Glucose Potassium Insulin Infusions in the Treatment of Acute Stroke Patients With Mild to Moderate Hyperglycemia

The Glucose Insulin in Stroke Trial (GIST)

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Background and Purpose—Hyperglycemia following acute stroke is strongly associated with subsequent mortality and impaired neurological recovery, but it is unknown whether maintenance of euglycemia in the acute phase improves prognosis. Furthermore, the safety of such intervention is not established.

Methods—In an explanatory, randomized, controlled trial to test safety, 53 acute (within 24 hours of ictus) stroke patients with mild to moderate hyperglycemia (plasma glucose between 7.0 and 17.0 mmol/L) were randomized to receive either a 24-hour infusion of 0.9% (154 mmol/L) saline or a glucose potassium insulin (GKI) infusion at 100 mL/h. The GKI consisted of 16 U human soluble insulin and 20 mmol potassium chloride in 500 mL 10% glucose. Blood glucose was measured every 2 hours with Boehringer Mannheim Glycaemie test strips, pulse and blood pressure were measured every 4 hours, and plasma glucose samples were taken every 8 hours. Insulin concentration in the GKI was altered according to BM glucose values.

Results—There were no statistically significant differences between the 2 groups at baseline. Twenty-five patients received GKI, 1 of whom required intravenous glucose for symptomatic hypoglycemia. Plasma glucose levels were nonsignificantly lower in the GKI group throughout the infusion period. Four-week mortality in the GKI group was 7 (28%), compared with 8 (32%) in the control group.

Conclusions—GKI infusions can be safely administered to acute stroke patients with mild to moderate hyperglycemia producing a physiological but attenuated glucose response to acute stroke, the effectiveness of which remains to be elucidated. (Stroke. 1999;30:793-799.)

Key Words: clinical trials ■ hyperglycemia ■ insulin ■ stroke

Epidemiological studies have consistently shown that diabetes mellitus (DM) increases the risk of stroke by approximately 2- to 3-fold. The prevalence of previously diagnosed DM in patients with acute stroke varies from 8% to 20%, and an additional 5% to 28% of patients may have unrecognized DM or impaired glucose tolerance (IGT). In addition, between 10% and 20% of patients have hyperglycemia at presentation with a normal glycosylated hemoglobin (HbA1c) concentration, as a consequence of the early hormonal response to cerebral ischemia. Therefore, depending on thresholds and definitions, between 20% and 50% of acute stroke patients have been shown to have hyperglycemia at presentation. Studies in animal models of permanent focal cerebral ischemia have shown that hyperglycemia either reduces infarct size, increases infarct size, or has no effect. However, most, though not all, clinical studies in humans have revealed a significant relationship between hyperglycemia and poor outcome after stroke in terms of mortality and neurological recovery. Some studies have suggested that the detrimental effect of hyperglycemia in acute stroke is more pronounced in patients with DM and that hyperglycemia may actually be beneficial in acute stroke patients without DM, depending on the presence or absence of collateral blood supply to the ischemia area of cerebral tissue.

Until recently, most authorities described hyperglycemia in stroke as a secondary phenomenon resulting from either the stress response to cerebral ischemia or underlying abnormal carbohydrate metabolism (IGT or DM). It has been argued that those with stress hyperglycemia have a poor prognosis conferred by the severity of the initial lesion, whereas those with DM have a poor prognosis because of the natural history of stroke in diabetic patients, and therefore active intervention to normalize mild to moderate elevations of blood glucose is often not instituted. However, hyperglycemia is known to be a risk factor for poor outcome following stroke irrespec-
tive of diabetic status, although a definitive statement on causality cannot be made in the absence of randomized controlled trial data. In addition, active intervention to normalize blood glucose levels in patients with acute myocardial infarction (MI) and hyperglycemia has become standard practice following the DIGAMI study. This randomized controlled trial demonstrated a 29% relative mortality reduction (18.6% versus 26%) in glucose/insulin-treated patients with acute MI and admission hyperglycemia of ≥11 mmol/L when compared with patients who received no intervention to lower plasma glucose levels.17,18

In view of these recent findings, there is now overwhelming evidence to support the concept of hyperglycemia-induced cerebral damage in the acute phase of stroke, irrespective of whether the patient has previously diagnosed diabetes, unrecognized diabetes, impaired glucose tolerance, or “stress hyperglycemia,” as previously categorized by our group.8 To date, there have been no published randomized controlled clinical trials investigating the hypothesis that normalization of plasma glucose levels in the acute phase of stroke improves clinical outcome. The Glucose Insulin in Stroke Trial (GIST) is a randomized controlled trial designed to determine whether glucose/insulin-induced and -maintained euglycemia in acute stroke patients with mild to moderate hyperglycemia can improve outcome after stroke. In this pilot study phase of GIST, we sought to define the methodology necessary to undertake a large, multicenter, randomized controlled trial of GKI therapy in acute stroke and, in particular, to determine the safety and practicality of GKI treatment with bedside monitoring in acute stroke. In addition, we aimed to describe further the plasma glucose response to acute stroke in GKI-treated patients and controls.

