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Considering hyperglycemia and thrombolysis in the stroke hyperglycemia insulin network effort (shine) trial

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Abstract

Hyperglycemia is associated with enhanced cortical toxicity and larger infarct volumes following focal cerebral ischemia. Initial blood glucose in acute ischemic stroke patients may also contribute to a differential response to thrombolysis (tPA) and affect risk of symptomatic intracerebral hemorrhage (sICH). The Stroke Hyperglycemia Insulin Network Effort (SHINE) study is a phase III single-blinded, randomized control trial comparing an intensive level of glucose control to standard of care glucose control in hyperglycemic stroke patients. In stratifying randomization by treatment with intravenous tPA, the SHINE trial offers a unique opportunity to evaluate an association between euglycemic control and outcomes from stroke thrombolysis in a prospective, comparative study. We hypothesize that normalization of blood glucose in the acute stroke setting may reduce risk of thrombolysis-induced sICH. With enrollment recently underway, the stratified results from the SHINE trial could substantially influence future treatment decisions for hyperglycemic stroke patients.

Keywords

stroke; hyperglycemia; glucose; thrombolysis; tPA; hemorrhage

Background

Of the more than 600,000 new ischemic strokes each year in the U.S., approximately 30–50% are hyperglycemic on admission, and this number is likely to grow.^{1,2} According to population data from the Greater Cincinnati/ Northern Kentucky Stroke Study, roughly 30% of incident strokes are diabetic and more likely to be young, African-American, and have additional cardiovascular risk factors than non-diabetics (Kissela Diabetes Care 2005).³ In both animal and human studies, hyperglycemia is associated with enhanced brain injury and worse outcomes following cerebral ischemia.^{4–12} Several early-phase clinical trials investigating treatment of hyperglycemia in ischemic stroke patients found intensive glucose control to be safe and suggested a potential clinical benefit in both diabetic and non-diabetic patients.^{13, 14} A single phase III study, the UK Glucose Insulin in Stroke Trial (GIST-UK) also demonstrated the safety of a glucose-insulin-potassium (GIK) infusion in acute ischemic stroke, but was stopped early with less than 50% enrollment and unable to demonstrate a treatment effect.¹⁵ A definitive phase III trial, the Stroke Hyperglycemia Insulin Network Effort (SHINE), is currently underway to compare standard of care glucose control to an intensive level of control in hyperglycemic acute ischemic stroke patients (www.clinicaltrials.gov; NCT01369069).¹⁶

In addition to having association with clinical outcome following stroke in general, hyperglycemia may also be associated with differential response to thrombolysis in the acute setting. In predictive risk modeling for administration of intravenous tissue plasminogen activator (IV tPA, alteplase), initial blood glucose is one of several variables associated with poorer outcomes, in addition to age, stroke severity, and onset-to-treatment time.^{17–19} Poor outcomes following thrombolysis associated with hyperglycemia may be mediated by an increased risk of symptomatic intracerebral hemorrhage (sICH), a rare complication of IV tPA in all treated ischemic stroke patients, but one which carries a high rate of morbidity and mortality, thus discouraging thrombolytic use in clinical practice.^{20, 21} Rates of sICH have varied in both clinical trials and observational studies of stroke thrombolysis between 2–8%; while some of the variance stems from differences in these populations, a portion reflects variation in study definition of sICH.^{22–24} Risk prediction scores for both poor outcomes and sICH in patients receiving IV tPA have been derived from several cohorts in which elevated serum glucose at baseline is a significant contributing factor. Though these tools remain to be fully validated in clinical practice, the concept of considering individual risk for outcomes in stroke thrombolysis has appeal.^{25–27}

The SHINE trial will stratify randomization by IV tPA treatment (0–4.5 hours) in hyperglycemic stroke patients, and therefore offers a unique opportunity to better understand the relationship between serum glucose and thrombolysis. We hypothesize that normalization of hyperglycemia in the acute stroke setting may reduce risk of thrombolysis-induced sICH. In the following sections, we further discuss the biological evidence supporting this hypothesis and describe an approach to define the association between hyperglycemia and post-tPA sICH through results of the upcoming SHINE trial.

