Glucose Regulation in Acute Stroke Patients (GRASP) Trial
A Randomized Pilot Trial

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Background and Purpose—Hyperglycemia is associated with worse outcome in patients with acute stroke.

Methods—We conducted a prospective, randomized, multicenter, 3-arm trial (tight control [target 70 to 110 mg/dL], loose control [target 70 to 200 mg/dL], and control usual care [70 to 300 mg/dL]) to assess the feasibility and safety of 2 insulin infusion protocol targets in patients with acute ischemic stroke. The planned sample was 72 subjects.

Results—A total of 74 subjects were enrolled. Seventy-two (97%) had data available for the primary analyses and 73 (99%) had 3-month clinical outcome data. Median age was 67 years, median National Institutes of Health Stroke Scale score was 8, median glucose was 163 mg/dL, and median time to randomization was 10.7 hours. Fifty-nine percent of patients were diabetic, 35% received thrombolysis, and 14% of subjects died within 3 months. The loose control and usual care groups had median glucose concentrations of 151 mg/dL. The tight control group had a median glucose concentration of 111 mg/dL. The loose control group spent 90% of the first 24 hours in target and the tight group 44% of time in target. There was only one symptomatic patient with hypoglycemia in the loose control group (4%) and zero in the tight control group. The overall rates of hypoglycemia (<55 mg/dL) were 4% in control, 4% in loose, and 30% in tight. Exploratory efficacy analysis was conducted.

Conclusions—Insulin infusion for patients with acute ischemic stroke is feasible and safe using the insulin infusion protocol in the Glucose Regulation in Acute Stroke Patients (GRASP) trial. Exploratory efficacy analysis supports further comparative study. (Stroke. 2009;40:3804-3809.)

Key Words: clinical trial glucose stroke

The association between hyperglycemia and poor outcome after acute ischemic stroke has been of interest for nearly 3 decades.¹ The lack of evidence to guide clinical care in the setting of hyperglycemia has been communicated in the 2003 American Heart Association/American Stroke Association guidelines, which suggest that treatment of hyperglycemia may be necessary if levels exceed 300 mg/dL.² American Heart Association/American Stroke Association guidelines from 2007 suggest treating at lower glucose levels based on expert opinion.³ Both of these statements acknowledge the lack of adequate evidence and call for additional clinical research to inform best practice for hyperglycemic patients with acute stroke.

Preclinical data in animal models of focal ischemia and reperfusion have long demonstrated the association between hyperglycemia and poor outcome.⁴⁻⁵ Even mild to moderate elevations in glucose portend greater injury. Insulin treatment that controls hyperglycemia can reduce infarct volume and improve performance on functional outcome measures.⁶⁻⁷ Imaging studies in humans demonstrate greater infarct volumes, worse functional outcome,⁸ and reduced salvageable tissue in patients with hyperglycemia.

Data from the critical care literature have supported aggressive insulin infusion therapy to improve clinical outcome in critically ill patients.¹⁰ More recently, the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study suggested that application of a tight control strategy to a broadly selected intensive care unit population resulted in greater mortality in the tight control group.¹¹ These contradictory results have resulted in clinical equipoise for the critical care community and even more uncertainty in other populations. We designed and conducted the Glucose Regulation in Acute Stroke Patients (GRASP) trial to understand the therapeutic potential for tight versus more conventional glucose control in hyperglycemic
patients with acute ischemic stroke. The primary objective of the GRASP trial was to assess the safety and feasibility of glucose/insulin/potassium therapy at 2 different target glucose concentrations in patients with acute ischemic stroke.

**Methods**

The GRASP trial was a multicenter, prospective, randomized, unblinded (with blinded outcomes) study of hyperglycemic patients with acute stroke patients with glucose/insulin/potassium in patients with acute ischemic stroke. The International Clinical Trials Registry number is NCT00282867.

