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Is post-stroke hyperglycemia a marker of stroke severity and prognosis: A pilot study

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Abstract

Background: Various physiological parameters like blood pressure, temperature, blood sugar after onset of stroke have been proposed as possible marker of stroke prognosis. Objective: To study the glycaemic status after acute stroke and assess the role of glycaemic status along with other clinical parameters in influencing stroke outcome. *Method*: Forty-two confirmed stroke patients attending hospital within 6 hours of onset of stroke onset were included in the study. The time lag for hospitalization, blood pressure, blood sugar, HbA1c, stroke severity according to Toronto Scale, demographic factors, stroke onset type, type of stroke, past history of stroke, diabetes, and hypertension were recorded. The outcome was whether patient survived at the end of forth week. *Results*: Twenty-one percent of patients who were not known diabetic found to be hyperglycemic though their HBA1C level was normal. Eighty-nine percent of such patients died. This rate was significantly higher than patients known to be diabetic with raised sugar and HBA1c level (26% patients, 12% mortality). There was strong and significant association between stroke severity and poor outcome. Strong and significant association was also found between stroke severity and blood sugar level. Modeling of stroke outcome using decision tree analysis (QUEST) found stroke severity as most important and significant predictor especially for severe stroke cases. In mild and moderately severe stroke, high sugar level was found to be a predictor, though not statistically significant.
Conclusion: This study suggests that stroke severity is the most important predictor of stroke outcome, with high sugar level as a marker of stroke severity.

INTRODUCTION

The influence of diabetes mellitus as an independent predictor of the incidence of ischemic stroke is well recognized and relates to a variety of causes.[1] Similarly, several studies have indicated that patients with diabetes are more likely to die or to have substantial neurological disability after acute stroke than nondiabetic subjects.[2] However, between 20% and 40% of patients admitted with ischemic stroke are hyperglycemic, often without a pre-existing diagnosis of diabetes[3]. A meta-analysis by Capes *et al*[4] suggests that the relative risk of death in hyperglycemic nondiabetic stroke patients is increased by 3.3 (95% confidence interval, 2.3 to 4.6). Recent analyses of both prospective and case control studies have confirmed the importance of acute hyperglycemia as a predictor of outcome after stroke.[5,6,7]

Although there is compelling evidence that hyperglycemia has an effect on stroke outcome, debate continues as to whether the effect is independent of the influence of diabetes or initial stroke severity[8, 9]or an indicator of more severe illness with an increased response to stress.[10,11] Furthermore, it is not known whether hyperglycemia in patients without critical illness admitted to general hospital wards is associated with poor outcome.

It has been suggested that admission hyperglycemia is a marker of extensive brain damage leading to a greater increase in stress hormones resulting in hyperglycemia.[12,13,14] However, van Kooten *et al*[15], who also found a significant association between hyperglycemia on admission and stroke outcome, did not find a correlation between catecholamine and glucose levels, implying that increased stress was not responsible for the hyperglycemia.

If hyperglycemia is proven to be an independent predictor of poor outcome, a policy for early detection and glucose control may be warranted. Being a cheap and easily available test, such a

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prognostic factor is likely to be immense value in poorly equipped centers catering for stroke patients. We sought to address this issue with the following objectives. Firstly, to study the blood sugar level at the time of hospitalization for stroke. Secondly, to ascertain whether the high sugar level if seen during admission can be explained in terms of diabetes based on history and glycosylated hemoglobin level. Thirdly, to assess whether this blood sugar level shows any association with outcome of stroke, i.e. whether survived or not. Fourthly, to study the relationship between standardized measure of stroke severity with glycaemic status and stroke outcome. Fifthly, to study the relative contribution of demographic and other clinical parameters in influencing stroke outcome.

