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Analysis of Glycaemic Levels as an Independent Predictor of Outcome in Acute Ischaemic Stroke

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ABSTRACT

Stroke is one of the important causes for long term disability and second leading cause of death worldwide. Two thirds of stroke deaths worldwide occur in developing countries. Incidence and prevalence of stroke has been steadily increasing in India. Incidence rate of stroke is approaching western figures of 145/100000 population. Increasing interest has been focused on the role of hyperglycaemia in the evolution of acute ischaemic stroke (AIS). Hyperglycaemia arises in 30-40% of patients with acute ischaemic stroke, most of these individuals do not have history of diabetes mellitus. The study subjects consisted of 100 consecutive patients who presented to the Hospital with Acute ischaemic stroke within 24 hrs of symptom onset and had capillary blood glucose (CBG) measured on presentation. Hyperglycemia was defined as CBG >140 mg/dl. Patients with hyperglycemia were then stratified into those with stress hyperglycaemia, newly detected diabetes mellitus and with pre-existing diabetes mellitus (DM) for the purpose of analysis. Outcome of stroke in terms of functional impairment and 90 day mortality were studied. Patients with hyperglycaemia exhibited significantly greater functional impairment (P<0.0001) than those with normoglycemia. Outcome was poor in patients with hyperglycaemia. Stroke severity (P<0.001) and functional impairment (P<0.0001) were both significantly worse in patients with hyperglycaemia and no prior history of DM, when compared to patients with hyperglycaemia and previously diagnosed DM. Hyperglycaemia at stroke onset is associated with higher risk of poor outcome independent of the other variables. Patients with hyperglycemia at stroke onset, without prior history of DM have particularly poor prognosis, than that of patients with known diabetes.

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Key Words

Acute ischemic stroke, computerized axial tomography scan, digital subtraction angiography, glycated haemoglobin, transient ischemic attack

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INTRODUCTION

World Health Organization defines the clinical syndrome of stroke as rapidly developing clinical signs of focal or global disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin[1]. Stroke is the second leading cause of long-term disability in high-income countries and the second leading cause of death worldwide[2]. In 2005, 16 million people had a first stroke and 5.7 million died because of the effects of stroke[3]. It is important to recognize that it is not a single disease but a syndrome resulting from, numerous different pathophysiological processes which result in similar end organ damage[4]. The majority (about 80%) of stroke is ischemic, the remainder result from primary haemorrhage either intracerebral (15%) or in to the subarachnoid space (5%). The relation between disturbed glucose metabolism and ischaemic stroke is bidirectional. On one hand, people with diabetes have more than double the risk of ischaemic stroke after correction for other risk factors, compared to people without diabetes. On the other hand, acute stroke can give rise to abnormalities in glucose metabolism, which in turn could affect the outcome[6].

Differential Diagnosis of Hyperglycaemia in Acute Ischaemic Stroke[6]:

- Known pre-existing diabetes
- Newly diagnosed diabetes
- Fasting glucose >6.9 mmol/L (126 mg/dl) or random glucose >11.1 mmol/L (200 mg/dl), persisting after discharge[5].
- HbA1c ≥6.5% at admission indicates pre-existing type 2 diabetes[7].
- Stress hyperglycaemia
- Fasting glucose >6.9 mmol/L or random glucose >11.1 mmol/L, reverting to normal range after discharge[5].

