Treatment of Hyperglycemia In Ischemic Stroke (THIS)  
A Randomized Pilot Trial

Askiel Bruno, MD; Thomas A. Kent, MD; Bruce M. Coull, MD; Ravi R. Shankar, MD; Chandan Saha, PhD; Kyra J. Becker, MD; Brett M. Kissela, MD; Linda S. Williams, MD

Background and Purpose—Hyperglycemia may worsen brain injury during acute cerebral infarction. We tested the feasibility and tolerability of aggressive hyperglycemia correction with intravenous insulin compared with usual care during acute cerebral infarction.

Methods—We conducted a randomized, multicenter, blinded pilot trial for patients with cerebral infarction within 12 hours after onset, a baseline glucose value ≥8.3 mmol/L (≥150 mg/dL), and a National Institutes of Health Stroke Scale score of 3 to 22. Patients were randomized 2:1 to aggressive treatment with continuous intravenous insulin or subcutaneous insulin QID as needed (usual care). Target glucose levels were <7.2 mmol/L (<130 mg/dL) in the aggressive-treatment group and <11.1 mmol/L (<200 mg/dL) in the usual-care group. Glucose was monitored every 1 to 2 hours, and the protocol treatments continued for up to 72 hours. Final clinical outcomes were assessed at 3 months.

Results—We randomized 46 patients (31 to aggressive treatment and 15 to usual care). All patients in the aggressive-treatment group and 11 (73%) in the usual-care group had diabetes (P=0.008). Glucose levels were significantly lower in the aggressive-treatment group throughout protocol treatment (7.4 vs 10.5 mmol/L [133 vs 190 mg/dL], P<0.001). Hypoglycemia <3.3 mmol/L (<60 mg/dL) occurred only in the aggressive-treatment group (11 patients, 35%), 4 (13%) of whom had brief symptoms, including only 1 (3%) neurologic. Final clinical outcomes were nonsignificantly better in the aggressive-treatment group.

Conclusions—The intravenous insulin protocol corrected hyperglycemia during acute cerebral infarction significantly better than usual care without major adverse events and should be investigated in a clinical efficacy trial. (Stroke. 2008; 39:384-389.)

Key Words: brain infarction • diabetes mellitus • hyperglycemia • insulin

In animal studies, hyperglycemia during focal brain ischemia worsens outcomes, particularly in transient occlusion with reperfusion models. In human retrospective and observational studies, hyperglycemia during acute cerebral infarction has been linked to worse outcomes as well. The human studies were analyzed by controlling for multiple factors, including diabetes mellitus and stroke severity, thus suggesting that hyperglycemia worsens outcomes from acute stroke independent of the other factors. These findings led to the hypothesis that aggressive correction of hyperglycemia during acute cerebral infarction will limit brain damage and improve clinical outcomes. One recent efficacy trial of aggressive hyperglycemia correction during acute stroke, predominantly in patients without diabetes, has been reported and showed no benefit. One additional pilot trial of aggressive hyperglycemia correction during acute stroke has been reported, and another is in progress. Because aggressive correction of hyperglycemia with intravenous insulin during acute stroke involves substantial effort and cost and some risk, it is essential to determine whether such an intervention improves outcomes and to what extent. Thus, to collect data needed to optimize the design of a subsequent efficacy trial, we performed a pilot trial of aggressive versus usual hyperglycemia correction, predominantly in patients with diabetes mellitus.

Patients and Methods

The Treatment of Hyperglycemia in Ischemic Stroke (THIS) study was a National Institute of Neurological Disorders and Stroke-sponsored randomized, blinded, multicenter trial. Patients were enrolled between November 2002 and July 2006 at 5 US medical centers (see Appendix). The primary objective was to collect data about the safety, feasibility, and effectiveness of aggressive hyperglycemia correction with intravenous insulin during acute cerebral infarction. The secondary aim was to measure clinical outcomes in
this patient population to help optimize the design of an efficacy trial.

