of intravenous thrombolytic therapy in upper Egypt. We found that only 2.3% of the patients presented within the time window and only about 1.7% of acute ischemic stroke patients received thrombolytic therapy and this is in line with previous Egyptian publications. But less than international studies.

We have a relatively high percentage of hemorrhagic transformation (9.5%). Our result in line with Larrue et al 2001 who reported that; extreme HTs were typical in patients treated with r-tPA. Based on the term used (SICH or PH), between 8.8% and 11.8% of r-tPA patients had a serious hemorrhagic transformation.

In contrast, as previously observed in ECASS 10. Hemorrhagic Infarctions were not more frequent in r-tPA-treated patients. Furthermore, among patients with HI, the odds for bad outcomes were significantly lower in those given r-tPA than in those receiving placebo, suggesting that r-tPA may benefit some patients despite minor degrees of HT.

Hemorrhagic transformation relatively higher in the elderly and this is in line with the previous publication 7, but we found that the mean age of hemorrhagic transformation is relatively younger compared to previous studies. High admission NIHSS was associated with hemorrhagic transformation, and this agreed with previous publications. 9 History of IHD is associated with hemorrhagic transformation.

There was a statistically significant difference between admission and 24 h NIHSS reflecting the efficacy of thrombolytic therapy in our study population and this is worldwide, and FDA approved

The limitation of the study

A relatively small sample size makes it difficult to generalize our results.

Strength of the study

The first author is a qualified stroke consultant, and the last author is a qualified stroke physician (ESO member and NIHSS certified) and they were in contact with all patients on the study.

Table 2 differences between the two groups

<table>
<thead>
<tr>
<th></th>
<th>Group A N=19</th>
<th>Group B N=2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57 ±11</td>
<td>77±3</td>
<td>0.024</td>
</tr>
<tr>
<td>admission NIHSS</td>
<td>11±4</td>
<td>17±7</td>
<td>0.085</td>
</tr>
<tr>
<td>NIHSS 24h</td>
<td>5±4</td>
<td>17±7</td>
<td>0.001</td>
</tr>
<tr>
<td>HR</td>
<td>78±15</td>
<td>112±32</td>
<td>0.025</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>134±22</td>
<td>125±21</td>
<td>0.61</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>82±11</td>
<td>80±14</td>
<td>0.76</td>
</tr>
<tr>
<td>Sex, Female</td>
<td>11(52.4%)</td>
<td>2(9.5%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Rural, residence</td>
<td>13(61.9)</td>
<td>1(4.8%)</td>
<td>0.56</td>
</tr>
<tr>
<td>IHD</td>
<td>3(14.3%)</td>
<td>2(9.5%)</td>
<td>0.048</td>
</tr>
<tr>
<td>CHF</td>
<td>0(0%)</td>
<td>1(4.8%)</td>
<td>0.095</td>
</tr>
<tr>
<td>DM</td>
<td>1(48%)</td>
<td>1(48%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>16(76%)</td>
<td>2(9.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>8(38%)</td>
<td>0(0%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Small vessel</td>
<td>5(23.8%)</td>
<td>1(4.8%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Non-small vessel</td>
<td>1(6.6%)</td>
<td>1(4.8%)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

NIHSS; National Institute Of Health Stroke Scale, IHD; ischemic heart disease, CHD; congestive heart failure., HR; heart rate, DM; diabetes millets
Conclusion
Hemorrhagic transformation is a serious complication of thrombolytic therapy. Elderly, high NIHSS on admission, ischemic heart disease, and tachycardia is associated with hemorrhagic transformation after r-tPA treatment, but these risk factors need to be validated on an independent data set. Only a small percentage (1.7%) of acute ischemic stroke patients receiving thrombolytic therapy, this in need of further investigations.

Source of funding
Non

Acknowledgment
Non

Conflict of interest
The authors report no conflict of interest.

References