**Subjects and Methods**

The study was undertaken in a district general hospital (Sunderland Royal Hospital) serving a catchment population of 300 000 residents in the northeast section of England. All patients aged >18 years admitted to a centralized admissions unit with a clinical diagnosis of acute (within 24 hours of onset) stroke were screened to determine plasma glucose (Instrumentation Laboratories glucose oxidase IL-Glucose kit on a Monarch analyzer) and whole-blood glucose (BM Glycaemie test strip, Boehringer Mannheim). Stroke was defined as an acute disturbance of cerebral function of presumed vascular origin causing a neurological deficit lasting >24 hours or death within 24 hours.19 Patients presenting after 24 hours or with heart failure (New York Heart Association grades 3 or 4), renal failure (creatinine level >200 µmol/L), anemia (Hb <9 g/dL), radiological evidence of pneumonia, coma (Glasgow Coma Scale motor subscore of <4), previous disabling stroke (Modified Rankin score of >3), dementia, isolated posterior circulation syndromes without physical disability, pure language disorders, previously diagnosed insulin-treated DM (type 1 or 2), or subarachnoid hemorrhage were excluded. Consecutive patients satisfying these criteria and the definition of mild to moderate hyperglycemia (plasma glucose level of 7.0 mmol/L to 17.0 mmol/L) were randomized to trial treatment with GKI or 154 mmol/L (“normal”) saline (control) after informed consent was received from the patient or, where language problems existed, informed assent was received from the relative/caregiver. Randomization was undertaken by use of random number tables, with treatment allocations to GKI or control entered in sealed envelopes labeled with consecutive trial numbers by the trial statistician.

Blood samples for glucose, electrolyte, urea, creatinine, and full blood count were taken before randomization, and further samples for liver function, total blood calcium, erythrocyte sedimentation rate and HbA1c were taken as soon as practicable after randomization but always within 24 hours of admission. Plasma cortisol levels were determined at 9 AM on the morning after admission, and CT of the head was taken after randomization. Treatment consisted of a combined infusate of 500 mL 10% dextrose with 16 U human soluble insulin (Actrapid; Novo Nordisk) and 20 mmol potassium chloride (KCl); control treatment was 500 mL 154 mmol/L saline. Treatment was administered through a peripheral vein in the nonparetic arm at a fixed rate of 100 mL/h via a metered infusion device.

The trial treatments were commenced by general ward nursing staff, who also monitored and maintained the infusions over the next 24 hours, following specific, preprinted protocols. Monitoring was identical for each infusion. Blood pressure and pulse were taken at 4-hour intervals with a standard mercury sphygmomanometer and plasma glucose samples at 8-hour intervals. Monitoring through use of standard BM Glycaemie strips was at 2-hour intervals, with the aim of keeping glucose values between 4 and 7 mmol/L in the GKI group. In this group, test strip estimations of whole-blood glucose were made at the start of the infusion (time zero) and at 1 and 2 hours. When the value was maintained between 4 and 7 mmol/L, subsequent monitoring continued at 2-hour intervals. When the test strip value was outside this target range, the infusion was changed to one with 4 U less insulin if the glucose level was ≤4 mmol/L, or 4 U more insulin if the value was ≥7 mmol/L. Once the GKI infusion was changed, test strip monitoring continued hourly until the value was again stable within the target range, at which point bedside values were checked every 2 hours. If the test strip value dropped to ≤4 mmol/L, the GKI infusion was stopped and glucose levels checked every 15 minutes until the value was ≥4 mmol/L. If the test strip value failed to rise to this level after 30 minutes or if the patient had symptomatic hypoglycemia, 10 mL 50% glucose was administered intravenously. Once the test strip value was ≥4 mmol/L, the GKI infusion was changed as described above and restarted. No action was taken on the bedside values in the control group unless it rose to >17 mmol/L, in which case intervention with the GKI regime was initiated.