**Patients**

Patients presenting with cerebral infarction were screened for enrollment. Neuroimaging was required before randomization to exclude acute cerebral infarction mimics. Inclusion criteria were as follows: onset of symptoms within 12 hours before randomization, baseline blood glucose level \( \geq 8.3 \text{ mmol/L (150 mg/dL)} \), and baseline National Institutes of Health Stroke Scale (NIHSS) score of 3 to 22, with at least 2 points on the motor portion. We hypothesized that aggressive correction of hyperglycemia might be most effective when started as soon as possible after the onset of cerebral ischemia, and thus we enrolled patients and initiated protocol treatment as soon as possible after stroke onset. We also hypothesized that this type of intervention might be effective primarily when the brain cells were still viable (cerebral penumbra) and before reperfusion occurred.\(^3,8\)

Thus, we chose 12 hours as the enrollment limit because the cerebral penumbra is often still present at 12 hours after the onset of ischemia, based on magnetic resonance imaging and positron emission tomography criteria.\(^16-18\) and spontaneous or tissue plasminogen activator (tPA)–associated reperfusion in nonlacunar stroke is still occurring in some patients.\(^19-21\) We chose the hyperglycemia threshold for enrollment as 8.3 mmol/L (150 mg/dL) to include predominantly patients with diabetes mellitus, as their hyperglycemia during hospitalization is greater than in patients without diabetes,\(^5,10,22,23\) thus enabling a greater reduction of glucose levels.

Exclusion criteria were preexisting incapacitating illness equivalent to a modified Rankin Scale score \( \geq 3 \), indication for intravenous insulin therapy (such as acute myocardial infarction or diabetic ketoacidosis), or corticosteroid therapy. Hemoglobin A1C was measured in all patients on admission, and we defined diabetes mellitus as having it documented in the medical records or an elevated A1C level, based on magnetic resonance imaging and positron emission tomography criteria.\(^16-18\) and spontaneous or tissue plasminogen activator (tPA)–associated reperfusion in nonlacunar stroke is still occurring in some patients.\(^19-21\) We chose the hyperglycemia threshold for enrollment as 8.3 mmol/L (150 mg/dL) to include predominantly patients with diabetes mellitus, as their hyperglycemia during hospitalization is greater than in patients without diabetes,\(^5,10,22,23\) thus enabling a greater reduction of glucose levels.

Randomization and Blinding

All patients signed a valid, informed consent approved by institutional review boards at each center. To acquire a greater proportion of data about our novel aggressive intervention, we randomized patients to aggressive hyperglycemia correction or usual care in a 2:1 ratio, respectively. The acute intervention was single-blind (patients and families), and the final outcome assessment was double-blind.

The Data Management Center prepared lists of random treatment-group allocations in the specified 2:1 ratio and distributed these lists to the research pharmacists at each participating center. Unblinded research pharmacists at each center randomized patients according to the prepared lists and after randomization revealed the treatment group to the treating physicians and nurses so that they could administer the treatment protocols in an unblinded fashion. Before randomization, the investigators were blinded to the next treatment group. The patients and their families remained blinded throughout the trial. The final clinical assessment at 3 months was done by blinded investigators who had not participated in the acute care.

Patients in both groups received continuous intravenous infusions from bags with concealed labels and with periodic rate adjustments, as well as subcutaneous injections. Patients in the aggressive-treatment group received subcutaneous saline injections QID to simulate subcutaneous insulin injections in the usual-care group. Patients in the usual-care group received intravenous saline to simulate the intravenous insulin infusions in the aggressive-treatment group.

Interventions

On enrollment, all premorbid antidiabetic medications were temporarily discontinued until the study protocols were completed. Patients treated with tPA were admitted to intensive care units (medical, surgical, or neurocritical) according to standard practice. Patients not treated with tPA were admitted either to intensive care units or intermediate care units (also known as step-down or progressive care units), depending on the clinical condition of the patient and the preparedness of a specific unit to administer intravenous insulin. If an appropriate unit bed was not immediately available, protocol treatment began in the Emergency Department. The protocol treatments continued for 72 hours in both groups unless patients improved rapidly and were ready for discharge or died before this time point.