METHODS

Consecutive adult patients admitted to General Medicine and Neurology Department, Calcutta National Medical College during period July 2004-June 2005 with suspected stroke were included for the study, provided the patient reached the hospital within 6 hours of suspected stroke. The time lag between onset of first signs of suspected stroke and hospitalization was noted. Out of 53 such cases, 42 patients were included in the study after confirmation using CT scan and after excluding other potential differential diagnosis like space occupying lesion, sub-dural haematoma, and metabolic causes. For the purpose of this study, transient ischemic attack (TIA) and subarachnoid hemorrhage (SAH) were excluded. Each patient was clinically evaluated to assess general medical status and neurological deficits. In order to quantify stroke severity based on clinical features Toronto stroke scoring system[16] was used. The stroke severity was thus categorized as mild, moderate or severe.

Sample of blood for biochemical workup after admission was collected, and blood glucose and glycosylated hemoglobin was measured. The blood glucose measured was considered to be fasting sample if the patient had no caloric intake for last 8 hours (including i.v. dextrose). Otherwise, the blood sample was considered random sample. The patient's blood pressure at the time of admission was recorded and graded according to JNC-7.[17] All patents were given appropriate standard therapeutic care and were monitored during the stay in hospital (up to a maximum of 30 days). The other information collected was demographic profile of patient, past history of diabetes, hypertension, or stroke, stroke onset (whether rapid or gradual), type of stroke (whether hemorrhagic or thrombotic). The primary end point of the study was in-hospital mortality.

The patients were divided into 2 broad groups, good outcome groups (i.e. patients who survived), and poor outcome group (patient died). Based on fasting blood glucose or random sugar[18] (as measure of immediate short term glycaemic status) and HbA_{1c} [19] (to assess long term diabetes control in known diabetic and to rule out undetected diabetes patients), patients were also divided into: (1) History negative, immediate glycaemic status normal, HbA_{1c} <8; (2) History negative, immediate glycaemic status abnormal, HbA_{1c} <8; (3) History negative, immediate glycaemic status normal,, HbA_{1c} ≥8; (4) History negative, immediate glycaemic status abnormal,, HbA_{1c} ≥8; (5) History positive, immediate glycaemic status normal,, HbA_{1c} <8; (6) History positive, immediate glycaemic status abnormal,, HbA_{1c} <8; (7) History positive, immediate glycaemic status normal, HbA_{1c} ≥8; (8) History positive, immediate glycaemic status abnormal, HbA_{1c} ≥8.

Statistical method

Frequency of various categorical variables, mean, and standard deviation of various numerical variables were used as summary measures of the data. Chi-Squared test (or Fisher's Exact test when Chi-Squared test was not applicable) was used to test association between stroke outcome and various categorical variables. Monte Carlo Approximation was done if Fisher's Exact test was not possible to evaluate completely. In all cases, two-tailed tests were used, p value of less than 0.05 being considered statistically significant.
Statistical analysis was done with SPSS 9.0 for Windows software and numerical interval data comparison was done using Mann-Whitney's test.

In order to predict stroke outcome from other measures, we used tree classification technique.[20,21] *Classification trees* are used to predict membership of cases or objects in the classes of a categorical dependent variable from their measurements on one or more predictor variables. A classification tree is an empirical rule for predicting the class of an object from values of predictor variables. The goal is to produce subsets of the data which are as homogeneous as possible with respect to the target variable. For each split, each predictor is evaluated to find the best cut point (continuous predictors) or groupings of categories (nominal and ordinal predictors) based on improvement score or reduction in impurity. Then the predictors are compared, and the predictor with the best improvement is selected for the split. The process repeats recursively until one of the stopping rules is triggered.

The specific decision tree technique used in this study is *QUEST*[22] (Quick, Unbiased and Efficient Statistical Tree). Its advantages include: (1) QUEST uses an unbiased variable selection technique by default; (2) QUEST can easily handle categorical predictor variables with many categories. Our reason for choosing this technique was due to[20-22]: (1) Results summarized in a tree are very simple; (2) Tree methods are nonparametric and nonlinear, with no implicit assumption that the underlying relationships between the predictor variables and the dependent variable are linear; (3) Thus, tree methods are particularly well suited for data mining tasks, where there is often little *a priori* knowledge nor any coherent set of theories or predictions regarding which variables are related and how; (4) Tree methods can often reveal simple relationships between just a few variables that could have easily gone unnoticed using other analytic techniques; (5) Instead of constructing a mathematical function as in discriminant analysis, decision tree creates a hierarchical classification taking individual variables separately according to importance, a process closely resembling clinical decision-making.