The trial infusate continued for 24 hours, excluding stoppages, with a total volume of 2400 mL in every case. Patients were allowed to eat and drink as clinically appropriate while on either trial infusion. After the initial 24-hour infusion period, patients were maintained on the GKI, on saline, or on no fluids as clinical need dictated and were prescribed insulin according to clinical need. Further venous blood samples were taken at 24 and 48 hours for urea, electrolytes, and plasma glucose level. All antihypertensive therapy was discontinued on admission, in line with current local treatment protocols.

Clinical assessments were undertaken by 1 of 2 observers at randomization, at 24 hours, 48 hours, 7 days, and 4 weeks. Neurological impairment was assessed with the European Stroke Scale (ESS) and function with the Nottingham Extended Activities of Daily Living and 20-point Barthel Index. For this pilot study, clinical assessments were not blinded to the treatment allocation for practical reasons. Data were collected on standard pro formas and analyzed using SPSS version 7.5 for Windows 95 (SPSS Inc). Analyses of continuous variables within and between groups were undertaken using the Wilcoxon rank sum and Mann Whitney U tests, respectively, while categorical variables were analyzed using the χ² test. All outcomes were analyzed on an intention-to-treat basis. The study was granted local ethical committee approval before commencement, and all patients (or a first-degree relative when communication problems existed) gave informed consent or informed assent before randomization.

**Results**

Over a 7-month period, 245 consecutively admitted acute stroke patients were screened, of whom 33 (13.5%) had a recognized history of DM. Admission plasma glucose levels of ≥7.0 mmol/L were found in 115 (47%). Of these patients, 62 (25%) were ineligible for randomization, with the main exclusion criteria being presentation >24 hours
from ictus (n=24, 9.8%), coma (n=16, 6.5%), pneumonia (n=10, 4%), previously diagnosed insulin-treated type 1 or 2 DM (n=3, 1.2%), admission plasma glucose $>17.0$ mmol/L (n=3, 1.2%), previous disabling stroke (n=3, 1.2%), and dementia (n=3, 1.2%). Informed consent or informed assent was gained from all eligible patients or their relatives, and a total of 53 patients (21.6%) were randomized: 28 to active treatment with GKI and 25 to control treatment. Three patients were subsequently withdrawn from the trial as protocol violations; the first and second had a cerebral tumor and a subdural hematoma, respectively, on postrandomization head CT, and the third was incorrectly randomized in view of the presence of a right lower lobe pneumonia on admission that was confirmed on postrandomization chest x-ray. Fifty patients are therefore included in this analysis, with 25 in each treatment group. Follow-up at 4 weeks was complete. Comparison of basic demographic data and hematologic and biochemical variables revealed no significant differences between the 2 treatment groups at baseline (Table 1).

Of the patients in the GKI group, 21 (84%) received 2400 mL infusate compared with 24 (96%) in the control group. During the infusion period, 16 (64%) of the GKI group were kept nil by mouth because of impaired swallowing, compared with 14 (56%) of the control group. Tube feeding was not instituted in any of the patients during the infusion period. Two of the GKI group (8%) and 1 of the control group (4%) died within 72 hours of the commencement of infusion. Two (8%) of the control group, both of whom had previously diagnosed DM, required treatment with the GKI regime after 12 and 16 hours of saline therapy, respectively, because of BM values $>17$ mmol/L. Neither of these patients became hypoglycemic on the GKI regime. There were no cardiovascular adverse events (acute myocardial infarction, acute left ventricular failure, or recurrent stroke) during the infusion period in either group. The concentration of insulin in the GKI had to be changed at least once in 23 of the GKI group (92%); of these patients, the mean number of times the GKI required an alteration in insulin concentration was 2.5 (range, 1 to 6 times). The GKI protocol was not followed accurately in the first 2 GKI-treated patients. These 2 patients did not show any lowering of either plasma glucose values or BM test strip values, and hence their BM test strip values were above the target range throughout the infusion period. However, the protocol was followed accurately in the subsequent 23 GKI-treated patients. The number of patients outside the target range of 4 to 7 mmol/L on BM test strip monitoring at
TABLE 2. Mean Plasma Glucose and BM Test Strip Values in the GKI Group and the Number of Patients Above the Target Range of 4 to 7 mmol/L on BM Test Strip