We designed a standardized usual-care protocol to resemble the usual care given to acute stroke patients with hyperglycemia in our communities at that time (2000). Usual care consisted of a subcutaneous regular insulin sliding scale administered QID as needed. No insulin was given when the glucose value was \(<11.1 \text{ mmol/L (<200 mg/dL)} \).

The insulin doses were 2 U for glucose values of 11.1 to 13.9 mmol/L (200 to 250 mg/dL), 3 U for 13.9 to 16.7 mmol/L (251 to 300 mg/dL), 4 U for 16.7 to 19.4 mmol/L (301 to 350 mg/dL), 6 U for 19.4 to 22.2 mmol/L (351 to 400 mg/dL), 7 U for 22.2 to 25.0 mmol/L (401 to 450 mg/dL), and 8 U for 25.0 to 29.9 mmol/L (451 to 499 mg/dL). Capillary glucose was monitored every 2 hours in the usual-care group. Because patients with diabetes mellitus and acute stroke have heterogeneous insulin sensitivities, the investigators were allowed to alter the insulin doses based on the initial patient responses to achieve glucose levels \(<11.1 \text{ mmol/L (<200 mg/dL)} \). When patients with diabetes resumed eating, they received additional subcutaneous regular insulin immediately after each meal at 0.12 U/kg, prorated for the portion of meal that was consumed. Investigators were also allowed to alter the meal insulin dose, based on individual responses, to maintain glucose levels \(<11.1 \text{ mmol/L (<200 mg/dL)} \).

Aggressive treatment consisted of continuous intravenous insulin infusion with rate adjustments according to protocol (Table 1). This protocol represents the current version after multiple modifications during the preliminary study\(^24\) and the early phase of this pilot trial. Capillary glucose was monitored hourly in the aggressive-treatment group. When patients with diabetes resumed eating, they received subcutaneous very rapidly acting insulin immediately after each meal, 1 U of insulin for each 20 g of carbohydrate consumed. Certified dieticians helped the nurses determine carbohydrate consumption. Investigators were allowed to alter the meal insulin dose based on individual responses to maintain glucose levels of 5.0 to 7.2 mmol/L (90 to 130 mg/dL). Insulin infusions were temporarily stopped when patients needed to leave their hospital units. Glucose was not included in the insulin solution. Serum potassium was measured daily, and potassium (20 mEq) was added to the insulin solution only when the potassium level was \(<3.5 \text{ mEq/L}\).

For symptomatic hypoglycemia (glucose \(<3.3 \text{ mmol/L}, \text{ or } <60 \text{ mg/dL}\), with symptoms of hypoglycemia), the protocol called for 25 mL of 50% dextrose, a glucose recheck in 20 minutes, and continuation of the protocol.

Clinical monitoring during hospitalization included a daily NIHSS assessment. After protocol treatment, management of hyperglycemia and diabetes mellitus was decided by the attending physicians according to the standard of care. All other nonglucose-related treatments were decided by the attending physicians on the basis of individual patient needs and the local standard of care.

**Outcomes**

An independent safety monitor (see Appendix) periodically reviewed all of the data and adverse events during this trial. The prespecified primary outcome was the mean glucose difference between the 2 groups during protocol treatment. All adverse events were monitored and documented. The main safety concern was hypoglycemia, defined as any glucose value \(<3.3 \text{ mmol/L (<60 mg/dL)} \) and any associated symptoms during protocol treatment. Each episode of hypoglycemia was documented with all associated symptoms, treatments, and duration on a designated form. For exploratory analysis, favorable clinical outcomes were a modified Rankin Scale score \( \leq 2 \), a modified Barthel Index score of 19 to 20, an NIHSS score \( \leq 2 \), and the Stroke-Specific Quality of Life scale at 3 months. The Stroke-Specific Quality of Life scale consists of multiple domains and the scores from each domain and the total range from 1.0 (worst) to 5.0 (best).\(^23\) This scale tends to have a normal distribution and can be
Table 1. IV Insulin in Acute Stroke Protocol

