Predictors of Hyperacute Clinical Worsening in Ischemic Stroke Patients Receiving Thrombolytic Therapy

Richard Leigh, BS; Osama O. Zaidat, MD; Muhammad F. Suri, MD; Gwendolyn Lynch, MD; Sophia Sundararajan, MD, PhD; Jeffrey L. Sunshine, MD, PhD; Robert Tarr, MD; Warren Selman, MD; Dennis M.D. Landis, MD; Jose I. Suarez, MD

Background and Purpose—Although long-term outcome determinants in acute ischemic stroke (AIS) patients have been defined, less is known about those predicting hyperacute worsening after thrombolytic therapy (TT). We investigated predictors of short-term clinical worsening (National Institutes of Health Stroke Scale [NIHSS] change ≥4 within 24 hours of admission).

Methods—We studied 201 AIS patients who received TT within 6 hours of symptom onset. We determined baseline demographics, comorbidities, NIHSS at baseline and at 24 hours after TT, head computed tomography scan before and within 24 hours after TT, and angiographic recanalization in patients treated with intra-arterial (IA) thrombolysis. Significance of relationships was evaluated by t test or Wilcoxon signed rank sum test. Logistic regression model (LRM) was fitted to determine independence of significant variables.

Results—Of 201 patients, 13% worsened, 39% improved, and 48% remained unchanged 24 hours after TT. Most patients (72%) received IA thrombolysis. Patients who deteriorated, compared with those who improved, were more likely to have complicating intracranial hemorrhage (ICH; P < 0.001), absent recanalization (P = 0.026), and higher blood glucose (BG; P = 0.049). Hyperglycemia (>150 mg/dL) was greater in patients who worsened even in presence of recanalization (P = 0.004, odds ratio [OR] 6.47). LRM showed that adjusted OR for increased risk of bad outcome and mortality for an increase of BG by 50 mg/dL is 1.56 and 1.38, respectively.

Conclusions—Hyperglycemia and ICH are independent predictors of hyperacute worsening in AIS patients receiving TT. Although recanalization is the purpose of IA thrombolysis, its impact on clinical improvement may not be apparent without strict BG control. (Stroke. 2004;35:1903-1907.)

Key Words: hyperglycemia ■ stroke, ischemic ■ thrombolysis ■ intracerebral hemorrhage ■ outcome

Improved imaging and thrombolytic therapy (TT) have revolutionized treatment of acute ischemic stroke (AIS), but implementation success has failed on long-term outcome. There is a need to identify which factors may influence in-hospital patient management with effects on outcome.

One assessment of patients’ progress is the National Institutes of Health stroke scale (NIHSS). This has been used to evaluate outcome after intravenous1–3 and intra-arterial (IA) recombinant tissue plasminogen activator (rt-PA) treatment4 and as secondary measure in trials of modification of core body temperature during AIS,5 along with imaging modalities such as head computed tomography (CT)5 and MRI.6 Apart from NIHSS, other factors such as hyperglycemia and intracranial hemorrhage (ICH) may impact outcome after AIS. Although elevated blood glucose concentration (BGC) during AIS has been associated with poor outcome and symptomatic ICH,8–11 underlying mechanisms are not clear. Furthermore, evidence suggests that strict control of BGC during AIS may improve outcome,12 and the possibility remains that hyperglycemia may be a result rather than a cause of ischemic injury. Recent studies show that hyperglycemia within 72 hours of admission may independently predict infarct expansion and worse functional outcome.13,14

Our study attempts to define predictors of change in NIHSS 24 hours after admission (ΔNIHSS) in sequential AIS patients treated with TT and whether such predictors would affect outcome in the recanalization setting.

Methods

Patient Selection

We reviewed the prospectively collected database of all patients presenting to our hospital within 6 hours of AIS onset from October 4, 1993, to November 24, 2001. We studied patients who received TT with urokinase (UK), rt-PA, or both administered intravenously, intra-arterially, or both. We collected admission and 24-hour NIHSS, time of stroke onset, time of TT, patients’ demographics, medical
comorbidities, admission BGC, blood pressure, core body temperature, and renal function tests.