**Study Population**

Patients were enrolled at the University of Virginia and Medical College of Georgia. Eligible patients were >17 years old with ischemic stroke onset within 24 hours, with glucose >110 mg/dL, and able to be treated within 2 hours. Potential subjects were excluded for renal dysfunction (creatinine ≥2.5 mg/dL), confounding illness, experimental therapy for the enrollment stroke, pregnancy, life-threatening condition limiting follow-up, missing stratification information, or for standard care indication for insulin infusion. The protocol was approved at both sites by the local Institutional Review Board and signed informed consent was obtained from the patient or legal representative before enrollment in all cases.

**Randomization and Blinding**

Randomization was stratified by glucose concentration and predicted probability of outcome as determined by a previously developed and validated model. Randomization was 1:1:1 and used randomly permuted blocks of randomly chosen block sizes of 3 or 6. The treating physician was unblinded to the assigned treatment but was excluded from assessing 3-month clinical outcomes. Outcome assessments were blinded.

**Treatment Protocol**

Patients randomized to the control group were treated as per the standard at that institution. Treatment of hyperglycemia, excluding intravenous insulin, was at the discretion of the treating physician, but patients were required to get insulin if their blood glucose was >300 mg/dL, per the American Heart Association/American Stroke Association guidelines at that time. The target glucose concentration range was prespecified as 70 mg/dL to 300 mg/dL. All patients who were assigned an insulin infusion received Novolin brand insulin in normal saline (1 U/1 mL) as a continuous infusion. Dosing was guided by the eProtocol-insulin electronic support system. eProtocol-insulin provided an individual recommendation for each dose adjustment for each patient based on a validated algorithm. Glucose concentrations were checked by point-of-care (Accu-chek) testing of capillary blood every 1 to 4 hours (as recommended by eProtocol-insulin) unless the subject was hypoglycemic (<55 mg/dL), in which case the hypoglycemia protocol of 15-minute checks was initiated. A glucose and potassium infusion including 1 L D5NS with 20 mEq potassium was delivered at a

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**Figure 1.** The diagram demonstrates the Consolidated Standards of Reporting Trials (CONSORT) style patient enrollment flow diagram.
constant rate of 100 mL/hr during periods of insulin infusion but not if insulin infusion was stopped. In addition, meal insulin (subcutaneous Humalog 1 U/15 g carbohydrate) was provided with each meal in the insulin infusion groups. Meals were specified (grams of carbohydrate and protein) by nutrition teams and those who were cleared to eat were fed orally. Tube feeds were allowed per standard care in those NPO (nothing by mouth). The target glucose concentration for the loose control group was prespecified as 70 mg/dL to 200 mg/dL and for tight control was 70 mg/dL to 110 mg/dL. All patients received investigational treatment for 5 days or until discharge, whichever came first.

Standardized stroke care was provided across sites as recommended by the American Heart Association/American Stroke Association stroke guidelines. Additionally, fluid status and electrolyte status were closely monitored in the patients receiving insulin infusion.

Outcomes

The primary outcomes were safety, as determined by hypoglycemia (blood glucose <55 mg/dL), symptomatic hypoglycemia, and feasibility as determined by in-target success at 24 hours. Symptomatic hypoglycemia was determined using a standardized symptom questionnaire of patient symptoms if the glucose fell <55 mg/dL. Patients unable to communicate were assessed for physiological signs and, if present, were assigned symptomatic status. Patients were evaluated for safety throughout the treatment period but were evaluated for feasibility at 24 hours. For purposes of calculating sample size, feasibility was defined as having 2 of 3 glucose concentrations closest to 24 hours within the target range. Further analyses assessed the glucose profiles by treatment group over the first 24 hours and the proportion of time on treatment that the patient’s glucose concentrations were in the target range.

Additional feasibility information included patient enrollment success, duration of treatment, and rate of acceptance of eProtocol-insulin recommendations.

Blinded follow-up evaluations for clinical outcomes occurred at 6 weeks (phone) and 3 months (in person). Two prespecified subgroup studies were conducted and included a continuous glucose monitoring study and a matrix metalloproteinase study, both of which will be described elsewhere.

