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Stress hyperglycemia affecting clinical outcome in ischemic stroke patients

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Abstract

Introduction: *Hyperglycemia is common in the early phase of stroke. The present study was aimed to assess the effect of stress hyperglycemia on the functional outcome in patients with ischemic stroke patients admitted to our indoor wards.*

Methodology: *This prospective study was conducted in the Department of Medicine, DY Patil School of Medicine, Navi Mumbai from June 2017 till June 2018 of patients who were admitted with the diagnosis of ischemic stroke. Stress hyperglemia was defined as fasting serum glucose levels at the first day after admission ≥126 mg/dl in patients without diabetes mellitus. Information regarding the demography, anthropometry, risk factors and blood sugar were noted. The severity of stroke was assessed with the National Institutes of Health Stroke Scale (NIHSS) and clinical outcome was assessed using the modified Rankin scale (mRS) at discharge.*

Results: *During the study period, a total of 106 patients were included and were classified as normoglycemic, stress hyperglycemic and diabetic. The mean age and gender distribution of the patients in all the three groups was similar. After 3 months, the NIHSS was significantly higher among patients with stress hyperglycemia as compared to those with normoglycemia. Further, asignificantly higher proportion of patients with stress hyperglycemia had a poor outcome (according to mRS) as compared to normoglycemics and similar to those with diabetics.*

Conclusions: *Ischemic stroke patients with stress hyperglycemia had worse clinical and functional outcome over a short-term follow up period. at 3rd month of follow-up.*

Keywords: *Stress hyperglycemia; Diabetes mellitus; Ischemic stroke; Outcome.*

Introduction

Hyperglycemia is common in the early phase of stroke and the prevalence of stress hyperglycemia has been observed in approximately two thirds of all ischemic stroke sub types on admission including lacunar strokes.[1] Stress hyperglycemia generally refers to a transient state of hyperglycemia during times of illnesses in individuals without prior evidence of diabetes mellitus. This form of hyperglycemia usually

resolves spontaneously after the acute phase of illness. In stroke patients, hyperglycemia has been recognized as a marker for in-hospital mortality. However, there is a considerable debate about whether hyperglycemia can affect the functional outcome in stroke patients. Few authors have concluded that hyperglycemia predicts increased stroke mortality irrespectiveof age, stroke type, and severity.[2] Other studies deny such an association and have concluded that hyperglycemia simply reflects a catecholamine-based stress response at the time of hospital admission.[3] Animal studies have suggested that hyperglycemia facilitates lactic acid production in ischemic tissue. Ishcemic penumbra may progress to infarction when there is excess lactate production and may result in poor clinical recovery and functional status of the patients. The present study was aimed to assess the effect of stress hyperglycemia on the functional outcome in patients with ischemic stroke patients admitted to our indoor wards.

Methodology

Study Design and Sampling

This prospective study was conducted in the Department of Medicine, DY Patil School of Medicine, Navi Mumbai between June 2017 till June 2018. We included patients who were admitted to our indoor ward with the diagnosis of ischemic stroke. Patients with recurrent ischemic stroke, haemorrhagic stroke, stroke with related complication (aspiration pneumonia, septicemia) and other neurological conditions were excluded from the study. Patients were diagnosed with ischemic stroke by the physicians based on the clinical findings and brain computed tomography. The purpose of the study was explained to the attendants of the patients and their informed consent was obtained. The study was approved by the institutional ethics committee. The stroke patients were classified as with diabetes mellitus if they had a history of a medical diagnosis of diabetes mellitus or taking anti-diabetic medications. Stress hyperglemia was defined as fasting serum glucose levels at the first day after admission ≥126 mg/dl in patients without diabetes mellitus. Rest of the patients were classified as normoglycemics.

