Lack of association between hyperglycaemia at arrival and clinical outcomes in acute stroke patients treated with tissue plasminogen activator

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Rationale **Hyperglycaemia is associated with adverse outcomes in some studies of acute ischaemic stroke.**

Aims **We hypothesised that in thrombolytic-treated stroke patients, hyperglycaemia would be independently associated with haemorrhagic transformation and unfavourable outcome.**

Design **Consecutive rt-PA-treated acute ischaemic stroke patients presenting to four emergency departments were analysed. Associations of initial blood glucose and survival to hospital discharge, symptomatic intracerebral haemorrhage, any form of intracerebral haemorrhage, and disability at hospital discharge were determined. Potentially confounding factors of age, National Institutes of Health Stroke Scale, and smoking were analysed by univariate logistic regression and those with $P < 0{\cdot}3$ included in the multivariate model.**

Study Outcome **In 268 patients, initial glucose values ranged from 62 to 507 mg/dl (mean 131). Elevated glucose at arrival was not significantly associated with any adverse clinical outcomes. A trend towards higher mortality in hyperglycaemic patients (odds ratio 1·71 per 100 mg/dl increase in glucose, 95% confidence interval 0·92–3·13, $P = 0{\cdot}08$) was seen, but is of unclear significance, and was not corroborated by effects on discharge disability, symptomatic intracerebral haemorrhage or intracerebral haemorrhage.**

Conclusions **Thrombolytic-treated stroke patients with hyperglycaemia at presentation did not have significantly worse outcomes than others in this cohort. These data fail to confirm previously described associations seen in similarly sized studies. Further study of these associations and their magnitude are necessary to better define the relationship between serum glucose and outcome in thrombolytic-treated acute ischaemic stroke.**

Key words: acute ischaemic stroke, hyperglycaemia, observational study, outcomes, thrombolysis

Introduction

Hyperglycaemia is common in the acute phase of ischaemic stroke and has been associated with adverse outcomes, specifically increased risk of haemorrhagic transformation, disability, increased health care costs and death in some studies (1, 2). In some experimental stroke models, hyperglycaemia increases reperfusion injury and infarct related haemorrhage (3, 4). It also has been shown to increase infarct volume in some human and animal studies (5, 6). In studies examining thrombolysis in ST-segment elevation myocardial infarction, hyperglycaemia diminishes the resolution of ST-segment elevation, suggesting hyperglycaemia attenuates the efficacy of thrombolysis (7). Only a small number of studies have examined the outcomes and complications of thrombolytic-treated stroke patients with hyperglycaemia (8–10).

Previous trials of intensive in-hospital control of glucose in stroke patients have been completed and others are ongoing (11–13). Recent trials of glucose lowering in stroke and intensive care have failed to demonstrate improved outcomes in patients with tight glycaemic control, illustrating the need for additional observational data on the relationship between glucose and stroke, especially in thrombolytic-treated patients (14, 15). The current acute stroke management guideline recommends treatment of hyperglycaemia and suggests use of insulin when glucose levels are in excess of 140 mg/dl, but does not specifically address or advocate glucose lowering before thrombolysis (16). Thrombolytic treatment guidelines in existence during the time period examined in this study recommended withholding tPA therapy when patients have very high glucose levels (>400 mg/dl) due to concerns of treating patients with clinical presentations mimicking acute ischaemic stroke (17).

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In this analysis, we hypothesised that in rt-PA-treated stroke patients, hyperglycaemia at presentation would be an independent risk factor for cerebral haemorrhage and for unfavourable clinical outcome. We determined the odds ratios (OR) for poor outcomes related to blood glucose on presentation in a large cohort of intravenous (IV) rt-PA-treated acute stroke patients.

Methods

Consecutive stroke patients treated with IV rt-PA between 1 January 1996 and 1 January 2005 were identified from four emergency departments (EDs) serving a contiguous, four county region in Michigan. The Institutional Review Board from each site approved the study before data collection. Four independent, trained study personnel completed all reviews using the paper chart and/or electronic medical record. A standardised data collection form was used. Cases were identified using four deliberately redundant methods: (1) discharge diagnoses containing any International Classified Diseases Version 9 (ICD-9) Code for cerebrovascular disease (430–437; 997·02) plus a procedure code for thrombolysis (99·10 or CPT codes 37195 or 37201); (2) review of hospital pharmacy logs of rt-PA use in ED; (3) review of site-specific stroke registries maintained for quality improvement purposes and (4) through review of Paul Coverdell National Acute Stroke Registry Data (5/2002–11/2002) for two of the hospitals.

Four outcomes were studied: survival to hospital discharge, symptomatic intracerebral haemorrhage (sICH), the presence of any intracerebral haemorrhage (ICH), and disability at hospital discharge as determined by modified Rankin score (mRS) calculated from chart review using previously reported methodology (18). All ICHs were classified by two independent radiologists using the definitions described in the European Cooperative Stroke Study (ECASS) (19). Symptomatic ICH was defined as parenchymal haemorrhage type 2 as outlined in ECASS. Disagreements were adjudicated by a third radiologist. Patients with a prestroke mRS score >1 were excluded from the outcome analysis of disability. These patients had preexisting disability and would not be expected to lose that disability after suffering from a stroke. Poststroke disability was defined as a mRS of 2 or greater at hospital discharge. The data were analysed using SPSS software (SPSS Inc., Chicago, IL).