Preclinical data

Previous animal models investigating the relationship between hyperglycemia and the effects of focal brain ischemia have yielded inconsistent results; but many older models pre-date thrombolysis and often induced permanent ischemic conditions.^{28–38} Numerous animal studies have suggested oxygen free radical formation and tissue acidosis, exacerbated by elevated blood glucose, as a mechanism for neural injury in hyperglycemic cerebral ischemia.^{39–41} As an example, a rabbit model of the ischemic penumbra found that hyperglycemia propagated cortical acidosis and the NADH redox state, as opposed to normoglycemic animals, supporting the hypothesis that glucose utilization mediates acidosis and infarction in ischemic brain tissue.⁷

A more recently published rat model compared the effects of tPA infusion in normoglycemic versus hyperglycemic rats with acute focal cerebral ischemia of the middle cerebral artery during reperfusion.⁴² Increasing blood glucose levels among rats treated with tPA was associated with greater blood-brain-barrier permeability and larger volumes of post-treatment hemorrhage. Moreover, hyperglycemic rats produced higher levels of the free radical superoxide, which is associated with blood-brain barrier disruption in ischemic brain parenchyma and vasculature following reperfusion.⁴³ Blocking superoxide production with an NADPH oxidase inhibitor (apocynin) resulted in decreased blood-brain barrier permeability, smaller infarct sizes, and smaller hemorrhagic volumes among rats of the same degree of hyperglycemia, suggesting a relationship between hyperglycemia and ischemic stroke thrombolysis mediated by superoxide.⁴² This suggestion is biologically plausible, as glucose may be the rate-limiting substrate for NADPH production (via the pentose phosphate pathway) and subsequent superoxide formation via NADPH oxidase (Table 1).^{7, 42, 44}

Taken together, these animal-derived data are encouraging for the conclusion that glucose control may play a role in limiting blood brain barrier disruption in acute stroke and reducing hemorrhagic conversion of ischemic brain tissue following reperfusion.

Clinical data

Human subjects research in hyperglycemic stroke thrombolysis, mostly retrospective and uncontrolled, supports an association between hyperglycemia and outcomes following thrombolysis, as demonstrated in several observational studies^{45–48} and subgroup analyses in large clinical trials of both intravenous and intra-arterial treatment.^{49–51} In a multivariable analysis of both treatment and placebo arms of the NINDS tPA Stroke Trial, the risk of sICH increased (OR 1.75, 95% CI 1.11–2.78) for every 100mg/dl increase in initial serum blood glucose, independent of stroke severity and history of diabetes.⁴⁹ Interestingly, this association was also independent of treatment arm, suggesting that tPA might not be in a causal pathway linking sICH to hyperglycemia, or that the sample size of sICH was too small to show a differential association. Hemorrhagic conversion of ischemic stroke may be related to hyperglycemia independent of pharmacological thrombolysis, but still mediated by reperfusion and oxidative stress on infarcted brain tissue.⁵²

Despite preliminary evidence suggesting detrimental effects of hyperglycemia on post-thrombolysis outcomes, the association has yet to be investigated in a prospective, controlled way, and equipoise remains as to whether treatment of hyperglycemia or risk stratification based on initial blood glucose is warranted in the acute stroke setting. Current American Heart Association/American Stroke Association (AHA/ASA) guidelines for the use of tPA for acute ischemic stroke suggest excluding patients for severe hyperglycemia greater than 400 mg/dL;^{53, 54} however, it should be noted that this upper limit blood glucose mirrors the somewhat arbitrary exclusion criterion from the original NINDS tPA Trial.⁵⁵ AHA/ASA guidelines for management of hyperglycemia in the acute stroke setting provide class II evidence for treatment of blood glucose with mention of several potential cutoffs, but with a final recommendation suggesting an upper limit 185 mg/dl. While no specific management strategy is offered, the guideline calls for definitive trials and class I data.⁵³ Current joint commission standards for certification of primary stroke centers require no specific management of hyperglycemia, and most centers continue to utilize generic sliding scale insulin protocols.⁵⁶

Clearly, questions persist as to whether intensive glucose thresholds and more regimented insulin-based therapy for hyperglycemia might improve the effectiveness and safety of thrombolysis for acute stroke patients. As tPA treated patients are required to receive ICU level of care to reduce post-thrombolysis complications, intensive insulin therapy could be highly generalizable and easily accepted within primary stroke centers.