**Thrombolytic Therapy**

During the study period, patients with AIS were treated with 1 of 3 modes of TT: intravenous, IA, or both (intravenous followed by IA). Patients presenting within 3 hours of symptom onset received 0.9 mg/kg IV rt-PA. Patients presenting 3 to 6 hours after onset underwent immediate cerebral angiography and IA TT. IA UK was used to limit to 1.5 million U, and from May 1999, IA rt-PA was given (total dose 0.9 mg/kg). Some patients presenting within 3 hours received intravenous (0.6 mg/kg) and IA (up to 0.3 mg/kg) rt-PA as part of an experimental protocol. We used no anticoagulants for 24 hours after TT. Our institutional review board approved our protocols, and patients or their legal representatives signed informed written consent before treatment.

**Neuroradiologic Evaluation**

Cerebral angiography abnormalities were classified as partial or complete vascular occlusions. Complete recanalization was defined as passage of contrast with comparable filling and clearance to patent vessels. However, if clearance rate was slower compared with normal arteries, recanalization was classified as partial.4

All patients had head CT immediately after TT and were classified as without abnormality, early signs of infarction, hemorrhagic infarction, or parenchymal hematoma.1,3 We defined symptomatic ICH as neurologic worsening ≥4 points in NIHSS attributable to the clot.

**Outcome Measures**

We used ∆NIHSS as outcome measure and divided patients into 3 groups:1 good outcome (decrease in NIHSS ≥4),2 bad outcome (increase in NIHSS ≥4),3 or unchanged. We also evaluated length of hospital stay (LOS) and in-house mortality.

**Statistical Analysis**

Univariate analysis was done using t test, Wilcoxon signed rank sum test, or χ² test. Logistic regression models (LRMs) were fitted to determine the independent association of significant variables with outcome. All covariates were entered in a stepwise fashion. Data are presented as mean±SD and median. Significance level was determined at P<0.05.

**Results**

We identified 1050 AIS patients who presented within 6 hours of symptom onset. Of these, 201 met our inclusion criteria.

**Demographics**

Most patients were white males with a mean age of 67 years (median 70). Sex, age, and race were not different between groups (P values of 0.284, 0.062, and 0.246, respectively; Table 1). Hypertension was the most common risk factor. Most patients had no previous stroke, TIA, or preexisting disability. Blood pressure, temperature, and renal function at admission were similar between groups (Table 2). Embolism was the most common mechanism of stroke.

**Thrombolytic Route**

Of all patients, 50% received IA TT, 28% received intravenous TT, and 21% received both (Table 2). The largest proportion of patients with good outcome was seen in those who received combined intravenous and IA TT (42% improvement). Despite the longer time to treatment for the IA group, its proportion of good outcomes (37%) was similar to that of the intravenous group (40%; Table 2). The median time to TT for all patients was 195 minutes without significant difference between good and bad outcome groups.

**Neuroimaging**

Symptomatic ICH was seen in 58% of patients with bad outcome and 3% of patients with good outcome (P<0.001; Table 2). The latter corresponds to 2 patients who deteriorated past the initial 24-hour period. Recanalization was observed immediately after TT in 91% of patients with good outcome and 59% of those with bad outcome (P=0.026). We had no data to assess the reocclusion rate.

**Blood Glucose Concentration**

Mean BGC for patients with good outcome at admission was 138 mg/dL, and it was 173 mg/dL for those with bad outcome (P=0.024). In patients who recanalized, BGC was significantly higher in those who deteriorated compared with those who improved (P=0.003), and a BGC >150 mg/dL was significantly more common in those with bad outcome (odds ratio [OR] 5.67; P=0.009). The proportion of diabetic patients was also slightly higher in patients with bad outcome who recanalized (38%) compared with those with good outcome (29%), but this was not statistically significant. Also of those patients who recanalized and had elevated BGC, 55% of those with bad outcome had diabetes, whereas 42% of those with good outcome did (P>0.05).

