Association of Admission Blood Glucose and Outcome in Patients Treated With Intravenous Thrombolysis

Results From the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR)

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Objective: To determine the association between admission blood glucose and outcome in ischemic stroke patients treated with thrombolysis.

Design: A prospective, open, multinational, observational study.

Setting: An ongoing Internet-based, academic-driven, interactive thrombolysis register.

Patients: Between 2002 and 2007, 16,049 patients were recorded in the SITS-ISTR.

Main Outcome Measure: Blood glucose was recorded at admission. Blood glucose was divided into the following categories: less than 80, 80-120 (reference range), 121-140, 141-160, 161-180, 181-200, and greater than 200 mg/dL. Outcomes were mortality and independence (modified Rankin Scale score of 0-2) at 3 months and symptomatic intracerebral hemorrhage (SICH) (National Institutes of Health Stroke Scale deterioration ≥4 points within 24 hours and type 2 parenchymal hemorrhage).

Results: In multivariable analysis, blood glucose as a continuous variable was independently associated with a higher mortality (P < .001), lower independence (P < .001), and an increased risk of SICH (P = .005). Blood glucose greater than 120 mg/dL as a categorical variable was associated with a significantly higher odds for mortality (odds ratio [OR], 1.24; 95% confidence interval [CI], 1.07-1.44; P = .004) and a lower odds for independence (OR, 0.58; 95% CI, 0.48-0.70; P < .001), and blood glucose from 181 to 200 mg/dL was associated with an increased risk of SICH (OR, 2.86; 95% CI, 1.69-4.83; P < .001) compared with the reference level. The trends of associations between blood glucose and outcomes were similar in patients with diabetes (17%) or without such history, except for mortality (P = .23) and SICH (P = .06) in which the association was not statistically significant in patients with diabetes.

Conclusions: Admission hyperglycemia was an independent predictor for poor outcome after stroke/thrombolysis, though SICH rates did not increase significantly until reaching 180 mg/dL. These results suggest that tight control of blood glucose may be indicated in the hyperacute phase following thrombolysis. Randomized trial data are needed.

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Hyperglycemia after stroke is a common observation and occurs in up to 60% of patients depending on the definition of hyperglycemia. Poststroke hyperglycemia may represent stress hyperglycemia, underlying impaired glucose tolerance or unrecognized diabetes, as a history of diabetes mellitus is reported in up to 20% of stroke patients. Poststroke hyperglycemia has been shown to be associated with poor outcome in many studies, even after adjustment for prognostic factors. Interestingly, a randomized controlled trial found no differences in mortality or functional outcomes in patients with admission hyperglycemia treated with glucose potassium insulin infusion compared with standard intravenous saline infusion. The study enrolled patients with moderate hyperglycemia; achieving glycemic control was delayed.

Several mechanisms have been proposed through which hyperglycemia might cause a detrimental effect on infarct evolution and outcome, such as anaerobic glycolysis leading to lactic acidosis, reperfusion-induced superoxide production.
increased matrix metalloproteinase-9 expression, and exacerbating blood-brain barrier damage. In ischemic stroke patients treated with thrombolysis, hyperglycemia was associated with lower recanalization rates and rapid lesion growth.

Current European Stroke Organization guidelines recommend treatment with insulin titration if serum glucose levels exceed 180 mg/dL (to convert to millimoles per liter, multiply by 0.0555) in patients with stroke, and the current American Heart Association stroke guidelines suggest intervention if glucose exceeds even 140 mg/dL, but thrombolysis is not contraindicated above these levels. In a clinical trial, intravenous thrombolysis was contraindicated if glucose level exceeded 400 mg/dL, but in clinical practice intervention is suggested at a much lower level (>180 mg/dL). To date, data are not available from large cohorts examining the association of very early glucose levels and outcome in ischemic stroke patients treated with thrombolysis. Moreover, the association between hyperglycemia and outcome in small previously published cohorts of ischemic stroke patients receiving thrombolysis is inconsistent, suggesting a worse outcome in hyperglycemic patients with or without history of diabetes despite thrombolysis-induced recanalization or a detrimental effect of persistent hyperglycemia during the initial 24 hours after thrombolysis only in patients without diabetes.

The primary aim of our study was to determine the effect of admission blood glucose on mortality, functional outcome, and the rate of symptomatic hemorrhage in a large cohort of patients treated with intravenous thrombolysis registered in the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR). The secondary aim was to determine if a history of diabetes altered the association between admission glucose and outcome, and the tertiary aim was to identify a blood glucose level that might warrant acute intervention in the setting of ischemic stroke.