| Glucose Level, mg/dL | Infusion Rate Adjustment | D10 Glucose Infusion | Repeat Glucose in
<table>
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<tbody>
<tr>
<td>≥160</td>
<td>Increase by 25% (previous rate x 1.25= new rate); no increase if glucose dropped ≥80 mg/dL per hour</td>
<td>None</td>
<td>1 hour</td>
</tr>
<tr>
<td>130–159</td>
<td>Increase by 10% (previous rate x 1.1= new rate); no increase if glucose dropped ≥80 mg/dL per hour</td>
<td>None</td>
<td>1 hour</td>
</tr>
<tr>
<td>90–129</td>
<td>No change</td>
<td>None</td>
<td>1 hour</td>
</tr>
<tr>
<td>80–89</td>
<td>Decrease by 50% (previous rate x 0.5= new rate)</td>
<td>None</td>
<td>1 hour</td>
</tr>
<tr>
<td>&lt;80</td>
<td>STOP infusion and RESTART at 50% previous rate when glucose ≥80 mg/dL (previous rate x 0.5= new rate)</td>
<td>200 mL/h until glucose ≥80 mg/dL</td>
<td>20 minutes</td>
</tr>
</tbody>
</table>

If symptomatic hypoglycemia (autonomic or neurologic symptoms), give 25 mL of 50% dextrose IV push STAT, do not give the D10 infusion, and page the study physician.

If not eating, give normal saline (0.1 mL SC) at ~08:00, 13:00, 18:00, and 22:00.

If eating, give very rapidly acting insulin (Lispro, Aspart SC) right after each meal, 1 U/20 g of carbohydrate eaten.

When glucose is <80 mg/dL, monitor for symptoms of hypoglycemia every 20 minutes and page study physician.

If infusion rate is <10 mL/h, stop infusion and monitor every 2 hours until glucose >130 mg/dL; restart infusion at the previous rate if glucose 131–159 mg/dL or at 40 mL/h if glucose ≥160 mg/dL.

Table 2. Baseline Characteristics and Stroke Subtypes of Patients in THIS Trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Usual Care (n=15)</th>
<th>Aggressive Treatment (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (±SD)</td>
<td>53±15</td>
<td>62±15</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>9 (60)</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Median NIHSS score (IQR)</td>
<td>10 (6–15)</td>
<td>9 (5–15)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)*</td>
<td>11 (73)</td>
<td>31 (100)†</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>12 (80)</td>
<td>27 (87)</td>
</tr>
<tr>
<td>Treated with standard IV tPA, n (%)</td>
<td>2 (13)</td>
<td>8 (26)</td>
</tr>
<tr>
<td>Lacunar stroke subtype, n (%)</td>
<td>4 (27)</td>
<td>10 (32)</td>
</tr>
<tr>
<td>Mean blood glucose, mg/dL (±SD)</td>
<td>271±100</td>
<td>260±79</td>
</tr>
</tbody>
</table>

*Diabetes mellitus defined as documented in the medical records or an elevated hemoglobin A1c.
†P=0.008.

Statistical Analysis

The Division of Biostatistics at the Indiana University School of Medicine managed the data and performed statistical analyses. A Wilcoxon rank-sum test compared the continuous variables, whereas a χ² and Fisher’s exact tests compared the dichotomous variables between the treatment groups at baseline and at 3 months. In addition, ANCOVA compared the glucose levels during protocol treatment and the final clinical outcomes between the groups while adjusting for age, baseline glucose level, baseline NIHSS score, diabetes, tPA treatment, and stroke subtype (lacunar versus nonlacunar). All ANCOVA assumptions were satisfied.

Results

We randomized 46 patients (31 to aggressive treatment and 15 to usual care). Table 2 shows the baseline patient characteristics. Randomization was effective, except that all 4 patients without diabetes were randomized to the usual-care group (1.2% chance, P=0.008). Table 3 shows the metabolic outcomes. The aggressive-treatment protocol corrected hyperglycemia significantly better than did usual care throughout the treatment period (P<0.001). The unadjusted mean glucose level during protocol treatment was 10.5±3.6 mmol/L (190±64 mg/dL) with usual care and 7.4±0.9 mmol/L (133±16 mg/dL) with aggressive treatment. After adjusting for potential confounding factors, the differ-
ence in mean glucose levels between the 2 groups during protocol treatment before patients resumed eating. ○, Usual-care group (n=15); □, aggressive-treatment group (n=31); interrupted line, the 4 patients without diabetes randomized to usual care.