**In-House Mortality**

In-hospital mortality rate was 16%. No patients with good outcome died, whereas 73% of those with bad outcome did. ∆NIHSS was significantly associated with in-house mortality (P<0.001). LOS was not significantly correlated with outcome.

| TABLE 1. Demographic Characteristics and Past Medical History of Study Population |
|-----------------|-----------------|-----------------|
| Characteristics | All Patients | Good Outcome | Bad Outcome |
| Age, y (mean±SD) | 67±13.3 | 66±13.5 | 71±12.1 |
| Female sex, % (SD) | 93 (46) | 28 (36) | 13 (50) |
| White race, % (SD) | 134 (67) | 47 (60) | 20 (77) |
| Past medical history | | | |
| Smoking, % (SD) | 31 (15) | 11 (14) | 2 (8) |
| Diabetes, % (SD) | 46 (23) | 17 (22) | 7 (27) |
| Hypertension, % (SD) | 123 (61) | 50 (64) | 17 (65) |
| Atrial fibrillation, % (SD) | 48 (24) | 18 (23) | 9 (35) |
| Angina pectoris, % (SD) | 29 (14) | 9 (12) | 5 (19) |
| Valvular heart disease, % (SD) | 17 (8) | 8 (10) | 0 (0) |
| Aspirin therapy, % (SD) | 47 (23) | 20 (26) | 6 (23) |
| Congestive heart failure, % (SD) | 27 (13) | 11 (14) | 3 (12) |
| Prior TIA, % (SD) | 16 (8) | 8 (10) | 1 (4) |
| Prior stroke, % (SD) | 57 (28) | 24 (31) | 8 (31) |
| Preexisting disability, % (SD) | 13 (6) | 6 (8) | 1 (4) |

TIA indicates transient ischemic attack.
TABLE 2. Main Clinical and Therapeutic Characteristics of Study Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n = 201)</th>
<th>Good Outcome (n = 78)</th>
<th>Bad Outcome (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median admission BGC in mg/dL (mean)</td>
<td>128 [65 446] (150±72.9)</td>
<td>122 [71 345] (138±59.1)</td>
<td>162.5 [65 345] (173±70.4)*</td>
</tr>
<tr>
<td>Median admission temperature in °C (mean)</td>
<td>36.7 [34.7, 40.0] (36.6±0.73)</td>
<td>36.8 [35.8, 37.7] (36.8±0.42)</td>
<td>36.2 [35.5, 36.8] (36.1±0.50)</td>
</tr>
<tr>
<td>Median systolic blood pressure in mm Hg (mean)</td>
<td>158 [84 224] (157±28)</td>
<td>159 [96 208] (155±26)</td>
<td>155 [84 208] (158±34)</td>
</tr>
<tr>
<td>Median time to therapy in minutes (mean)</td>
<td>195 [10 525] (214±100)</td>
<td>162 [10 525] (201±110)</td>
<td>257 [80 440] (241±102)</td>
</tr>
<tr>
<td>Median renal parameters</td>
<td>Cr in mg/dL (mean)</td>
<td>1 [0.8, 1.3] (1.2±0.8)</td>
<td>1.1 [0.8, 1.3] (1.3±1.0)</td>
</tr>
<tr>
<td>BUN in mg/dL (mean)</td>
<td>16 [13.2, 25] (22.9±17.7)</td>
<td>17 [13, 24.5] (22.6±19.1)</td>
<td>24 [16.8, 28.3] (24±13)</td>
</tr>
<tr>
<td>BUN/Cr in mg/dL (mean)</td>
<td>18 [14, 23.2] (19.6±8.3)</td>
<td>16.79 [12.6, 22.2] (18±6.7)</td>
<td>18.9 [15, 22.6] (20.7±9.6)</td>
</tr>
<tr>
<td>Median ΔNIHSS (mean)</td>
<td>2 [-26, 32] (1.5±7.4)</td>
<td>6 [4, 32] (7.3±4.8)</td>
<td>-12 [-26, -4] (-13±6.4)*</td>
</tr>
<tr>
<td>Recanalization (%)</td>
<td>115 (77)</td>
<td>53 (91)</td>
<td>13 (59)*</td>
</tr>
<tr>
<td>Presence of any ICH (%)</td>
<td>73 (36)</td>
<td>20 (26)</td>
<td>19 (73)</td>
</tr>
<tr>
<td>Symptomatic ICH (%)</td>
<td>29 (14)</td>
<td>2 (3)</td>
<td>15 (58)*</td>
</tr>
<tr>
<td>In-house mortality (%)</td>
<td>33 (16)</td>
<td>0 (0)</td>
<td>19 (73)*</td>
</tr>
<tr>
<td>Therapy used (%)</td>
<td>UK</td>
<td>106 (53)</td>
<td>39 (50)</td>
</tr>
<tr>
<td>rt-PA</td>
<td>90 (45)</td>
<td>36 (46)</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Both</td>
<td>5 (2)</td>
<td>3 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Route of thrombolytic administration (%)</td>
<td>IV</td>
<td>57 (28)</td>
<td>23 (29)</td>
</tr>
<tr>
<td>IA</td>
<td>101 (50)</td>
<td>37 (47)</td>
<td>16 (62)</td>
</tr>
<tr>
<td>IV+IA</td>
<td>43 (21)</td>
<td>18 (23)</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Mechanism of stroke (%)</td>
<td>Embolism</td>
<td>147 (73)</td>
<td>58 (74)</td>
</tr>
<tr>
<td>Occlusive</td>
<td>17 (8)</td>
<td>6 (8)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>37 (18)</td>
<td>14 (18)</td>
<td>5 (19)</td>
</tr>
</tbody>
</table>