METHODS

PATIENTS AND PROCEDURES

All patients entered in the SITS-ISTR between December 2002 and November 2007 were included in this study. The SITS-ISTR is an ongoing Internet-based, academic-driven, interactive thrombolysis register. The methodology of the SITS-ISTR, including the procedure for data collection and management, patient identification, and verification of source data, has been described previously. In brief, SITS-ISTR is a prospective, open, multinational, observational monitoring registry for clinical centers using thrombolysis for the treatment of acute ischemic stroke. The registry is open to all countries. The SITS-Monitoring Study (MOST) cohort is embedded within SITS-ISTR.

Baseline and demographic characteristics, stroke severity (as measured by the National Institutes of Health Stroke Scale [NIHSS]), time intervals, risk factors, blood glucose, blood pressure, medication history, and imaging scan (computed tomography and/or magnetic resonance imaging) data taken on admission were collected. Outcome measurements were NIHSS score at 2 hours, 24 hours, and 7 days; imaging scan data after treatment; and modified Rankin scale score at 3 months.

MAIN OUTCOME MEASURES

The study’s main outcome measures were mortality, independence, and symptomatic intracerebral hemorrhage (SICH). Mortality within 3 months was included and functional independence was defined as a modified Rankin scale score of 0 to 2 at 3 months. Symptomatic intracerebral hemorrhage per SITS-MOST was defined as deterioration in NIHSS score of 4 or more points within 24 hours and parenchymal hemorrhage type 2 in follow-up imaging scans 22 to 36 hours after the start of thrombolysis treatment. Symptomatic intracerebral hemorrhage according to the National Institute of Neurological Disorders and Stroke (NINDS) was defined as symptomatic (any deterioration in NIHSS score within 7 days) intracerebral hemorrhage of any type in any posttreatment imaging scans after the start of thrombolysis treatment.

CATEGORIZATION OF ADMISSION BLOOD GLUCOSE

Admission blood glucose was categorized as follows in an attempt to identify a treatment cutoff and owing to the possibility of a nonlinear association between glucose and outcome: less than 80, 80 to 120, 121-140, 141-160, 161-180, 181-200, and greater than 200. We chose a glucose range of 80 to 120 mg/dL as the reference group for comparisons, as this range is normally regarded as indicating normoglycemia.

STATISTICAL ANALYSIS

Descriptive statistics for the baseline and demographic data are presented for all patients and also classified by history of diabetes. Unknown values were excluded from the denominator when calculating proportions, as was done in the previous SITS publications. To calculate statistical significance of the difference between proportions, we used the chi square method; for medians, we used the Mann-Whitney U test. Multivariable logistic regression analyses were performed in an exploratory manner to find the association of admission blood glucose as a continuous variable with outcomes. For each outcome measurement, a separate multivariable analysis was performed. Owing to the very large sample size of our study, we entered all the available baseline and demographic variables listed in Table 1 into the multivariable model. We performed statistical interaction analysis between history of diabetes and admission glucose with outcome in the multivariable model to test whether it is justifiable to perform the subgroup analysis categorized by history of diabetes. Separate multivariable analysis was performed in the subgroup of patients according to history of diabetes. Admission blood glucose was also examined as a categorical variable in the whole cohort and the subgroup of patients by history of diabetes with outcome in the multivariable analyses. We also performed C statistic/receiver operating characteristic (ROC) curve analysis. The cutoff level for glucose was estimated by maximizing the Youden Index. P < .05 was considered statistically significant. For univariate statistical analysis, Statistica software, version 8.0, was used, and for multivariable and ROC analysis, R, version 2.10.1, was used.

RESULTS

BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Between December 2002 and November 15, 2007, 16,049 patients from 31 countries with confirmed baseline data
were recorded in the SITS-ISTR. Of these, 2735 (17%) patients had a history of diabetes, 13052 (81.3%) had no history of diabetes, and for 259 (1.6%) patients the history of diabetes was unknown. Admission glucose was recorded in 15336 (95.6%) patients.

Baseline and demographic characteristics for all patients (also dichotomized according to the history of diabetes) are shown in Table 1. Patients with diabetes were 2 years older and had 1 point higher median NIHSS scores compared with patients without diabetes. Most other baseline data also significantly disadvantaged the patients with diabetes compared with patients without.