<table>
<thead>
<tr>
<th>Time From Start of Infusion, h</th>
<th>GKI Group</th>
<th>Patients Above Target Range of 4–7 mmol/L, n (%)</th>
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<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>0</td>
<td>9.1 (2.6)</td>
<td>8.9 (2.3)</td>
</tr>
<tr>
<td>2</td>
<td>7.3 (2.1)</td>
<td>6.8 (2.5)</td>
</tr>
<tr>
<td>4</td>
<td>7.1 (3.2)</td>
<td>6.6 (3.0)</td>
</tr>
<tr>
<td>8</td>
<td>6.4 (3.2)</td>
<td>6.6 (3.0)</td>
</tr>
<tr>
<td>10</td>
<td>6.5 (2.9)</td>
<td>6.6 (3.1)</td>
</tr>
<tr>
<td>12</td>
<td>6.6 (3.1)</td>
<td>6.6 (3.1)</td>
</tr>
<tr>
<td>14</td>
<td>6.1 (3.2)</td>
<td>6.1 (2.0)</td>
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<tr>
<td>16</td>
<td>6.5 (2.2)</td>
<td>6.1 (2.0)</td>
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<tr>
<td>18</td>
<td>7.0 (1.7)</td>
<td>6.9 (3.1)</td>
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<tr>
<td>20</td>
<td>6.9 (3.1)</td>
<td>6.9 (2.2)</td>
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<tr>
<td>22</td>
<td>6.9 (2.2)</td>
<td>6.6 (2.5)</td>
</tr>
<tr>
<td>24</td>
<td>6.9 (3.1)</td>
<td>6.6 (2.5)</td>
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Comparison between plasma glucose and BM test strip values at each 8 hour plasma glucose sampling point (Mann-Whitney U test).

Figure 1. Mean 48-hour plasma glucose profiles in both treatment groups.

Discussion

Despite numerous previous clinical trials investigating a wide variety of potential acute stroke therapies, there is still no simple, safe, and effective medical treatment for the vast majority of patients with acute stroke. The number of patients who are likely to benefit from highly specialized interventions such as thrombolysis is likely to remain small, and although clinical trials are continuing to investigate neuroprotective therapies, results from previous studies have been almost uniformly disappointing, despite high expectations. The evidence for hyperglycemia-induced and -potentiated damage to neurons within the ischemic penumbra in the acute phase is becoming overwhelming, yet the clinical benefit of intervention to lower plasma glucose levels remains unknown. This benefit can only be adequately investigated within the framework of a randomized controlled clinical trial such as GIST. Ideally, the trial would be of double-blind design to eliminate observer bias, but because of the potential dangers of hypoglycemia in acute stroke, such a design is both impractical and clinically unsafe. To minimize observer bias, all long-term outcome assessments in the main trial would be undertaken by an independent observer blinded to the treatment regimes.

One of the major objectives of this study was to establish the safety of insulin treatment in mild to moderate hyperglycemia during the acute phase of stroke, at a time when up to 30% of stroke patients are unable to report symptoms because of communication difficulties. In deciding our eligibility criteria, we excluded patients in whom a poor prognosis was predetermined by the presence of coma and those in whom administration of large volumes of intravenous fluid could be clinically unsafe. Similarly, patients in whom active infection was present.

24-hour trial infusion period, including the 2 control patients with DM who received GKI therapy during the infusion period.

When the blood pressure profiles over the treatment period were examined, treatment with GKI was associated with a significantly lower systolic blood pressure at 4, 12, and 16 hours, although baseline systolic blood pressure values were not well matched between treatment groups ($P<0.05$ for 4-,12-, and 16-hour time points; Mann-Whitney $U$ test; Figure 2). In addition, GKI was associated with a significant reduction in pulse pressure (systolic blood pressure – diastolic blood pressure) between admission and 24 hours ($P=0.037$, Mann Whitney $U$ test). There were no significant changes in electrolyte, urea, or creatinine concentrations at 24 or 48 hours when compared with admission values in the 2 groups.

In the GKI group, 7 patients (28%) had died at 4 weeks, none of whom had previously diagnosed DM, compared with 8 patients (32%) in the control group, 1 of whom had previously diagnosed DM. (Table 3). There were no significant differences between treatment groups in mean total ESS or Barthel Index scores at each assessment interval. However, a decline in mean total ESS scores was observed in the control group in the first 48 hours, unlike in GKI patients, where an improvement was observed.
may have an abnormal stress response to stroke, and these subjects were also excluded. Excluding patients with coma also enabled us to determine the likely side-effect profile of treatment, in particular the presence of symptomatic hypoglycemia. Another important consideration to be clarified for a future randomized controlled trial was the constituent components of the GKI infusion at a time when the acute phase response may confer additional peripheral insulin resistance. The DIGAMI study demonstrated that glucose/insulin infusions are safe to use in hyperglycemic patients with myocardial infarction, because symptoms of hypoglycemia were relatively rare and generally mild. We have confirmed these findings in a population of hyperglycemic acute stroke patients; only 1 patient had definite symptomatic hypoglycemia, and none of the 8-hour plasma glucose levels in the GKI-treated group were <2.2 mmol/L. In addition, there was no excess of early cardiovascular adverse events or deaths in the treatment group, providing further evidence for the safety of the GKI infusion in the acute phase.