The SHINE trial

The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial is an NIH-NINDS funded, blinded, randomized-controlled, phase III efficacy study comparing insulin infusion for intensive blood glucose control to standard of care glucose control in hyperglycemic acute ischemic stroke patients. The trial combines the efforts from two previous NIH-NINDS funded middle phase trials, Glucose Regulation in Acute Stroke Patients (GRASP) and Treatment of Hyperglycemia In Stroke (THIS), that demonstrated safety and feasibility of insulin infusion for intensive glucose control in the acute stroke setting.^{13, 14} Although the GRASP trial was not powered to determine efficacy (N = 74 in three treatment groups: tight glucose control, loose glucose control, usual care), an exploratory efficacy analysis was supportive of further comparative study.¹⁴ Additionally, combined analysis of the GRASP

and THIS trials also was consistent with potential efficacy of more intensive glucose control (K.C.J. unpublished data).

As the definitive phase III study, the SHINE trial is designed to determine the efficacy of intensive glucose control with continuous insulin infusion (target 80–130 mg/dL) versus standard of care subcutaneous insulin sliding scale (target $\leq$ 180 mg/dL) in hyperglycemic ischemic stroke patients within 12 h of symptom onset. The primary efficacy outcome will be a severity-adjusted difference between groups in functional ability measured by the modified Rankin Scale (mRS) at 90 days following stroke onset.^{57, 58} As an additional aim, SHINE will verify the safety of intensive glucose control with IV insulin infusion (measured by both symptoms and severity of hypoglycemia $\leq$ 40 mg/dL) using a validated, commercially available computerized decision support tool (GlucoStabilizer®) during the period of acute ischemic stroke for up to 72 h. SHINE is a multicenter effort including approximately 60 U.S. sites in cooperation with the NINDS-funded Neurological Emergency Treatment Trials network (NETT).⁵⁹ With goal enrollment of 1400 patients (700 per arm), the study will have 80% power to detect a 7% absolute difference in the primary outcome.

Eligibility criteria for SHINE include a 12-h window from stroke symptom onset, but a 3-h window for door to initiation of study treatment. Notably, randomization in the trial will be stratified by IV tPA treatment assuring balance of thrombolysis patients in the two treatment arms. Therefore, an opportunity exists to use the SHINE trial as a prospective medium to better understand the relationship between hyperglycemia and thrombolysis, but also the implications of normalizing blood glucose coincident with treatment and potential reperfusion. In the phase II GRASP trial (N = 74), 35% of participants received IV tPA and no safety issues occurred in conjunction with insulin infusion. There were no occurrences of sICH and treatment with tPA did not alter results from the exploratory outcomes analysis, although again the middle-phase trial was not powered to determine these associations.¹⁴

In the SHINE trial, however, a pre-specified analysis of the effect of normalizing hyperglycemia on post-thrombolysis sICH in the acute stroke setting is possible. As mentioned, the odds of sICH in the NINDS tPA Trial increased by 1.75 per 100mg/dL increase in initial blood glucose, and patients with sICH had a mean admission blood glucose of 187 ± 114 mg/dL compared with 148 ± 72 mg/dL in those without.⁴⁹ In a multicenter review of 1,205 patients treated in routine clinical practice, the rate of sICH was also found to increase with greater initial blood glucose levels. While the overall rate of sICH in this cohort was 6% (mirroring the NINDS tPA Trial rate of 6.4%), the rate of sICH in patients with initial blood glucose >125 mg/dL was greater than 10%, and for >150 mg/dL exceeded 13%. Additionally, baseline diabetes mellitus independently increased the risk of sICH (OR 2.23, 1.21–4.13).⁶⁰ Therefore, it is reasonable to assume that the expected post-thrombolysis sICH rate among the control arm in the SHINE trial, with eligibility requiring initial blood glucose $\leq$ 110 mg/dL in diabetics and $\leq$ 150 mg/dL in non-diabetics, will also be higher than the 6% sICH rate in all stroke patients. If the expected IV tPA treatment frequency among SHINE participants is 35% (N = 490, 245/group), then the study would have 80% power to see a 7% decrease in the rate of sICH with intensive treatment of hyperglycemia compared with standard-of-care controls. Achieving this sample size is a reasonable expectation given similar rates of IV tPA use in phase II studies.^{13, 14} If only 30% of participants received IV tPA (N = 420, 210/group), there would still be 74% power to see a similar effect (Fig. 1).