Categorized glucose level was distributed as follows: glucose under 80 mg/dL was found in 350 patients (2.3%), 80 to 120 mg/dL in 7889 (51.4%) patients, 121 to 160 mg/dL in 3091 (20.2%) patients, 141 to 160 mg/dL in 1577 (10.3%) patients, 161 to 180 mg/dL in 912 (6.0%) patients, 181 to 200 mg/dL in 462 (3.0%) patients, and greater than 200 mg/dL in 350 patients (2.3%).

**EFFECT OF ADMISSION BLOOD GLUCOSE ON OUTCOME FOR THE WHOLE COHORT**

Table 2 shows the results from the ROC curve analysis. The C statistics for outcomes derived from ROC analyses were between 0.53 and 0.60.

Table 3 shows the admission blood glucose according to the main outcomes. Patients with poor outcome (mortality, modified Rankin scale score of 3-6, and SICH) had a higher admission glucose compared with patients with good outcomes.

In the multivariable analysis, admission hyperglycemia (as a continuous variable) (Figure 1) was significantly associated with higher mortality and lower functional independence at 3 months. Each 10-mg/dL increase in admission glucose level was associated with an increase in odds ratio (OR) of 1.03 (95% confidence interval [CI], 1.02-1.04) for mortality and a decrease in OR of 0.96 (95% CI, 0.95-0.97) for functional independence.

Admission hyperglycemia was also associated with higher rates of SICH per both definitions (Figure 1). Each 10-mg/dL increase in admission glucose was associated with an increase in OR of 1.04 (95% CI, 1.01-1.07) for SICH per SITS-MOST and 1.05 (95% CI, 1.04-1.07) for SICH per NINDS.

Figure 2 shows the adjusted ORs of glucose levels as categorical variables compared with the reference level (80-120 mg/dL) for each outcome derived from the multivariable analyses. The OR for mortality (Figure 2A) was significantly higher in those with a glucose level above 120 mg/dL (for glucose level of 121-140 mg/dL: OR, 1.24; 95% CI, 1.07-1.44; P=.004). For the survivors (Figure 2B),
the OR for functional independence (modified Rankin scale score of 0-2) was significantly lower with a glucose level above 120 mg/dL (for glucose level of 121-140 mg/dL: OR, 0.80; 95% CI, 0.72-0.90; \( P < .001 \)).

The OR for SICH per SITS-MOST definition (Figure 2C) was significantly higher in those with a glucose level of 181 to 200 mg/dL (OR, 2.86; 95% CI, 1.69-4.83; \( P < .001 \)). However, statistical significance disappeared for glucose level greater than 200 mg/dL. The OR for SICH per the NINDS definition (Figure 2D) was significantly higher with glucose level above 140 mg/dL (OR, 1.43; 95% CI, 1.16-1.76; \( P < .001 \)).

### Table 2. Univariate ORs, C Statistics, and Cutoff Level for Glucose by Main Outcome for All Patients and According to History of Diabetes

<table>
<thead>
<tr>
<th>Outcome Variable by Diabetes History</th>
<th>OR (95% CI) ( ^a )</th>
<th>C Statistic ( ^b )</th>
<th>Glucose Cutoff, mg/dL ( ^c )</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality within 3 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1.054 (1.044-1.063)</td>
<td>0.597</td>
<td>126.0</td>
<td>52.3</td>
<td>62.1</td>
</tr>
<tr>
<td>Yes</td>
<td>1.099 (0.995-1.023)</td>
<td>0.528</td>
<td>174.6</td>
<td>47.1</td>
<td>58.9</td>
</tr>
<tr>
<td>No</td>
<td>1.080 (1.063-1.098)</td>
<td>0.568</td>
<td>109.8</td>
<td>68.2</td>
<td>44.6</td>
</tr>
<tr>
<td>Rate of independence ( ^d ) at 3 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.946 (0.939-0.954)</td>
<td>0.579</td>
<td>123.0</td>
<td>49.3</td>
<td>62.7</td>
</tr>
<tr>
<td>Yes</td>
<td>0.977 (0.965-0.989)</td>
<td>0.548</td>
<td>145.0</td>
<td>65.1</td>
<td>43.1</td>
</tr>
<tr>
<td>No</td>
<td>0.931 (0.919-0.944)</td>
<td>0.568</td>
<td>110.0</td>
<td>61.4</td>
<td>49.4</td>
</tr>
<tr>
<td>SICH per SITS-MOST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1.044 (1.024-1.064)</td>
<td>0.574</td>
<td>139.0</td>
<td>40.6</td>
<td>73.4</td>
</tr>
<tr>
<td>Yes</td>
<td>1.020 (0.988-1.053)</td>
<td>0.549</td>
<td>180.0</td>
<td>56.1</td>
<td>61.1</td>
</tr>
<tr>
<td>No</td>
<td>1.050 (1.019-1.081)</td>
<td>0.561</td>
<td>131.4</td>
<td>37.2</td>
<td>75.3</td>
</tr>
<tr>
<td>SICH per NINDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1.059 (1.049-1.070)</td>
<td>0.598</td>
<td>137.0</td>
<td>42.8</td>
<td>72.9</td>
</tr>
<tr>
<td>Yes</td>
<td>1.033 (1.016-1.049)</td>
<td>0.586</td>
<td>177.0</td>
<td>54.5</td>
<td>61.2</td>
</tr>
<tr>
<td>No</td>
<td>1.080 (1.061-1.100)</td>
<td>0.579</td>
<td>131.0</td>
<td>36.3</td>
<td>75.4</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; SICH, symptomatic intracerebral hemorrhage; SITS-MOST, Safe Implementation of Treatments in Stroke Monitoring Study.