Safety

An independent safety monitor (B.M.K.) reviewed and adjudicated all adverse events in a blinded fashion for the relationship to investigational treatment. A National Institutes of Health–National Institute of Neurological Diseases and Stroke-appointed Data Safety and Monitoring Board consisting of 2 neurologists, an endocrinologist, and a statistician oversaw the conduct and safety of the trial.

Statistical Analysis

Using the method of Blackwelder, we determined that a sample of 24 observations per group would provide 90% power for declaring the treatments not equivalent with a 16% hypoglycemic rate in the treated group assuming a 1% rate in the control group. Type I error was 2.5% to allow for both loose and tight control rates to be compared with control. We allowed for a 10% withdrawal rate.

Feasibility for the loose and tight control groups was defined as having at least 19 of the 24 patients brought into target within 24 hours. An exploratory time in target analysis for the first 24 hours was also conducted.

Additionally, an exploratory efficacy analysis was completed exploring the unadjusted and adjusted modified Rankin Scale. A post hoc analysis examining the subgroup of patients that resembled the Treatment of Hyperglycemic In Stroke Trial (THIS) patients was conducted and included only those patients with National Institutes of Health Stroke Scale score of 3 to 22 and enrollment glucose of ≥150 mg/dL. A responder analysis that defines favorable outcome based on severity of baseline National Institutes of Health Stroke Scale score was conducted as a post hoc analysis as well. Adjusted analyses included adjustment for predicted probability of outcome; glucose concentration, and tissue plasminogen activator treatment.

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of All Enrolled Patients (n=74)</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
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<tr>
<td>Median age, years (IQR)</td>
</tr>
<tr>
<td>Men, N (%)</td>
</tr>
<tr>
<td>Median NIHSS (IQR)</td>
</tr>
<tr>
<td>Diabetes mellitus, N (%)</td>
</tr>
<tr>
<td>Treatment with intravenous recombinant tissue plasminogen activator, N (%)</td>
</tr>
<tr>
<td>Lacunar stroke subtype, N (%)</td>
</tr>
<tr>
<td>Median blood glucose, mg/dL</td>
</tr>
<tr>
<td>Black race, N (%)</td>
</tr>
<tr>
<td>Median hours to randomization (IQR)</td>
</tr>
</tbody>
</table>

Diabetes mellitus defined as a known history of diabetes before enrollment in the trial. IQR indicates interquartile range.

Results

Study enrollment occurred between May 20, 2006, and November 26, 2007. A total of 653 patients were screened and 74 subjects were enrolled. Three reasons for ineligibility (glucose level, not stroke, time) accounted for 85% of the 579 exclusions (Figure 1). Twenty-five patients were randomized to control treatment, 25 to loose control therapy, and 24 to tight control therapy. One subject from loose control and one from tight control were discharged before the primary safety and feasibility outcome assessments. Both of those patients provided 3-month efficacy outcome data. One subject in usual care was lost to follow-up (incarcerated) and no 3-month data were available. Enrollment occurred slightly ahead of schedule as demonstrated in Supplemental Figure I (available at http://stroke.ahajournals.org). All subjects received their assigned treatment and were analyzed in the treatment group to which they were assigned.

A total of 38 patients were enrolled at University of Virginia and 36 at the Medical College of Georgia. The baseline characteristics of the patients are shown in Table 1.

Primary Outcome Results

The tight control group had a 30% rate of at least one hypoglycemic event, whereas the usual care group and the loose control group each had a rate of 4% (P=0.05 for tight versus control, Fisher exact test). The single subject in the trial that had symptomatic hypoglycemia was in the loose control group.