The associations between outcomes and initial glucose were determined by logistic regression. Preexisting diagnosis of diabetes was substituted for glucose in a subsequent analysis but was not included in the initial model due to the strong interaction with glucose. Potentially confounding factors of age, National Institutes of Health Stroke Scale (NIHSS), and smoking within last year were analysed by univariate logistic regression and those with $P<0·3$ were included in a multivariate model. These variables were prespecified and were chosen for this analysis as the only pretreatment factors ($P<0·1$) from the NINDS rt-PA trial, which were predictive of symptomatic haemorrhage (20, 21). The same logistic regression methodology as above was also used separately on the patients with and without preexisting diabetes.

The OR for each adverse outcome per 100 mg/dl increment in initial glucose was calculated with 95% confidence intervals. Linear regression was performed between the baseline NIHSS and the presenting glucose to determine whether an association between these variables existed.

Results

Two hundred and seventy-three consecutive tPA-treated acute stroke patients were studied. Initial blood glucose measurements obtained in the ED were documented for 268 patients; five patients with unknown glucose were excluded. Only one patient had documented treatment with insulin in the ED (initial glucose 206 mg/dl).

Initial glucose ranged from 62 to 507 mg/dl with a mean of 131. In hospital mortality was 12·8%. Symptomatic ICH occurred in 6·6% of cases and any ICH in 9·9%. Smoking within the past year, baseline NIHSS, and age were significant predictors on univariate analyses and were included in all of the final models examining the relationship between initial glucose and clinical outcomes. The associations between elevated glucose at arrival and disability, death, ICH and sICH in tPA-treated stroke patients were weak and did not reach statistical significance, though there was a trend towards significance in the association between glucose and death (Table 1). Trends were stronger for an association between glucose and death than with discharge disability, sICH or ICH. When the analysis was repeated in patients with and without a prior diagnosis of diabetes, the associations between glucose and the study outcomes also did not achieve statistical significance. Outcomes for patients at increasing glucose levels are presented in Figs 1 and 2 (three outlying patients with glucose >300 mg/dl are not included in these figures). The correlation between baseline NIHSS and presenting glucose was minimal (adjusted R^2 $-0·002$). This relationship is plotted in the Appendix.

When diabetes was substituted for glucose in the analysis, a significant association with the outcomes still was not seen (Table 2). There was a trend towards a decreased likelihood of both ICH and sICH, but higher death rates in patients with diabetes. Tobacco use was not significantly associated with any of the outcomes.

Discussion

One limitation of this study is the sample size. Although not statistically significant, some of the OR found in this study are of magnitudes that conceivably may have achieved significance with a larger sample. Another limitation is that glucose at presentation was lower in this cohort than what had been observed in prior studies of stroke thrombolysis (19, 22). Hyperglycaemia was less common both in patients with and without known diabetes compared with other studies, likely

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Table 1 Relationship of increasing glucose to outcomes by multivariate analysis controlling for age, smoking within past year and stroke severity

Outcome	Adjusted OR per 100 mg/dl increase in glucose	95% CI	*P*
Death	1·71	0·92–3·13	0·08
Disability	2·00	0·78–5·09	0·15
sICH	1·16	0·43–3·13	0·70
Any ICH	1·19	0·53–2·68	0·68

OR, odds ratio; CI, confidence interval; sICH, symptomatic intracerebral haemorrhage; ICH, intracerebral haemorrhage.

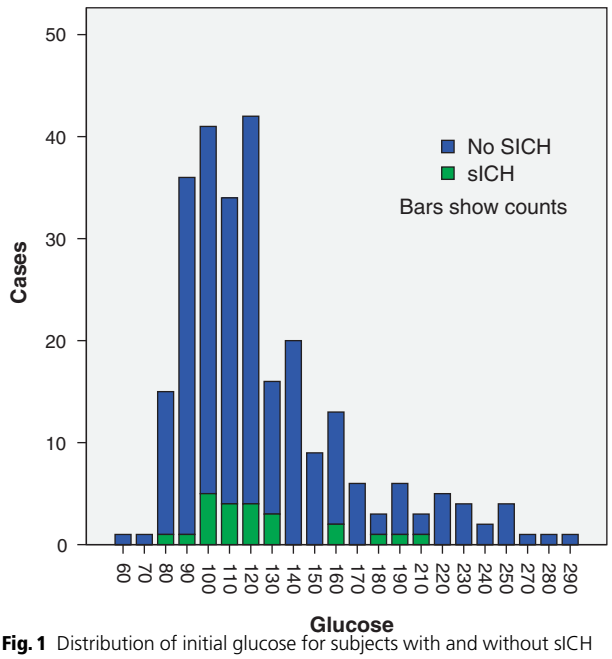

Fig. 1 Distribution of initial glucose for subjects with and without sICH within 36 h of tPA treatment. Distribution of glucose at presentation in study in mg/dl. Four cases presented with glucose > 300 mg/dl and none had sICH within 36 h of treatment. sICH, symptomatic intracerebral haemorrhage.