\( ^a \) Odds per change of 10-mg/dL glucose change.

\( ^b \) Area under the receiver operating characteristic curve.

\( ^c \) Cutoff estimated by maximizing the Youden Index.

\( ^d \) Modified Rankin scale score of 0 to 2.

### Table 3. Main Outcome for All Patients and According to History of Diabetes

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>All Patients, No./ Total No. (%)</th>
<th>Glucose Level by Events vs Nonevents, Median (IQR), mg/dL</th>
<th>OR (95% CI) ( ^a )</th>
<th>C Statistic ( ^b )</th>
<th>Glucose Cutoff, mg/dL ( ^c )</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality within 3 mo</td>
<td>2038/13 834 (14.7)</td>
<td>127 (108-158) vs 116 (101-139)</td>
<td>1.054 (1.044-1.063)</td>
<td>0.597</td>
<td>126.0</td>
<td>52.3</td>
<td>62.1</td>
</tr>
<tr>
<td>Yes</td>
<td>1.009 (0.995-1.023)</td>
<td>115 (105-136) vs 122 (105-148)</td>
<td>0.946 (0.939-0.954)</td>
<td>0.579</td>
<td>123.0</td>
<td>49.3</td>
<td>62.7</td>
</tr>
<tr>
<td>No</td>
<td>1.080 (1.063-1.098)</td>
<td>128 (110-135) vs 128 (108-167)</td>
<td>0.931 (0.919-0.944)</td>
<td>0.568</td>
<td>110.0</td>
<td>61.4</td>
<td>49.4</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IQR, interquartile range; NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; SICH, symptomatic intracerebral hemorrhage; SITS-MOST, Safe Implementation of Treatments in Stroke Monitoring Study.

\( ^a \) Derived from multivariable analysis.

\( ^b \) Cutoff estimated by maximizing the Youden Index.

\( ^c \) National Institutes of Health Stroke Scale score worsening of 4 or more points within 24 hours plus type 2 intracerebral hemorrhage.

\( ^d \) Any National Institutes of Health Stroke Scale deterioration within 7 days or death plus any intracerebral hemorrhage.
betes compared with patients without diabetes. In the univariate analysis, patients with diabetes had a statistically significant poor outcome compared with patients without diabetes. After adjustment for baseline characteristics in the multivariable analysis, patients with diabetes had a higher odds for mortality and a lower odds for functional independence at 3 months (Table 3).

There was no statistically significant difference in the SICH rates between patients with and without diabetes in the multivariable analysis.

In the multivariable analysis, admission hyperglycemia (as a continuous variable) (Figure 1) was associated with higher mortality and lower functional independence at 3 months (Table 3). There was no statistically significant difference in the SICH rates between patients with and without diabetes in the multivariable analysis.

In the multivariable analysis, admission hyperglycemia (as a continuous variable) (Figure 1) was associated with higher mortality and lower functional independence at 3 months and also a higher rate of SICH in patients without history of diabetes. In patients with diabetes, the trend was very similar, but the association of glucose with mortality and SICH per SITS-MOST did not quite reach statistical significance.

Figure 2 also shows the adjusted ORs of glucose levels as categorical variables compared with the reference level (80-120 mg/dL) according to history of diabetes. The ORs for mortality and functional independence (Figure 2A and B) were significantly higher with a glucose level above 120 mg/dL in patients without history of diabetes, and the corresponding glucose levels in patients with diabetes were 181 to 200 mg/dL for mortality and above 160 mg/dL for functional independence.