Comment

Extrapolating from aforementioned animal models, a pathological link between hyperglycemia and post-tPA sICH may stem from oxidative stress on ischemic parenchyma and vasculature, reperfusion injury, and blood-brain barrier disruption (Table 2). Subgroup analyses from stroke treatment trials and observational studies support further exploration of the hypothesis that intensive glucose control could improve patient outcomes following stroke thrombolysis.

Intravenous tPA remains the only FDA approved treatment for acute ischemic stroke in the United States. Fear of the risk of sICH continues to be the number one reason physicians provide for withholding IV tPA treatment in the emergency stroke setting. Identifying ways to mitigate this risk is vital to increasing the number of stroke patients treated, and such data could have enormous generalizability and impact. Initial blood glucose is one of the few consistently identified, modifiable risk factors for both sICH and poorer disability following thrombolysis, and it is possible that intervening with early intensive insulin therapy could improve outcomes in hyperglycemic stroke patients. Middle phase trials have demonstrated safety and feasibility of this method, and thrombolysis patients are already admitted to an intensive environment conducive to insulin infusion.

Considering the ever-rising prevalence of obesity and diabetes mellitus, particularly among young people, a better understanding of the impact of hyperglycemia in stroke treatment and outcomes is imperative. Extrapolating estimates from the U.S. Census Bureau in data, the number of incident strokes among adults in the U.S. will more than double by the year 2050; with large increases in the aged, African-American, and Hispanic populations.² As the co-prevalence of stroke and diabetes mounts, so does the need to appropriately consider and treat hyperglycemia in the acute stroke setting.

Translating animal data and early phase trials further, the SHINE trial offers a unique opportunity to investigate the effect of intensive hyperglycemic control versus standard care in acute stroke thrombolysis, under the hypothesis that normalization of initial blood glucose may decrease the risk of sICH. With enrollment underway, such data could substantially affect treatment decisions for hyperglycemic ischemic stroke patients going forward.

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Figure 1. Power analysis to see a 7% difference in sICH rate for tPA treated participants in SHINE between intensive and standard of care glucose control: y -axis = power ($1-\beta$), x -axis = effect size (green = 35% tPA rate ($n = 245/\text{grp}$); red = 30% tPA rate ($n = 210/\text{grp}$)).

Table 1

Glucose as a substrate for production of NADPH and superoxide

Production of NADPH from glucose (pentose phosphate pathway):
Glucose -> Glucose-6-Phosphate -> (NADP ⁺ -> NADPH) -> pentose sugars
Production of superoxide from NADPH oxidase:
Oxygen + NADPH -> (NADPH Oxidase) -> superoxide + NADP + H ⁺

Table 1

Comparison of hyperglycemic rat model of thrombolysis in focal cerebral ischemia⁴² versus SHINE trial parameters

Animal model	SHINE trial
90 min transient ischemia model tPA started 80 min, reperfusion 90 min. Normoglycemic 3 h after reperfusion (hyperglycemic ~ 4.5 h). Normoglycemic and sacrificed at 3 days.	< 3 h ischemic stroke and tPA. tPA started by 180 min, possible reperfusion. Initiation w/in 3 h of ED arrival – probably w/in 2 h of tPA. Normoglycemia < 4 h in most (hyperglycemia ~8 h; Rx grp). Normoglycemic for 3 days.