The other primary outcome was feasibility of glucose control. The median glucose concentrations for the entire treatment period were 151, 151, and 111 mg/dL for usual care, loose control, and tight control groups, respectively. Figure 2 demonstrates how glucose concentrations changed over the first 24-hour period. Overall, there was a 97% adherence to the eProtocol-insulin recommendations for the 2 insulin infusion...
groups. Additionally, our trial demonstrated that in the usual care group, 88% received subcutaneous insulin as standard care treatment.

Of the 23 patients assessed for feasibility in the tight control group, 44% (95% CI, 23% to 66%) met the prespecified feasibility criterion of being in target at 24 hours. Significantly greater feasibility ($P < 0.001$, Fisher exact test) was observed in the loose control group, in which 92% (95% CI, 73% to 99%) of the 24 patients were in target at 24 hours.

A secondary analysis was conducted to assess the percentage of time in the first 24 hours that patients’ glucose levels were in the treatment-specific target range. In the loose control group, the median time in range was 90%; for the tight control group, the median time in range was 44%. In a post hoc analysis of the 70- to 130-mg/dL range used in the THIS trial, the median time in target was 64% for the tight control group.

Additional feasibility data included that 58% of GRASP patients were enrolled within 12 hours of symptom onset and 98% were started on therapy within 2 hours of established eligibility. The median time on the protocol was 75 hours and standard care patient discharge was the primary reason for early discontinuation.

**Safety**

Table 2 lists the frequencies of death and serious adverse events in the 3 groups. A total of 10 patients were dead at 3 months. The loose control group had a significantly greater proportion of deaths (25%) than the usual care group (4%);
Table 2. Serious Adverse Events

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Usual Care (N=25)</td>
</tr>
<tr>
<td>None</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Fatal</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

χ², P=0.29.

NIHSS indicates National Institutes of Health Stroke Scale.

Exploratory Efficacy
This pilot trial of safety and feasibility was not designed or powered to assess efficacy. None of the comparisons between treatment groups were statistically significant, and the efficacy analysis was purely exploratory. The unadjusted outcomes are shown in Table 3. Adjustment for predicted probability of outcome and glucose level did not substantially change the estimate of treatment effect (Figure 3). The analysis using the subgroup of patients with National Institutes of Health Stroke Scale of 3 to 22 and baseline glucose of ≥150 mg/dL (to resemble the THIS trial) demonstrated a larger odds of favorable outcome in the tight control group but not in the loose control group. Additionally, a responder analysis of the same subgroup demonstrated an 18% favorable outcome in the control group and a 40%

Table 3. Functional Clinical Outcomes at 3 Months in the GRASP Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Usual Care (N=24)</th>
<th>Loose Control (N=25)</th>
<th>Tight Control (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1, N (%)</td>
<td>8 (33%)</td>
<td>7 (25%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>Barthe Index 95–100, N (%)</td>
<td>12 (50%)</td>
<td>15 (40%)</td>
<td>13 (54%)</td>
</tr>
<tr>
<td>NIHSS ≥1, N (%)</td>
<td>7/22 (32%)</td>
<td>5/21 (24%)</td>
<td>6/23 (26%)</td>
</tr>
<tr>
<td>SIS score (±SD) (mean of 8 domains)</td>
<td>71.7 (20.4)</td>
<td>66.2 (25.5)</td>
<td>68.7 (19.1)</td>
</tr>
<tr>
<td>Death, N (%)</td>
<td>1 (4%)</td>
<td>6 (24%)</td>
<td>3 (13%)</td>
</tr>
</tbody>
</table>

*Two patients in the usual care group, 4 in the loose control group, and 3 in the tight control group were evaluated only by phone at 3 months.

NIHSS indicates National Institutes of Health Stroke Scale; SIS, Stroke Impact Scale. None of these comparisons are statistically different.

Figure 3. Unadjusted and adjusted odds of favorable outcome by modified Rankin Scale (0, 1) at 3 months in the loose control group compared with usual care and the tight control group compared with usual care. The null line (0) reflects the usual care group. THIS is the Treatment of Hyperglycemia in Ischemic Stroke trial and the adjusted analysis for THIS included the subgroup that resembles the THIS trial patients.