The OR for SICH per the SITS-MOST definition (Figure 2C) was significantly higher in those with a glucose level of 181 to 200 mg/dL for both subgroups of patients according to history of diabetes. For SICH according to the NINDS definition (Figure 2D), the corresponding glucose levels were above 140 mg/dL in patients without a history of diabetes and more than 180 mg/dL in patients with diabetes.
With more than 16 000 ischemic stroke patients treated with intravenous thrombolysis, this open registry-based study is the largest study defining the strong association of early poststroke hyperglycemia not only with higher mortality and lower functional independence but also with higher postthrombolytic SICH rates (Figure 1). The independent association of hyperglycemia with higher SICH rate is of particular importance in acute ischemic stroke patients treated with thrombolysis. Glucose was measured hyperacutely, ie, on admission, in most cases within the 3 hours of thrombolysis with median onset to treatment time of 2 hours 25 minutes. Robust hyperglycemia after stroke is a short-lived phenomenon in many patients, especially those without a history of diabetes, as the initial hyperglycemia often normalizes rapidly during the first 10 hours. Therefore, confirmation of the association between hyperacute hyperglycemia with long-term outcome is of particular relevance.

Our results from a subgroup analysis according to the history of diabetes were consistent with the meta-analysis of Capes and coauthors for patients without history of diabetes that hyperglycemia increased mortality and decreased functional independence (Figure 1). However, we also observed a similar trend of association between hyperglycemia and poor outcome at 3 months in patients with diabetes, but the association of glucose with mortality within 3 months did not quite reach statistical significance. On the contrary, Capes and coauthors did not find any association of hyperglycemia with poor outcome in patients with diabetes.

Previous small studies identified various cutoff levels of hyperglycemia that were associated with poor outcome. Fuentes and coworkers (n=476) found that a glucose level of 155 mg/dL or above at any time within the first 48 hours of stroke onset was an independent predictor of poor outcome. Poppe et al (n=1098) found that admission glucose greater than 144 mg/dL was an independent predictor of poor outcome. In our ROC curve analysis, we found a glucose cutoff level for higher mortality at 126 mg/dL and lower functional independence (modified Rankin scale score of 0-2 at 3 months) at 123 mg/dL. When we categorized admission glucose and compared it with 80 to 120 mg/dL as a reference level, we found that glucose level above 120 mg/dL was associated with a higher mortality and lower functional independence for the whole cohort and also in patients without diabetes (Figure 2A and B).

Studies examining the effect of admission glucose on outcome in relation to recanalization have also found inconsistent cutoff levels for glucose, but this is probably explained by small sample sizes. Alvarez-Sabin and coworkers (n=73) found that admission glucose greater than 140 mg/dL was the only independent predictor of poor neurological improvement at 24 hours despite successful recanalization after intravenous thrombolysis, while Ribo et al (n=139) found that admission glucose greater than 158 mg/dL was the only independent predictor of no recanalization. Our data are not directly comparable with these findings.

As expected from the baseline characteristics, patients with diabetes had a worse outcome in all parameters compared with patients without diabetes in the univariate analysis, as most of the baseline characteristics place patients with diabetes at a disadvantage. When we adjusted for baseline imbalances, we did not find any significant difference in SICH rates between patients with and without a history of diabetes, suggesting that diabetes itself does not increase the risk of SICH following thrombolysis (Table 3). Poor outcome at 3 months in patients with diabetes suggests other complications, such as infection related to diabetes. The cutoff level of glucose for poor outcome seems lower in patients without a history of diabetes (Table 2 and Figure 2) than in patients with a history of diabetes, but the number of patients with a history of diabetes was less than one-fifth and SICH rate in general was already infrequent, which compromises the statistical power for this analysis. It is also important to note that the association of hyperglycemia with poor outcome was stronger than the history of diabetes.

There are a few limitations of this study. First, it is an observational exploratory study based on retrospective analysis. Second, missing data may have influenced the results; we do not know whether these patients were treated with any antidiabetic medication. Lastly, we do not have any time course data on glucose levels. However, the strength of our study is its very large sample size (>16 000) compared with previous studies.

Despite the aforementioned limitations, the present study, based on a very large prospective database of stroke thrombolysis, confirms that hyperglycemia in the hyperacute stage is an independent predictor of higher rates of SICH and mortality and lower rates of functional independence. Admission glucose level above 120 mg/dL increased the risk of death and reduced the rate of functional independence, but SICH rates did not increase significantly up to 180 mg/dL. These results suggest that tight control of blood glucose may be indicated in the hyperacute phase following thrombolysis. Randomized trial data are needed.

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REFERENCES


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Announcement

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