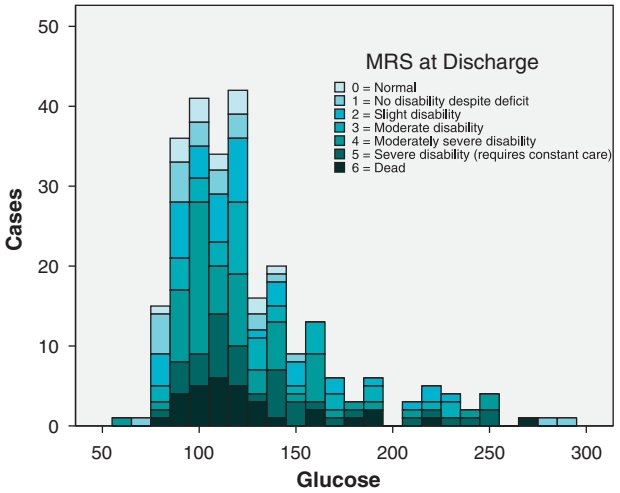

Fig. 2 Level of disability at discharge by initial glucose. Distribution of glucose measurements at presentation measured in mg/dl by level of disability is depicted. One patient with glucose of 312 mg/dl had mRS of 2, one patient with glucose of 325 mg/dl had mRS of 4. Two patients died in the hospital with glucoses of 323 and 507 mg/dl. mRS, modified Rankin Scale.

Table 2 Relationship of diabetes by history to outcomes by multivariate analysis controlling for age, smoking within past year and stroke severity

Outcome	Adjusted OR for diabetes vs. nondiabetics	95% CI	*P*
Death	1·99	0·89–4·46	0·094
Disability	2·3	0·733–7·243	0·153
sICH	0·33	0·072–1·50	0·15
Any ICH	0·34	0·0968–1·2011	0·094

OR, odds ratio; CI, confidence interval; sICH, symptomatic intracerebral haemorrhage; ICH, intracerebral haemorrhage.

making adverse effects harder to identify. In addition, trends in the glucose values over the course of the hospitalisation were not collected. In addition, we had a relatively small number of events and this limited the number of covariates that could be included in the logistic regression model. Last, data on insulin use outside of the ED were not collected which ideally would be controlled for since post-tPA control of hyperglycaemia may affect the post-tPA clinical outcomes and haemorrhage rates.

Two prior studies have specifically examined the relationship between glucose level and stroke outcomes in thrombolytic-treated or eligible patients in the NINDS tPA stroke trial (1, 20). An analysis of the treatment group alone, in which glucose was treated as a dichotomous variable (with a cut-off of 300 mg/dl), showed no statistical difference in outcomes (20). However, a more recent analysis that included both treatment and control groups, examined glucose as a continuous variable and concluded that hyperglycaemia on presentation was associated with significantly lower odds of favourable outcome and significantly higher odds for sICH, regardless of tPA treatment (1).

Our study did not confirm a significant association between hyperglycaemia and outcomes, either because there is no such association, or because the association is too small to be detected in this analysis of 268 patients. Hyperglycaemia on presentation in acute ischaemic stroke patients treated with tPA was not significantly associated with mortality, disability, ICH or sICH. Associations too small to be detected with this sample size cannot be ruled out, however, prior reports have linked hyperglycaemia to adverse outcomes in similarly sized or smaller cohorts (8, 21, 23). These data do not disprove the potential adverse effects of sustained hyperglycaemia. In addition, these data do not suggest any significant attenuation of thrombolytic efficacy related to early hyperglycaemia at presentation within three hours of stroke onset. A larger analysis of pooled trial data may be more revealing, and may assist in the design of a hyper-acute prehospital or EDs glucose

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lowering therapy trial in acute stroke patients who receive tPA. Further studies are necessary to better define the relationship between serum glucose and outcome in tPA-treated acute ischaemic stroke.

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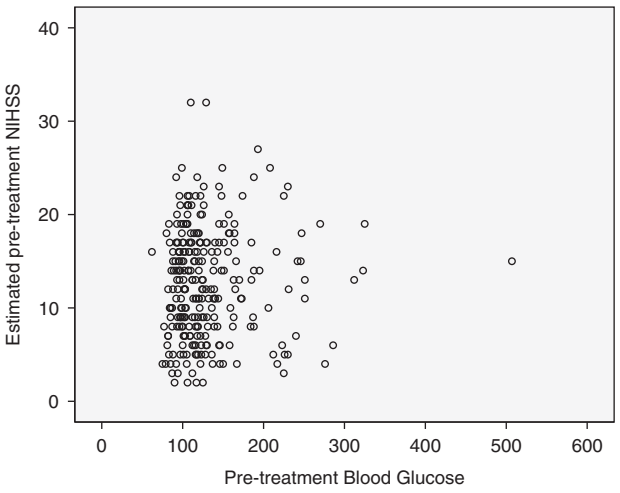
Appendix



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