The most commonly reported serious adverse events included neurosensory, stroke extension or new stroke, congestive heart failure, pneumonia/pneumonitis, brain edema, and cellulitis. Of these, one was definitely related (congestive heart failure) and 4 were probably related (one congestive heart failure, 3 cellulitis [in the same patient]) to treatment. No safety issues occurred related to treatment with tissue plasminogen activator in combination with the intervention.

Discussion
These data demonstrate the safety and feasibility of glucose concentration control in an acute ischemic stroke population using insulin infusion. Only a single symptomatic hypoglycemia event occurred in the insulin infusion groups and none occurred in the tight control group, although there was a 30% asymptomatic event rate. The loose control group had similar glucose concentrations and the same rate of overall hypoglycemic events as the control group. These data suggest no benefit to a loose control approach using insulin infusion therapy because subcutaneous insulin therapy is safer, less resource-intensive, and produced nearly identical glucose concentration control results. Although a typical tight control patient spent only 44% of the first 24 hours in target, this includes the initiation time. Additionally, when the post hoc analysis of the 70 to 130-mg/dL target was assessed, a typical subject spent 64% of the first 24 hours in target, an acceptable rate for a tight control protocol.

In this trial, patients were enrolled successfully, randomized rapidly, received their appropriate treatment, there was excellent adherence to the eProtocol-insulin recommendations, and glucose concentration levels were appropriately discriminated between the control group and the tight control group. Although any comments on efficacy are not warranted based on these data, this trial has informed future trials on the control group rates of favorable outcome as well as the population most likely to benefit from the treatment. The post hoc analysis of the population of patients constructed to resemble the THIS trial17 suggested that a more narrow population of hyperglycemic diabetics with moderate to severe strokes may benefit most from this intervention.

Another finding that informs future trial design is demonstrated by the success of our stratification by predicted proba-
bility of outcome. This predicted probability included 6 major risk predictors, which could not have been individually stratified or balanced by randomization in a small middle-phase trial. Stratifying by this predicted probability allowed us to balance risk across treatment groups despite a small sample. These data can now be added to the data from the other glucose control trials,17,20–22 which have provided valuable information to guide future trials. The THIS trial, consistent with our data, suggest potential benefit of aggressive glucose regulation in a hyperglycemic diabetic population with moderate to severe strokes. The UK Glucose Insulin in Stroke Trial (GIST-UK) trial,20 Kriessel trial,21 and Walters trial22 all support excluding nondiabetics from such a trial because they tend to self-correct and enter the target range without intervention.

Our study has limitations. It was powered to assess safety and feasibility, not efficacy, and the encouraging results should be interpreted with extreme caution. Our study design allowed the control patients to be on usual care stroke wards, whereas most of the insulin infusion patients were in intensive care units or neurological stepdown units. This differential care may have impacted the outcomes of patients, the rates of reported serious adverse events, and may have confounded our results. In addition, because eProtocol-insulin was used in the insulin infusion groups and not in the control group, the frequency of glucose checks was increased in these 2 groups relative to the control and again may have confounded results. If this confounding effect were present, we would have expected benefit in both insulin infusion treatment groups. The lack of suggested benefit in the loose control group, but a hint of suggested benefit in the tight group, argues against this possibility. Finally, we recognize that this patient population was acquired from only 2 sites so larger sampling will be necessary to assess the generalizability of these results.

Overall, this middle-phase trial has provided information to inform future trials on safety, feasibility, target range (“dose”), duration of treatment, time to treatment, the community-accepted usual care, safety with tissue plasminogen activator, expected lost to follow-up rates, and the population most likely to respond to treatment. These data are critically important to support the design of future trials, which are supported by current American Heart Association/American Stroke Association guidelines. An appropriately powered Phase III trial of glucose concentration control in patients with acute ischemic stroke is warranted.

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Disclosures
None.

References


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