Data Collection and Data Analysis

Using a pre-tested, semi-structured questionnaire, demographic data of the patients were noted. Anthropometric data were collected to obtain the body mass index of the pateints. Further, information about the various risk factors of stroke like hypertension, smoking, alcohol and coronary heart disease were enquired. All the readings of blood sugar measurements were noted for all the patient. The severity of stroke was assessed at admission and at three months follow up with the National Institutes of Health Stroke Scale (NIHSS). The clinical outcome was assessed using the modified Rankin scale (mRS) at discharge. Patients were classified as having poor clinical outcome if their mRS was less than 3. Only those patients who were alive at their 3 month follow up were included in the final analysis. All data were analyzed with the statistical package SPSS (version 21.0; IBM Corp). Data are presented as percentages for qualitative variables and as mean and standard deviation for quantitative variables. Differences in categorical variables between groups were assessed with the chi-square test, while differences in continuous variables between groups were assessed with student's t test. In all cases, a two-tailed $p < 0.05$ was considered significant.

Results

During the study period, a total of 106 patients were included and were classified as normoglycemic, stress hyperglycemic and diabetic. The mean age and gender distribution of the patients in all the three groups was similar (Table 1). Body mass index of normoglycemic, stress hyperglycemic and diabetic patients were $22.44 \pm 4.67 kg/m^2$, 25.95 ± 5.28 kg/m^2 and $26.72 \pm 2.91 kg/m^2$ respectively. Most common risk factors

reported by the patients were hypertension, smoking, alcohol and family history of coronary heart disease. Presence of coronary heart disease was significantly higher among patients with stress hyperglycemia and diabetes mellitus as compared to normoglycemics. Random blood sugar was found to be significantly higher among patients with stress hyperglycemia and diabetes as compared to normaglycemics. Fasting blood sugar at the time of admission was significantly higher among patients with diabetes (147.89 ± 7.2mg%) as compared to normoglycemics (97.45 ± 7.55 mg%) and those with stress hyperglycemia (101.32 ± 6.95 mg%). At their 3 month follow up fasting blood sugar and Hb A1C was significantly higher among diabetics as compared to normoglycemics and those with stress hyperglycemia. Functional status of the patients was assessed with NIHSS and at the time of admission, it was significantly poor in patients with stress hyperglycemia and diabetics (Table 2). After 3 months, the NIHSS was significantly poor among patients with stress hyperglycemia (12.44 ± 2.93) as compared to those with normoglycemia (8.15 ± 3.18), p value <0.05. Similarly, functional status was significantly poor among in patients with diabetes as compared to those with normoglycemia (p value <0.01). When assessed for functional status at the time of discharge from the hospital using the mRS, a significantly higher proportion of patients with stress hyperglycemia had a poor outcome as compared to normoglycemics and similar to those with diabetics.

Table 1 Distribution of patients according to their baseline socio-demographic and clinical characteristics

Variables	NG (n=27)	SH(n=34)	DM(n=45)	NG vs SH	NG vs DM	SH vs DM
Age (in years)	65.14 ± 3.22	68.29 ± 5.10	64.33 ± 6.74	NS	NS	NS
Gender						
Male	15 (55%)	21 (62%)	28 (62%)	NS	NS	NS
Female	12 (45%)	13 (38%)	17 (38%)	NS	NS	NS
BMI (kg/m^2)	22.44 ± 4.67	25.95 ± 5.28	26.72 ± 2.91	NS	<0.05	NS
Risk factors						
Hypertension	13 (48%)	14 (41%)	18 (40%)	NS	NS	NS
CAD	0 (0%)	2 (6%)	3 (7%)	<0.05	<0.05	NS
Smoking	11 (41%)	14 (41%)	16 (35%)	NS	NS	NS
Alcoholism	14 (52%)	12 (35%)	13 (29%)	<0.05	<0.05	NS
Family history for CAD	7 (26%)	9 (26%)	14 (31%)	NS	NS	NS
RBS (mg%)	119.44 ± 6.12	176.32 ± 5.21	189.64 ± 8.24	<0.01	<0.01	NS
FBS (mg%)						
At admission	97.45 ± 7.55	101.32 ± 6.95	147.89 ± 7.2	NS	<0.05	<0.05
At 3 months	82.72 ± 5.40	86.70 ± 4.92	124.68 ± 5.11	NS	<0.05	<0.01
HbA1C (%)	5.64 ± 0.33	5.72 ± 0.92	7.25 ± 1.07	NS	<0.05	<0.05

