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Original Contributions

Poststroke Hyperglycemia

Natural History and Immediate Management

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Abstract

Background and Purpose—Poststroke hyperglycemia (PSH) is a frequent finding for which there is currently no evidence to justify routine treatment. The United Kingdom Glucose Insulin in Stroke Trial (GIST-UK) is the only trial of glucose modulation in acute stroke from which evidence can be derived for the immediate management of PSH. Using safety-monitoring data from the trial we aimed to describe the immediate recovery of PSH in treated and control patients, thus providing evidence for the use of glucose/potassium/insulin (GKI) infusions as a means of maintaining euglycemia.

Methods—GIST-UK is a multicenter randomized controlled trial of GKI or saline infusions in acute stroke patients presenting with mild to moderate hyperglycemia (admission plasma glucose, 6.0 to 17 mmol). We analyzed the capillary BM and plasma glucose values in the 2 treatment groups to describe the recovery of PSH and the effectiveness of the GIST treatment regimen in maintaining euglycemia.

Results—The majority of patients have only moderate PSH (mean plasma glucose, 8.37±SD 2.13). Without specific intervention, mean plasma glucose levels decline spontaneously. Treatment with the GIST GKI regimen rapidly achieved euglycemia at significantly lower levels than with saline hydration alone. Euglycemia was achieved with a median of 2 changes to the GKI regimen and a low risk of hypoglycemia.

Conclusions—GKI infusions as described in the GIST trial are a safe and effective means of correcting PSH and maintaining euglycemia in the acute phase of stroke. The clinical benefits of routine management of hyperglycemia remain to be determined.

Key Words: clinical trials • hyperglycemia • stroke • stroke management • stroke, acute

Introduction

There is accumulating evidence demonstrating the effectiveness of stroke unit care with benefits of reduced mortality, dependency, and institutionalization.¹ Recent studies not only have clarified the process of stroke unit care that is associated with such benefits but also provide evidence to suggest that factors such as early hydration and mobilization...
are important in distinguishing specialist from conventional care. While some stroke unit interventions are evidence based, there remains uncertainty regarding the management of physiological variables such as blood glucose, blood pressure, hypoxia, hydration, and temperature.

Several large clinical studies have now demonstrated a positive association between poststroke hyperglycemia (PSH) and poor outcome from stroke, greater mortality, and reduced functional recovery. What is unclear is to what extent PSH is a "normal" physiological response, or whether hyperglycemia per se increases cerebral damage in the acute phase. There are accumulating clinical data to suggest that much of this response is associated with impaired glucose metabolism, with the prevalence of previously unrecognized diabetes mellitus (DM) or impaired glucose tolerance preceding stroke as high as 42%. There are many potential mechanisms by which hyperglycemia can exert a harmful effect on cerebral tissue, and it is probable that an important relationship exists between hyperglycemia and stroke outcome. It remains to be determined whether lowering and maintaining normal glucose levels in the immediate aftermath of stroke can modify this outcome.

In the meantime, in order to consider how best to manage PSH, we require not only further information regarding the natural history of acute hyperglycemia in managed stroke care but also evidence for the effectiveness, safety, and practicability of routine intervention in acute stroke patients.

Subjects and Methods

The Glucose Insulin in Stroke Trial (GIST-UK) is a multicenter randomized controlled trial that seeks to determine whether outcome from acute stroke can be favorably influenced by glucose/potassium/insulin (GKI)–induced and -maintained euglycemia. Eligible subjects are adult acute stroke patients (cerebral infarction and primary intracerebral hemorrhage, CT proven before or after randomization) and presenting <24 hours from symptom onset with admission plasma glucose >6.0 mmol/L and <17 mmol/L. Patients presenting with coma, a history of insulin-requiring DM, anemia, renal failure, congestive heart failure, or significant preexisting disability are excluded. Treatment comprises either (1) continuous intravenous infusion of 10% dextrose plus 20 mmol potassium chloride with variable-dose soluble human Actrapid insulin (initial insulin 16 U) or (2) 0.9% normal saline (154 mmol/L sodium) at 100 mL/hour for 24 hours in both groups.

The objective of GKI treatment is to maintain capillary blood glucose between 4 to 7 mmol/L for the duration of the infusion, whereas in the control group, no specific intervention for hyperglycemia is made unless glucose rises >17 mmol/L or clinical conditions dictate.

Randomization is made on the basis of the admission plasma glucose level, following which capillary whole-blood glucose levels are monitored at the bedside using Boehringer-Mannheim (BM) glycemic test-strip monitoring. Monitoring is performed hourly for 2 hours then every 2 hours thereafter.
unless values are unstable, in which case they continue to be recorded hourly. Venous samples for plasma glucose are taken at 8, 16, and 24 hours from the time control or GKI treatment starts. Blood samples are taken for estimation of plasma urea and electrolytes on admission and after 24 hours of trial treatment.