RESULTS

The study comprised of 42 subjects (Median age 60 years, mean age=60 ± 13 years, range 25-88 years), 24 (57%) were males (Median age 56 years, mean 56 ± 15 years, range 25-81 years), 18 (43%) were females (Median age 62 years, mean age 65 ± 10 years, range 52-88 years).

The majority (57%) of the stroke cases were of very rapid onset (i.e. within minutes) followed by rapid onset cases (33%). Majority (60%) of the strokes were infarct, followed by hemorrhage (33%). Most of the stroke cases were of moderate severity (48%), followed by severe stroke (36%). The majority of the patients were known hypertensive (74%). However, the majority of patients had no history of diabetes (74%) or TIA (74%). At the time admission, most (86%) had blood pressure in stage 2 category according to JNC-7 classification; only 7% had normal blood pressure. Overall, 41% of the patients died, the rest survived.

Table 1 shows comparison of demographic and clinical features between the 2 outcome groups. Poor prognosis was observed in relatively older patients, females, history of hypertension and diabetes. History of TIA or cerebrovascular accident did not influence outcome of stroke, as majority of those who died did not have such history. However, none these differences was statistically significant.

Table 1: Comparison of demographic and clinical features between the two outcome groups

	Patient died	Patient Survived	P value
Age in years	64.9 ± 9.3	56.5 ± 14.6	NS
Sex	Male = 9 (38%) Female = 8 (44%)	Male = 15 (63%) Female = 10 (56%)	NS
Past history of TIA/CVA	Yes = 4 (36%) No = 13 (42%)	Yes = 7 (64%) No = 18 (58%)	NS
Past history of hypertension	Yes = 15 (48%) No = 2 (18%)	Yes = 16 (52%) No = 9 (82%)	NS
History of diabetes mellitus	Yes = 5(46%) No = 12 (39%)	Yes = 6 (55%) No = 19 (61%)	NS

NS: not significant
TIA: transient ischaemic attack
CVA: cerebrovascular accident

Table 2: Comparison of stroke related features between the two outcome groups

	Patient died	Patient Survived	P value
Onset	Progressive within days = 0 (0%) Rapid within hours = 4 (29%) Very rapid within minutes = 13 (54%) Abrupt within seconds = 0 (0%)	Progressive within days = 1(100%) Rapid within hours = 10 (71%) Very rapid within minutes = 11 (46%) Abrupt within seconds = 3 (100%)	NS
Type of CVA	Embolism = 0 (0%) Infarct = 10 (40%) Hemorrhage = 7 (50%)	Embolism = 3 (100%) Infarct = 15 (60%) Hemorrhage = 7 (50%)	NS
Stroke severity	Mild = 0 (0%) Moderate = 2 (10%) Severe = 15 (100%)	Mild = 7 (100%) Moderate = 18 (90%) Severe = 0 (0%)	p<0.001
Presence of Hypertension during admission	Normal = 0 (0%) Pre-hypertensive = 0 (0%) Stage I hypertension = 0 (0%) Stage 2 hypertension = 17 (47%)	Normal = 3 (100%) Pre-hypertensive = 2 (100%) Stage hypertension = 1 (100%) Stage 2 hypertension = 19 (53%)	NS
Time lag in hours	4.5 ± 0.5	4.5 ± 0.7	NS

NS: not significant
CVA: cerebrovascular accident

Table 2 shows comparison of stroke related features between the 2 outcome groups. Poor prognosis was observed in very rapid onset stroke, hemorrhagic stroke and patients brought to hospital earlier. However, only stroke severity was found to have significant association with stroke outcome.