The Figure shows the glucose levels during the initial 24 hours of protocol treatment before patients resumed eating. During the initial 4 hours, glucose levels dropped somewhat faster and below 7.2 mmol/L (130 mg/dL) in the aggressive-treatment group. The 4 patients without diabetes had considerably lower glucose levels than did the entire usual-care group, although they remained somewhat elevated, at 7.2 to 8.9 mmol/L (130 to 160 mg/dL) during the initial 15 hours of treatment. After the initial 24 hours, glucose levels increased transiently after meals in both groups, as seen in our preliminary study. Nonetheless, it seems that the opportunity to correct hyperglycemia with our aggressive protocol during the early phase of this trial is considerable lower in the aggressive-treatment group than in the usual-care group (Table 3, the Figure). The mean adjusted glucose difference of 3.7 mmol/L (66 mg/dL) between groups in this trial is greater than in any of the previous intervention trials of aggressive hyperglycemia correction. A more rapid or greater hyperglycemia correction in this patient population would likely be both more labor-intensive and more risky.

It is important to consider the 4 patients without diabetes who were randomized to usual care. Although they had persistent mild hyperglycemia, their glucose levels were considerably lower than in patients with diabetes at the start of treatment (the Figure) and resembled the levels in the aggressive-treatment group throughout the remainder of protocol treatment (7.0 to 7.5 mmol/L, or 127 to 135 mg/dL; Table 3, Results section). These subjects likely had transient reactive (stress) hyperglycemia and perhaps impaired glucose tolerance or mild diabetes mellitus. Relatively mild and persistent hyperglycemia in acute stroke patients without known diabetes mellitus has been reported, but glucose metabolism in such patients has rarely been studied in detail. Nonetheless, it seems that the opportunity to correct hyperglycemia with our aggressive protocol during decreased, the mean glucose level did not increase (7.4 mmol/L, or 133 mg/dL, in the initial 16 patients and 7.3 mmol/L, or 131 mg/dL, in the subsequent 15 patients).

### Discussion

This pilot trial has demonstrated the effectiveness and tolerability of aggressive hyperglycemia correction with our intravenous insulin protocol during acute cerebral infarction in patients with diabetes mellitus. In the aggressive-treatment group, the mean glucose value dropped from 14.4 mmol/L (260 mg/dL) at baseline to 6.7 mmol/L (121 mg/dL) after 4 hours of protocol treatment. Throughout protocol treatment, glucose levels were considerably lower in the aggressive-treatment group than in the usual-care group (Table 3, the Figure). The mean adjusted glucose difference of 3.7 mmol/L (66 mg/dL) between groups in this trial is greater than in any of the previous intervention trials of aggressive hyperglycemia correction. A more rapid or greater hyperglycemia correction in this patient population would likely be both more labor-intensive and more risky.

### Table 4. Clinical Outcomes in THIS Pilot Trial at 3 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Usual Care (n=15)</th>
<th>Aggressive Treatment (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified rankin scale score ≤2, n (%)</td>
<td>7 (47)</td>
<td>16 (52)</td>
</tr>
<tr>
<td>Modified Barthel index 19–20, n (%)</td>
<td>7 (47)</td>
<td>15 (48)</td>
</tr>
<tr>
<td>NIHSS score ≤2, n (%)</td>
<td>3/13 (23)</td>
<td>11/29 (38)</td>
</tr>
<tr>
<td>SSQOL score</td>
<td>3.63±0.95</td>
<td>3.57±1.08</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>0</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

SSQOL indicates Stroke Specific Quality-of-Life Scale. None of these comparisons were statistically significant (all P values ≥0.35 for unadjusted and ≥0.09 for adjusted comparisons).
acute cerebral infarction in patients without diabetes is limited.