Changes to the GKI regimen are made on the basis of a target capillary glucose range of 4 to 7 mmol/L. This equates with a plasma glucose range of 4.6 to 8.0 mmol/L, the upper limit of which is a threshold at which poor outcome has been described. A detailed algorithm for the GKI infusion is provided at ward level and standardized across all centers. The insulin component in the GKI is adjusted in increments of 4 U to maintain capillary glucose BM recordings in the range of 4 to 7 mmol/L. If BM readings are >7 mmol/L, the GKI is discarded and a replacement regimen containing 4 extra units started. The process is repeated if readings persist >7 mmol/L after 60 minutes. For the purpose of the GIST monitoring protocol, trial hypoglycemia was defined as a capillary glucose <4 mmol/L. Where BM readings are <4 mmol/L, the infusion is discontinued and BMs measured at 15-minute intervals until ≥4 mmol/L, at which point a replacement GKI containing 4 fewer units of insulin is started. If a patient has symptomatic hypoglycemia or the BM does not rise spontaneously to ≥4 mmol/L after 30 minutes, 10 mL of 50% glucose solution is administered intravenously before starting a replacement GKI with 4 fewer units of insulin.

Following the 24-hour trial treatment period there are many factors that may influence the subsequent management of stroke patients (clinical, ethical, nutritional), and subsequent management of blood glucose, nutrition, and intravenous fluids is at the supervising clinician’s discretion.

Compliance of collaborating centers with the trial protocol is determined by safety data comparing capillary glucose monitoring with plasma glucose values every 8 hours for the 24-hour treatment period. These data provide a unique insight into not only the natural history of glucose levels following acute stroke in patients treated with a standardized rehydration regimen but also the effectiveness of the GIST GKI regimen in maintaining euglycemia.

Statistical Methods
All data were recorded on patient-specific case record forms within randomizing centers and subjected to source data verification by the GIST-UK trial coordinators. Data were independently entered into the trial database and analyzed using SPSS for Windows version 10.1 and S-Plus version 6.1 (Professional). General linear models were used throughout, with the addition of confirmatory nonparametric testing where distributional tests approached statistical significance.

Results
The first 452 patients recruited to GIST-UK are reported in this article. Patients were recruited across 5 clinical centers. Mean age was 74.8 years (SD 9.9), and 241 (53.3%) were women. There was a history of type 2 DM in 69 (15.3%) patients. Overall, mean admission plasma glucose was 8.37
(SD 2.13) mmol/L, (median, 7.7; range, 6.0 to 16.6). Figure 1 shows the frequency distribution of admission plasma glucose in all patients. The majority of patients (81.3%) had admission plasma glucose values <10.0 mmol/L. After randomization, 221 (49%) patients received GKI, 231 (51%) patients saline. There were no significant differences between treatment groups for basic demographic variables (Table). The overall mean time from stroke symptom onset to start of treatment was 13.14 hours (SD=6.08; median, 13.0 hours; and range, 1.05 to 24.00 hours). There were no clinically significant changes in plasma sodium or potassium levels after GKI or saline infusion.

**Figure 1.** Frequency distribution of admission plasma glucose in all patients.

To describe the recovery of PSH, mean plasma glucose values for the 2 treatment groups were compared at each time interval throughout the 24-hour treatment period (Figure 2). The GKI group had a nonsignificantly higher mean admission plasma glucose level than the saline group (mean difference=-0.19). At 8 hours the difference crossed over with significantly lower mean plasma glucose in the GKI group (mean difference=0.58); at 16 hours this had risen to 0.86, while at 24 hours the difference was 0.61. A general linear model (analysis of covariance) was applied to adjust for the difference in admission glucose between the 2 groups. The adjusted differences between means were significant at each of the 3 intervals (P<0.01 throughout). Figure 2 shows the mean values for both groups.

**Figure 2.** Mean plasma glucose levels in the GKI and saline treatment groups. P values are for between-group analyses.
For both treatment groups, there were significant differences between mean glucose levels on admission and each of the subsequent intervals throughout the 24 hours, \( P < 0.001 \) throughout (repeated measures ANOVA). Within each treatment group none of the postadmission mean glucose levels were significantly different from the other intervals, ie, stable euglycemia was achieved.

Overall, mean plasma glucose levels declined in both treatment groups (Figure 2). For the saline group, mean plasma glucose values remained above the randomization threshold but within the therapeutic target of 4 to 7 mmol/L from 8 to 24 hours. For the GKI-treated patients, mean plasma glucose levels remained within therapeutic target from 8 hours to completion of the infusion (Figure 2).

**Adjustment of Insulin Dose and Frequency of Changes to GKI Regimen**

To achieve the monitoring targets, the overall median number of changes to the GKI infusion was 2 per patient. Figure 3 shows the frequency distribution of changes to the GKI regimen to correct both trial hyperglycemia (capillary glucose >7.0 mmol/L) and trial hypoglycemia (<4.0 mmol/L).

There were 20 (9%) cases of trial hypoglycemia (capillary glucose <4 mmol/L 30 minutes after discontinuation of GKI) who received intravenous dextrose.