The incidence of stroke also increases with increasing age. Thus, many stroke patients may have undetected diabetes at the time of the stroke., subsequent examination in the hospital or following treatment for stroke may identify the previously undetected diabetes. The improved clinical diagnosis of stroke by computerized tomography and magnetic resonance imaging has probably increased the measured incidence of stroke in the population, especially among older individuals who receive more frequent and intensive medical care. Further, there is probably a very high prevalence of "silent" cerebral infarction that can be documented by these new noninvasive techniques. The incidence and prevalence of stroke among diabetic patients may, therefore be higher now than was suggested in the past[7]. Diabetes mellitus is a risk factor for both an excess incidence and mortality from stroke[8]. The first edition of diabetes in America documented the strong association of diabetes with risk of stroke, especially stroke due to vascular disease and infarction[9]. In patients younger than 60 years, the relative risk of stroke in those with diabetes versus those without diabetes is double[6]. Sex and ethnic origin also modulate the risk of stroke in people with diabetes. The risk is higher in women (hazard ratio 2.8, 95% CI 2.4-3.4) than in men (2.2, 1.8-2.5)[6]. Diabetes causes atherosclerotic changes in the heart and cerebral arteries and is associated with different subtypes of ischaemic stroke, including lacunar, large artery occlusive and thromboembolic strokes[6]. Diabetes-associated risk factors for stroke include not only diabetes-specific factors (eg -hyperglycaemia) and vascular risk factors (eg- hypertension, dyslipidaemia) but also genetic, demo graphic and lifestyle factors[6]. Diabetes also favours atherogenesis because of various lipid abnormalities like hypertriglyceridimia, low HDL cholesterol and high triglycerides-enriched HDL. Glycosylation of lipoproteins and oxidation of lipoproteins leads to atheroma formation. Hyperglycaemia in the acute phase of stroke has been established as a predictor of poor outcome in non-diabetic patients. There is dispute, however, whether a raised plasma glucose concentration is independently associated with a poor prognosis. Several studies have suggested that hyperglycaemia in non-diabetic patients after acute stroke is a stress response reflecting more severe neurological damage. Stress hyperglycaemia usually resolves spontaneously after dissipation of the acute illness. The stress reaction that results in hyperglycaemia is initiated by activation of the hypothalamic-pituitary-adrenal axis, which leads to raised amounts of glucocorticoids (cortisol) and activation of the sympathetic autonomic nervous system. Increased levels of stress hormones stimulate glucose production by glycogenolysis, gluconeogenesis, proteolysis and lipolysis. Augmented epinephrine also can result in insulin resistance and hyperinsulinaemia. Compared with patients with normoglycaemia, the unadjusted relative risk of in-hospital or 30-day mortality after an ischaemic stroke in individuals who are hyperglycaemic at admission is 3.3 in those without known diabetes and 2.0 in those with a known history of diabetes[6]. This increased risk is independent of other predictors of poor outcome. The present study was undertaken in a prospective manner to evaluate the effect of glycaemia status on the outcome of stroke.

MATERIALS AND METHODS

The present study is a prospective longitudinal study. A total of 100 patients with acute ischaemic stroke, fulfilling the inclusion criteria included in the study.

Type of Study: Prospective longitudinal study.

Method of Data Collection:

Inclusion Criteria: The patients who has presented with Acute Ischaemic Stroke within 24hrs of symptom onset and has blood glucose measured on presentation.

Exclusion Criteria:

- Haemorrhagic stroke.
- Recurrent stroke.

Study Design: It is longitudinal study done in patients presenting with clinical features of acute ischaemic stroke and confirmed by using computed tomography/magnetic resonance imaging scan of brain. Glycemic status(capillary blood glucose on admission, Fasting plasma glucose, post prandial glucose, glycosylated haemoglobin [HbA1c]) and neurological status assessed. The patients who presented with features suggestive of acute ischaemic stroke within 24hrs of symptom onset were assessed and a detailed history, thorough clinical examination was done and blood glucose levels were measured at the time of presentation. Patient`s demographic, clinical, detailed history regarding temporal profile of stroke and risk factors like hypertension, diabetes mellitus, smoking, alcohol intake, previous strokes and laboratory details were collected in a pre-tested proforma. Patients where stratified into normoglycaemics (CBG<140mg/dl) and hyperglycaemics (CBG >140mg/dl) and patients with hyperglycemia were again sub- divided into those with and without prior history of diabetes. Brain CT/MRI scan with or without contrast was done to confirm Ischaemic stroke. NIH stroke scale was used for the neurological examination that was performed at the time of presentation to assess stroke severity.

The Five Categories of Severity of Stroke are:

Stroke Severity:

No Stroke	0
Minor Stroke	1-4
Moderate Stroke	5-15
Moderate to Severe Stroke	16-20

Severe Stroke: Functional impairment was assessed by using Modified Rankin scale (MRS) at the time of admission, discharge and at 90 days of follow up.