Table 3 shows glycaemic status of the patients at the time of admission. Twenty-one percent of patients had high fasting sugar without being known diabetic and had normal HbA_{1c} level. Seven percent of patients had high fasting sugar without being known diabetic but had high HbA_{1c} level. Eighty-nine percent of patients who had raised sugar level in spite of having no history of diabetes and had normal HbA_{1c} died. This rate was much higher than observed in patients known to be diabetic with raised sugar and HbA_{1c} level. The observed difference was highly significant ($p<0.001$, using Fisher's Exact test with Monte Carlo Approximation.)

Table 4 shows stroke severity according to glycaemic status. Significant association exists between stroke severity and high sugar level, with higher sugar level in severe stroke patients. However, there was no significant association between stroke severity with glycosylated hemoglobin level.

Table 3: Comparison of glycaemic status of the two outcome groups at the time of admission

	Died	Survived	Total
No history of diabetes, sugar normal, HbA_{1c} <8	2 (11%)	17 (89%)	19
No history of diabetes, sugar abnormal, HbA_{1c} <8	8 (89%)*	1 (11%)	9
No history of diabetes, sugar abnormal, HbA_{1c} ≥8	2 (67%)	1 (33%)	3
History of diabetes, sugar abnormal, HbA_{1c} ≥8	5 (46%)*	6 (54%)	11
Total	17 (41%)	25 (59%)	42

*P<0.001

Table 4: Stroke severity according to glycaemic status

Stroke severity	Mild (N=7)	Moderate (N=20)	Severe (N=15)	P value
Blood sugar high	2	8	13	P=0.006
HbA_{1c} High	2	6	5	NS