It is unclear at this time whether aggressive correction of hyperglycemia during acute cerebral infarction might be beneficial for all patients with hyperglycemia or perhaps only for those with or without diabetes mellitus. However, an efficacy trial of hyperglycemia correction with intravenous insulin during acute stroke predominantly in patients without diabetes showed no clinical benefit. In that trial, only 17% of patients had diabetes mellitus and 12% had intracerebral hemorrhage. The mean glucose level in the saline (control) group was ~6.8 mmol/L (123 mg/dL) between 8 and 24 hours of treatment, and the mean glucose difference between the 2 groups was only 0.57 mmol/L (10.3 mg/dL). We suspect that greater reductions in glucose levels might be needed to show a clinical benefit. However, a greater reduction in glucose levels in patients without diabetes is likely more challenging and risky. Although not comparable to stroke, greater reductions in glucose levels during acute myocardial infarction improved clinical outcomes in the first DIGAMI trial (2.2 mmol/L, or 38 mg/dL), but smaller reductions in the second DIGAMI trial (0.9 mmol/L, or 16 mg/dL) did not.

Although glucose levels <3.3 mmol/L (<60 mg/dL) occurred in a relatively high proportion of patients (35%) in this trial, there were no sequelaee. Our definition of hypoglycemia was rather liberal owing to the preliminary nature of this trial. The rate of hypoglycemia decreased in the second half of this trial, likely the result of protocol modifications, and without worsening glycemic control. This trial did not include glucose or potassium in the insulin solution, whereas other trials of aggressive hyperglycemia correction did, and it is unclear how this approach compares between trials. It is possible that adding glucose to the insulin solution might have reduced the rate of hypoglycemia in this trial, although it might have also reduced the magnitude of hyperglycemia correction. Based on the similar potassium levels in the 2 groups, routine addition of potassium does not seem necessary.

This pilot trial was not designed to test clinical efficacy, and the somewhat better clinical outcomes in the aggressive-treatment group are not statistically significant (Table 4). This patient sample is small and heterogeneous. For example, tPA-treated patients may be more vulnerable to hyperglycemia because of their increased rate of reperfusion, and thus may benefit most from tight glucose control. Conversely, patients with lacunar infarcts caused by occlusion of small, penetrating cerebral arterioles may benefit least from tight glucose control because of their lack of reperfusion. This trial is too small to adequately address these hypotheses.

Aggressive intravenous insulin protocols like ours are relatively labor-intensive in an effort to maximize hyperglycemia correction while avoiding hypoglycemia. Such protocols need to be administered in care units prepared to use intravenous insulin effectively and safely, which carries added cost. Therefore, we believe that it is important to test the safety and efficacy of the aggressive intervention in a large clinical trial. In addition, computerized insulin infusion algorithms and continuous glucose monitoring systems are available and may offer some advantages to our protocol. However, their widespread feasibility, safety, and cost remain to be established in acute stroke.

Appendix

Study Personnel

Indiana University, Indianapolis, Ind: principal investigator Askiel Bruno, MD; coordinators Alison Sears, RN, and Kelley Faber, MS; principal statistician Chandan Saha, PhD; co-investigators Linda S. Williams, MD, William J. Jones, MD, and James D. Fleck, MD; endocrinologist Ravi R. Shankar, MD.

University of Cincinnati, Cincinnati, Ohio: Brett Kissela, MD; coordinators Kathleen Alwell and Joyce Ziegler; endocrinologist Barbara Ramlo-Halstead.

Baylor College of Medicine, Houston, Tex: Thomas A. Kent, MD, and Pitchaiah Mandava, MD; endocrinologist Glenn Cunningham, MD; coordinator Jane Anderson, RN, APN.

University of Washington, Seattle, Wash: Kyra J. Becker, MD; coordinator Michael S. Fruin, MN, RN, ARNP-CS.

University of Arizona, Tucson, Ariz: Bruce M. Coull, MD, and Jeremy R Payne, MD, PhD; coordinator Denise Bruck.

Independent Safety Monitor

David Sherman, MD, University of Texas, San Antonio.

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Disclosures

None.

References

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