Modified Rankin Scale (MRS):

Score Description

- No symptoms at all.
- No significant disability despite symptoms., able to carry out all usual duties and activities.
- Slight disability., unable to carry out all previous activities, but able to look after own affairs without assistance.
- Moderate disability., requiring some help, but able to walk without assistance.
- Moderately severe disability., unable to walk without assistance and unable to attend to own bodily needs without assistance.
- Severe disability., bedridden, incontinent and requiring constant nursing care and attention.
- Dead.

Neurological Outcome After 90 Days was Graded as Follows

- **Good:** Patients who can return to normal or previous activities, slight or moderate disability (MRS: 0-3)
- **Poor:** Patients who are dependent on others for daily living activities, severe paresis to plegia. Moderate to severe or severe disability or dead (MRs 4-6).

This assessment was done immediately after admission and it was repeated at the time of discharge and at 90 days after discharge. Patients were categorized as dead or survived with or without improvement.

The Following Investigations were Done in all the Cases:

- Measurement of capillary blood glucose levels at the time of presentation using one touch verio instrument manufactured by life scan.
- Complete haemogram by Sysmex XN-1000.
- Urea, creatinine (estimated by urease and enzymatic method respectively.)
- RBS (Random Blood Sugars), FBS (Fasting Blood Sugar), PPBS (Post Prandial Blood Sugar) by glucose oxidase and peroxidase method using automated analyser.
- HbA1c by High Performance Liquid Chromatography (HPLC) method using D10 haemoglobin system, Bioradin in Department of Biochemistry.
- Fasting lipid profile by cholesterol oxidase method using automated analyser in department of Biochemistry.
- **Brain CT / MRI Scan:** To confirm the infarct and other details using 128 slice CT machine and 3T MRI machine in department of Radiology.

Statistical Methods: The descriptive statistics was used to summarize the data. Mean, Median, Standard Deviation and proportions were calculated. Inferential statistics was performed using independent t test. A $P<0.05$ is considered as significant statistically. All the

statistical analysis were done using SPSS version 21.0. The graphs were made using Microsoft Excel.

RESULTS AND DISCUSSIONS

Out of 100 Acute Ischaemic Stroke patients, 61 were males and 39 were females, percentage of male subjects was higher. In the present study, 49 patients had history of hypertension and 21 patients had history of diabetes at presentation with stroke. In the present study alcoholism was seen in 42 % and 30 % of the patients had addiction to smoking/ tobacco chewing, Dyslipidaemia was present in 58% patients.

Table 1: The Severity of Stoke at Presentation to the Hospital According to NIH Stroke Scale

NIH stroke severity	No. of cases	Percentage
Minor Stroke	25	25
Moderate stroke	42	42
Moderate-severe stroke	18	18.0
Severe stroke	15	15.0
Total	100	100.0

In the present study 25% patients had minor stroke, 42% patients had moderate stroke, 33% patients had moderate to severe and severe stroke. In this study, 54% of stroke patients had CBG >140 mg/dl (stress hyperglycaemia, newly detected diabetes and previously diagnosed diabetes), 46% patients had glucose <140 mg/dl at the time of presentation. In the present study, 56% of the patients had blood pressure more than 140/90 mm Hg and 44% patients had blood pressure less than 140/90 mm Hg. In the present study, 45% patients were normoglycaemic and 21% were having stress hyperglycaemia, 16% were newly detected diabetics, 18% patients were diagnosed to be having DM prior to event of stroke. In the present study, 58.0% patients had dyslipidaemia.