Cr indicates serum creatinine; BUN, blood urea nitrogen.
*Values are statistically significant (P<0.05) compared with those of patients with good outcome.

Logistic Regression Models
LRMs were constructed for ΔNIHSS and mortality. We adjusted for ICH, recanalization, BGC, sex, and age. Initial LRMs showed ICH (OR, 125.9; CI, 15 to >999) and recanalization (OR, 17.9; CI, 2.8 to 1114.8) to be the only independent outcome predictors. The out-of-bounds CI for ICH is largely attributable to the fact that univariate analysis demonstrated that only 2 patients with ICH had good outcome, making the model unstable. Removing ICH from models established recanalization (OR, 7.55; CI, 1.9 to 29.9) and BGC (OR, 1.009; CI, 1.001 to 1.017) as independent outcome predictors. The adjusted OR to estimate impact of a 50 mg/dL change in BGC was 1.56. LRMs also revealed that ICH (OR, 7.1; CI, 2.7 to 18.9) and BGC (OR, 1.006; CI, 1.001 to 1.011) were independent mortality predictors. The adjusted OR to estimate impact of a 50 mg/dL change in BGC was 1.38.

Discussion
Our data suggest that AIS patients receiving TT who deteriorate during the 24 hours after admission have higher rates of hyperglycemia, ICH, and death compared with patients who improve. Deterioration is also evident in patients who recanalize but have hyperglycemia. This observation is very enticing because the first 24 hours after AIS are important. Therapeutic interventions are more likely to impact on outcome when executed during this period. However, few studies have applied a standardized examination during the first 24 hours, such as ΔNIHSS, and attempted to identify factors that are associated with this clinical deterioration. Our results raise 2 main issues: (1) How could elevated BGC negate effects of TT and recanalization? and (2) Can we aggressively treat elevated BGC within 24 hours of symptom onset to modify clinical outcome? We will address these issues in the ensuing discussion.

Effect of Hyperglycemia on AIS Outcome
Association of hyperglycemia and worsened outcome after cerebral ischemia has been reported in animal models for >25 years. However, initial human studies reported no association between hyperglycemia and stroke outcome, suggesting that the former represented a stress response to the latter. Several reports since then have shown that hyperglycemia, especially immediately after symptom onset, is indeed related to worse outcome in patients with AIS. It has also been reported that hyperglycemia also increases odds for ICH after TT. Furthermore, admission hyperglycemia has been associated...
with increased short- and long-term mortality and increased in-patient charges for patients with AIS.25,26 Our findings support this body of evidence. In addition, confirming previous results,27 we also found that history of diabetes may not be a predictor of poor outcome because the effect of hyperglycemia is more evident in nondiabetic patients.