The second objective the study sought to address was whether the 2-hour interval for monitoring and maintenance of the GKI infusion was a significant problem for nursing staff on emergency admissions wards that may routinely accept other medical emergencies. Thus, GIST was designed to be as pragmatic as possible for both nursing staff and patients in a nonintensive care ward environment. Patients were allowed to eat and drink as normal, if safe to do so, during the trial infusion period to minimize conflict with current hydration and nutritional strategies. A 24-hour infusion period was chosen to reflect existing evidence that neurons in the ischemic penumbra show evidence of cellular activity on positron emission tomography (PET) and MRI spectroscopy scanning up to and potentially beyond this period. The duration of the infusion was balanced against the practicalities for nursing staff of maintaining such an infusion for >24 hours, the issue of safety in patients where the acute stress response is dissipating, and the need for early mobilization and supported nutrition of stroke patients. Although 92% of the GKI infusions were changed at least once during the infusion period, this was not a significant drain on nursing staff time, and it is clear from the plasma glucose profiles that hypoglycemia is not encountered with the doses of insulin used in the protocol. The learning curve for GKI therapy was short, with only the first 2 patients showing

<table>
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<tr>
<th>TABLE 3. Clinical Assessments and Outcomes</th>
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<tr>
<td>GKI Group</td>
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<tr>
<td>Mean (SD) Barthel Index score at 24 h, max. 20</td>
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<tr>
<td>Mean (SD) admission Glasgow Coma Scale score, max. 15</td>
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<tr>
<td>Mean (SD) admission total ESS score, max. 100</td>
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<tr>
<td>Mean (SD) total ESS score at 24 h</td>
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<tr>
<td>Mean (SD) total ESS score at 48 h</td>
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<tr>
<td>Mean (SD) total ESS score at 7 d</td>
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<tr>
<td>Mean (SD) total ESS score at 4 wk</td>
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<tr>
<td>Mean (SD) Barthel Index score at 4 wk</td>
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<tr>
<td>Mortality at 4 wk, n (%)</td>
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</table>

Max indicates maximum.
nonsignificant lowering of plasma glucose levels, suggesting appropriate caution at the beginning of the study.

The third objective was to describe the physiological plasma glucose response to acute stroke. This is clearly shown by the control group mean plasma glucose profile as a fall in plasma glucose level over the first 8 hours followed by a flattening of the curve over the next 40 hours. In the GKI group the plasma glucose profile was lowered by the administration of insulin but closely followed the physiological curve and converged with it after the 24-hour treatment period across all previously described categories of stroke patient. Interestingly, we have also demonstrated a significant reduction in systolic blood pressure in the GKI-treated group, although the mean baseline systolic blood pressure was nonsignificantly higher in the control group. The physiological mechanism by which this may occur is unclear. Short-term insulin infusion, under euglycemic clamp conditions, has been shown to significantly increase plasma renin activity and serum angiotensin II concentrations and to reduce serum aldosterone levels, because of insulin’s hypokalemic effect, through stimulation of the sodium/potassium transmembrane ion pump. Insulin infusion has also been shown to induce increased norepinephrine secretion in normal men. All of these changes would be expected to elevate blood pressure, although some workers have demonstrated a small fall in diastolic blood pressure following insulin infusion, possibly mediated by peripheral vasodilatation through increased sympathetic activity. Alternately, insulin may exert this effect centrally by increasing sympathetic activity. Insulin infusion, possibly mediated by peripheral vasodilation, lowers the plasma glucose level to within the normal range without significant risk of hypoglycemia, cardiovascular adverse events, or excess mortality at 4 weeks. The small numbers involved in this pilot study mean that an assessment of the clinical effectiveness of GKI therapy is impossible at this early stage. Therefore, the beneficial effects of this potential new treatment for hyperglycemic acute stroke patients remain to be elucidated through use of this stated methodology in the main GIST study.

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References


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