Table 2 : Stroke Severity at 90 Days Follow up According to MRS Score

Stroke severity after 3 months	No. of cases	Percentage
< = 3	57	57.0
>3	43	43.0
Total	100	100.0

In the present study, 57% of the patients were suffering from severe stroke related disability after 3 months of stroke event. During study period total 6 patients died because of stroke and stroke related problems, among those patients 5 were having hyperglycaemia (>140 mg/dl) at presentation, and remaining 1 patient is normoglycaemic (<140 mg/dl) at presentation. In the present study among the patients with MRS>3 at 90 days follow-up, 81.5% had hyperglycaemia (>140 mg/dl), 4.3% patients were normoglycaemic (<140 mg/dl). In our study Among all these 3 subgroups of hyperglycaemic individuals, 85.7% of the patients with stress hyperglycaemia are associated with worse outcome, 87.5% individuals with newly detected DM and 66.7% of patients with previous history of DM were associated with worse outcome at the end of 3 months. In the present study 40.5% of the patients who had moderate stroke according to NIH stroke scale at presentation suffered from severe stoke at 90 days follow up. Nearly 77.8% of the patients who had moderate-severe stroke according to NIH stroke scale at presentation suffered from severe stoke at 90 days follow up. 68.5% of patients who were having MRS score 5 were associated with poor outcome at 90 days follow-up. 41.2% of patients who were having MRS score 4 were associated with poor outcome at 90 days follow-up. 63.2% of patients who were having MRS score 5 at discharge were associated with poor outcome at 90 days follow-up. 53.8% of patients who were having MRS score 4 at discharge were associated with poor outcome at 90 days follow-up. The present study involved 100 acute ischemic stroke patients who satisfied the inclusion criteria. In the present study, the majority of the patients 92 (92%) were in the age group of 41-80 yrs with a mean age 60.61, only 4 (4.0%) patients were <40 yrs and 4 (4%) above 80 yrs. Age is the single most important risk factor for stroke. For each successive 10 years after age 55, the stroke rate >doubles in both men and women 10. In the present study men (61%) were at greater risk of stroke than women (39%) which is similar to the studies done by Stead[11] Kostulas[12]. Women have lower stroke incidence than men because of genetic factors, positive effects of estrogen on the cerebral circulation, low blood pressure levels. Moreover, ischemic heart disease, peripheral artery disease and cigarette smoking are more prevalent among male stroke patients. The various risk factors associated with the stroke in this study were hypertension 49%, diabetes 21%, smoking 30% and ethanol abuse 42%. Hypertension is the most prevalent modifiable risk factor for stroke. The prevalence of hypertension increases with age, thus as the population ages, hypertension will become an even greater threat to public health and is likely to increase as life expectancy increases. The Framingham Heart Study investigators reported the lifetime risk of hypertension to be approximately 90% for men and women who were non-hypertensive at age 55 or 65 years and survived to ages 80-85 years old. Percentage of population with diabetes in present study is almost similar to that of studies of Kostulas *et al* and Megherbi[13]. The observation in the present study, mean systolic and diastolic blood pressure on admission was higher which is similar to the studies done by Kamel[14]. In patients with a previous stroke, statins reduce the risk of both ischemic stroke and other vascular events but also

increase the risk of hemorrhagic stroke. Accordingly, current guidelines recommend the same lipid targets for the primary and secondary prevention of both stroke and CHD. In this study we found that hyperglycaemia at the time of presentation with Acute Ischaemic Stroke conferred a worse prognosis. This has been shown in numerous previous studies but debate continues as whether it is a contributing factor to the more severe stroke or merely a stress response. In this study the patients with hyperglycemia had significantly more severe strokes (MRS>3) and the association with increased risk for death persisted even after adjustment for confounding factors. Whether early intervention with measures to aggressively control blood glucose levels in these patients may favourably influence their clinical course awaits clarification from randomized clinical trials. However restoration of normoglycaemia as soon as possible should be encouraged, although conclusive evidence of decreased risk with this approach is lacking.

CONCLUSION

Hyperglycaemia at stroke onset is associated with higher risk of poor outcome. A capillary blood glucose concentration above 140mg/dl at acute ischaemic stroke predicts higher mortality and morbidity. Patients with hyperglycemia at stroke onset, without prior history of DM have particularly poor prognosis, than that of patients with known diabetes. Hyperglycaemia predicts higher mortality and morbidity after acute ishaemic stroke. Hyperglycaemia is not solely a stress response to neurological insult, as it predicts outcome.

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