Animal models have tried to clarify a mechanistic link between hyperglycemia and stroke outcome.17,28–40 Most of these data support the notion that pre-existing hyperglycemia worsens outcome in reversible cerebral ischemia but are less convincing for permanent focal occlusion models. The main possible mechanisms linking hyperglycemia with worse outcome obtained from these studies can be summarized as follows: (1) hyperglycemia-induced endothelial damage; (2) increased expression of adhesion molecules; (3) generation of vasodilating or antithrombotic substances such as nitric oxide; (4) deteriorating tissue acidosis; (5) production of reactive oxygen species; (6) suppression of neuronal survival signals; and (7) worsening of the degree of blood–brain barrier breakdown. Acute ischemic penumbra or collaterally perfused ischemic regions appear to be particularly susceptible to these effects.30

Despite the body of evidence from animal models, there is a paucity of human studies confirming mechanisms by which hyperglycemia impacts on outcome after AIS. A recent study using MRI has demonstrated that hyperglycemia in AIS promotes progression of areas with decreased perfusion into infarction via increased tissue acidosis.12 This study also confirmed that an area of the brain similar to ischemic penumbra in animal models is particularly susceptible to such progression.

Potential Effects of Aggressive Elevated BGC Management

Our LRM found BGC to be an independent predictor of in-house mortality. When examining ΔNIHSS, BGC could not be separated from ICH as a predictor of bad outcome, potentially because of inadequacy of our data. However, difficulty in separating these 2 variables may be somewhat expected because hyperglycemia has been independently associated with ICH after TT for AIS, and this in turn has been predictive of mortality.9,11,23,24 Removing ICH from the model resulted in BGC being a significant independent outcome predictor. Thus, both ΔNIHSS and in-house mortality are related to elevated BGC.

The question of whether aggressive treatment of elevated BGC can impact outcome of patients receiving TT for AIS remains difficult to answer. Administration of aggressive insulin therapy in patients with acute myocardial infarction has resulted in conflicting results.41 The main reason may be that most of these studies were performed in the prethrombolysis era and that dosages, duration of treatment, and routes of administration differed among studies. This is in contrast with a recent study showing reduced morbidity and mortality in critically ill patients admitted to a surgical intensive care unit who were treated with intensive insulin therapy.42 Preliminary data on AIS patients suggest that insulin infusions can be administered safely.43 Efficacy of such treatment remains to be determined. Our results suggest that a clinical trial designed to answer this important question is necessary.

Study Limitations

Our study has several limitations. Although data collection was done in a prospective fashion, analysis is retrospective and may be subject to bias. Our patients were treated with different thrombolytic agents and via different routes. A more homogeneous population may have been more desirable. Our study lacks a control group. Other potential limitations include our definition of hyperglycemia and the method used to define it. Use of a single measure of BGC at a variable time after stroke onset may be problematic.14 It is possible that multiple measurements before and after thrombolysis may improve accuracy of the effect of hyperglycemia on outcome. We did not obtain glycosylated hemoglobin in our patients. It is also possible that the negative effect on outcome observed in patients with hyperglycemia may have been an additive effect of diagnosed and undiagnosed diabetes mellitus.13 However, we found no association between known history of diabetes and outcome. Our definition of hyperglycemia was arbitrary and basically centered around the mean BGC found in our population. However, several other studies have chosen similar BGC thresholds (usually BGC >140 mg/dL).13,43 Finally, our results represent the experience of a single center and may not be applicable to all patients with AIS with TT.

Conclusions

The purpose of this study was to identify measures to guide and improve day-to-day management of AIS patients in the critical care unit after TT. Specifically, we confirmed validity of ΔNIHSS as an accurate predictor of short-term outcome. Concurrently, we established a significant relationship between BGC and short-term outcome even in patients with confirmed recanalization. The role of BGC in short-term outcome is interesting because it is a value that is measured easily and can be influenced readily in the critical care setting.

References

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