**Capillary and Plasma Glucose Monitoring and Variation Between Centers**

When capillary glucose values were compared with their corresponding plasma glucose values, there was a statistically significant and moderate correlation at each time point for both GKI and saline.
groups (average correlation, $r=0.55$, $P<0.001$).

Patients were recruited to this cohort from 5 clinical centers across the United Kingdom. A comparison between centers showed no significant difference for mean plasma glucose values at each assessment interval.

**Control of Plasma Glucose in Patients With History of Diabetes Mellitus**

The total number of units of insulin administered during the 24-hour treatment period was determined from the infusion records for each patient. The mean number of units of insulin administered was significantly greater in patients with a history of DM (mean, 111.00 U; SD 32.48) compared with those with no history of DM (mean, 82.4; SD 25.38), $P<0.001$. Patients with DM required significantly more changes to their GKI regimen to correct a capillary glucose $>7$ mmol/L (mean, 4.2; SD 2.25) when compared with patients with no DM (mean, 2.3; SD 1.3), $P<0.001$. There was no significant difference in the number of times the GKI infusion was discontinued due to a capillary glucose level $<4$ mmol/L between patients with or without DM (mean number of discontinuations, 0.3 and 0.8, respectively).

**Discussion**

This study describes the natural history of PSH in patients treated with either a standardized hydration regimen or active euglycemic intervention. Although there is some evidence for an initial modest rise in glucose levels following acute stroke, this is most likely to occur in the first 6 hours, after which plasma glucose begins to fall as demonstrated by our data. Furthermore, while hyperglycemia may be a frequent finding, the majority of patients presenting within 24 hours of acute stroke have only moderate elevations in plasma glucose. This is an important observation since early studies described an association between hyperglycemia and poor outcome from stroke with a plasma glucose threshold of $>8$ mmol/L. Most recently, clinical data have demonstrated stroke severity and mortality rising with increasing glucose levels even in initially euglycemic patients and independent of stroke type or location. It seems probable that any association between glucose and stroke outcome extends across a range of glucose levels, and like blood pressure, no precise threshold exists above which increased risk is suddenly conferred.

National Clinical Guidelines (RCP) and a National Service Framework now direct the management of acute stroke in the United Kingdom. In the absence of evidence from randomized clinical trials, it is suggested that local guidelines are developed for the management of physiological variables. Such an approach has the potential to introduce considerable variations in acute stroke care, notwithstanding the possibility of minimizing benefit or even introducing unnecessary risk for unproven interventions. Furthermore, it is possible that the treatment benefit of any stroke-specific therapy may be minimized without appropriate management of these variables.

When managing PSH it is important to consider whether the objective is merely to seek biochemical
normality (euglycemia) or to attempt to confer an additional treatment benefit through the co-administration of insulin. Although insulin has been shown to be neuroprotective in both global and focal cerebral ischemia,\textsuperscript{15,16} the clinical benefits of euglycemia and/or insulin treatment after stroke have yet to be determined. In this study we have demonstrated that without specific intervention, plasma glucose levels fall spontaneously to nearly "normal" levels.

It is important that guidelines for the routine management of PSH address the potential risks of inducing hypoglycemia or potentiating hyperglycemia, from which additional harm may be conferred. The GIST GKI regimen rapidly achieved euglycemia in the majority of patients at significantly lower levels than would occur with saline hydration alone. Furthermore, this euglycemia was stable throughout the 24-hour treatment period and was not associated with wide fluctuations in mean glucose levels. In order to try and further minimize the potential adverse effects of hypoglycemia on cerebral metabolism,\textsuperscript{17} the GIST GKI regimen was specifically designed to reduce the incidence of true hypoglycemia with a trial hypoglycemia threshold of $<4$ mmol/L capillary whole blood equivalent to a plasma glucose of 4.6 mmol/L.

We found no significant difference in mean plasma glucose values between randomizing centers. All centers had a physician with a specific interest in stroke and the GKI regimen was delivered by a combination of the emergency admitting team and the host stroke unit team. Nursing staff undertook all capillary glucose monitoring and changes in the GKI insulin concentrations in accord with the trial protocol. Thus the GIST treatment regimen was safe, effective, and practicable across a range of UK hospitals.

The routine management of hyperglycemia after myocardial infarction is now accepted as standard practice, with clinical trial evidence demonstrating that treatment with a GKI infusion for $\geq 24$ hours followed by subcutaneous insulin 4 times daily for $\geq 3$ months is associated with significant mortality reductions up to 12 months after the acute event.\textsuperscript{18}

In acute stroke care, the approach to blood glucose has often been to observe, intervening only if hyperglycemia is increasing or if the patient’s clinical condition dictates that treatment is necessary. Indeed, in many instances, rising blood glucose and clinical decline may not necessarily result in therapeutic intervention in the absence of proven benefit.

When confronted with PSH, the attending physician needs to decide if such hyperglycemia should be treated, and how? The GIST GKI regimen is the only evidence-based approach from which we can describe "how" to manage PSH. For the more clinically relevant question, "Should PSH be routinely treated?", we now require outcome data from large randomized trials such as GIST-UK to direct practice.

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