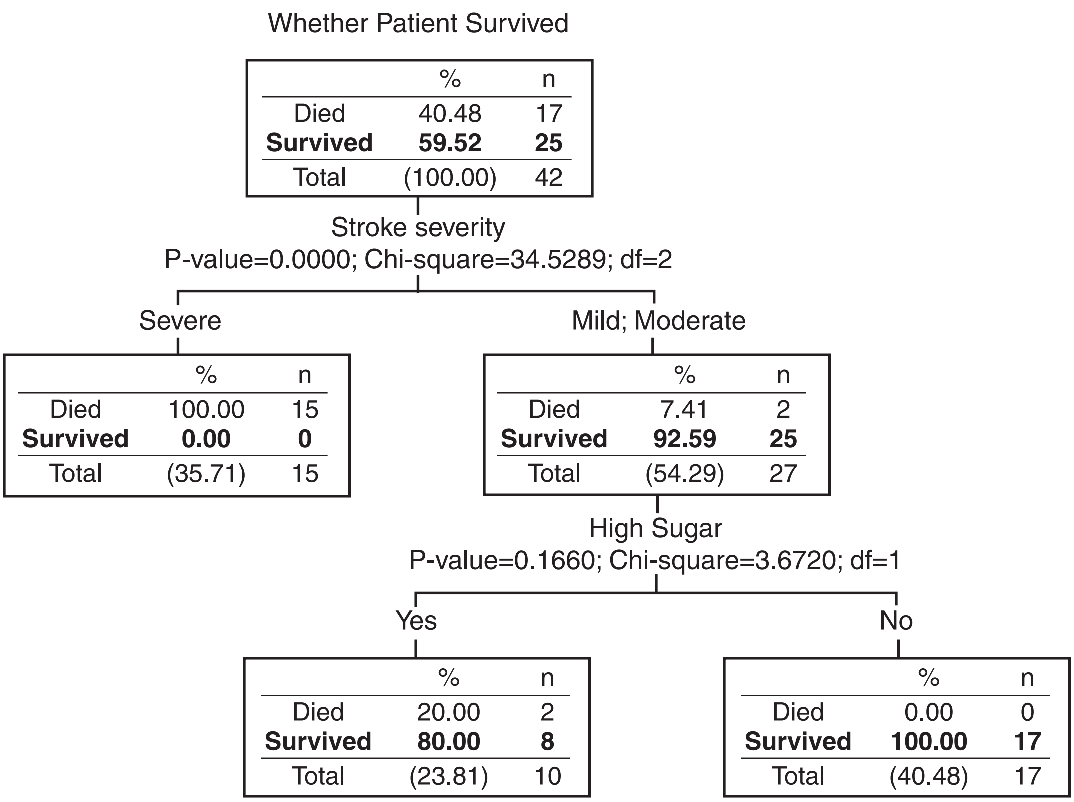
NS: not significant

Figure 1 shows decision tree (Quest) analysis to predict patient's survival. Stroke severity emerges as most important and significant predictor especially for severe stroke cases. In mild and moderately severe stroke, high sugar level was a predictor, though this was not statistically significant.

DISCUSSION

This study suggests that stroke severity is the most important predictor of stroke outcome, with high sugar level as a marker of stroke severity. Our study finding of poor prognosis among non-diabetic patients with hyperglycemia after stroke is interesting. Similar findings were reported by Vancheri *et al*[23], who found hyperglycemia in an third of non-diabetic acute stroke patients. Strong and significant association between stroke severity and glycaemic status found in our study and severity seems to suggest that glycaemic status may serve as a biochemical marker of stroke severity.

This brings us to the question raised by Vancheri *et al*[23] as to whether hyperglycemia is an



Misclassification Risk Estimate=4.76%

Figure 1: Decision tree (QUEST) analysis to predict patient's survival

acute stress response or a reflection of underlying diabetes. Since our study used HbA1c to screen for undetected diabetes, the possibility of underlying diabetes as explanation of hyperglycemia seen after stroke may not be valid for our patients.

One may argue that the patients might have high sugar prior to the stroke. However, certain findings from the study seem to go against this and support our view that sugar level rose after the stroke. Blood glucose level showed strong association with stroke severity. Also, glycosylated hemoglobin was not found to show association with stroke severity. Using the above results we concur with Murros *et al*[24] that hyperglycemia seen in our study is related to the stroke event.

However, the issue of stress-induced hyperglycemia is far more difficult to address. Indeed researchers like Christensen and Boysen[25] suggested that hyperglycemia in acute stroke is primarily an epiphenomenon related to stroke severity. Our study seems to support this view. However the issue is complicated as it is difficult statistically to disentangle the two strongly co-related predictor variables (here severity and hyperglycemia) used to predict stroke outcome. Certain arguments though, can be used to clarify this. When two variables are closely related, like stroke severity and blood glucose, the one that is the most accurately measured (glucose concentration in this example) will always emerge as the stronger variable even if it is in fact less important.[26] Since, our study found stroke severity as the stronger predictor; it definitely is more important. Our study used decision tree (QUEST) to clarify this situation. Stroke severity emerged as a strongly significant predictor of outcome, with hyperglycemia as non-significant predictor in less severe cases.

Animal models of focal cerebral ischemia suggested that the type of vessel occlusion, the presence of collateral blood flow, and occurrence of reperfusion were relevant and that hyperglycemia might influence neuronal damage through accentuated tissue acidosis and lactate generation.[21,22] Using MR spectroscopy, researchers have demonstrated a mechanistic link between admission hyperglycemia and stroke outcome involving infarct growth through recruitment of penumbral tissue and increased cerebral lactate production.[23]

Our study however, has some shortcomings. Due to exclusion criteria of patients coming to hospital after 6 hours of stroke were excluded thus reducing the sample size. Serial study of biochemical parameters could not be done due to resource constraints. The follow-up period was brief. The control group patients in whom specific sugar control measurements were taken along with those in whom it was not were not studied, thus specific risk of death as a consequence of post stroke hyperglycemia could not be assessed. Since it was difficult to assess when the patient took his/her last meal, we had to consider the blood sugar levels as random levels, and this led to under-diagnosis of hyperglycemia, as some samples might have been fasting sugar levels.

To conclude, hyperglycemia following stroke may serve as a predictor of stroke severity, which can be helpful as a screening measure in les equipped centers for early referral. The influence of high sugar level in affecting stroke outcome in mild to moderate stroke needs further exploration.

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