NG: normoglycemia; SH: stress hyperglycemia; DM: diabetes mellitus; BMI: body mass index; CAD: coronary artery disease; RBS: random blood sugar; FBS: Fasting blood sugar; NS: not significant

Table 2 Functional outcome of patients included in the study

Functional status	NG (n=27)	SH (n=34)	DM(n=45)	NG vs SH	NG vs DM	SH vs DM
NIH Stroke Scale						
At admission	13.09 ± 4.57	15.69 ± 3.17	19.83 ± 4.92	NS	<0.05	<0.05
At 3 months	8.15 ± 3.18	12.44 ± 2.93	15.09 ± 3.53	<0.05	<0.01	<0.05
mRS at discharge						
< 3	21 (78%)	16 (47%)	24 (53%)	<0.05	<0.05	NS
≥ 3	6 (22%)	18 (53%)	21 (47%)			

NG: normoglycemia; SH: stress hyperglycemia; DM: diabetes mellitus

Discussion

The issue of hyperglycemia in patients with acute stroke continues to generate a lot of debate. The present study was done to assess the impact of stress hyperglycmeia on the clinical outcome in patients with ischemic stroke. We found that as compared to normoglycemics, patients with stress hyperglycemia had a higher fasting blood sugar

and NIHSS at three months and their HbA1C levels were also high. Clinical outcome measured by mRS was also reported by a significantly higher proportion of patients with stress hyperglycmia as compared to normoglycemics. Hyperglycemia is common in patients with acute stroke, occurring in upto 60% of patients overall and approximately 12- 53% of acute stroke patients without a prior diagnosis of diabetes [4] Hyperglycemia whether manifesting as diabetes mellitus or stress hyperglycemia is associated with poor prognosis both in terms of mortality and functional recovery, irrespective of patient's age, severity of condition or stroke subtype.[5]

The underlying mechanism of how hyperglycemia affects stroke severity and outcome is incompletely understood. It has been suggested that hyperglycemia influences brain lactate production, as well as the progression of at-risk tissue to infarction, and has an important role in influencing stroke prognosis. A close correlation between acute blood glucose and lactate levels in ischemic brain has been demonstrated,[6] a finding which has been documented in animal studies as well[7]. Furthermore, increased lactate production has been shown to be closely associated with reduced penumbral salvage. This was demonstrated in animal studies that hyperglycemia before reperfusion is known to enhance anaerobic metabolism in penumbral tissue. The resultant lactate accumulation leads to intracellular acidosis, which may accelerate irreversible injury by direct neuronal toxicity or via secondary effects on the ischemic cascade, such as increased free-radical formation, enhanced glutamate release, and altered intracellular calcium regulation.[8]

At three month follow up period, we observed a worse clinical outcome in patients with stress hyperglycemia. This is similar to a a retrospective study which reported higher mortality at 90 days in non-diabetic patients with non-fasting glucose levels >130 mg/dl at admission, independently of stroke severity.[9] This study added to the findings of a previously published meta-analysis that reported that non- diabetic patients with stress hyperglycemia had higher risk for poor functional recovery up to 6 months after stroke.[10] The findings of the meta-analysis could be flawed as only unadjusted associations between stress hyperglycemia and functional outcome were reported and stroke severity was not factored in. These results are in contrast to the finding by a study with longer follow-up, in which stress hyperglycemia did not predict mortality at 1 year in non-diabetic patients when stroke severity was included in multivariate analyses.[11]

There are a few limitations of this study. First, we obtained blood sugar levels at the time of admission and later follow ups. A continuous glucose monitoring with a subcutaneous device in acute stroke will provide much more detailed information. Second, absolute lactate concentrations could not be obtained in the patients, which would have given us better clinical picture. Third, we excluded haemorrhagic stroke patients, which limited out ability to investigate the association between stress hyperglycemia and stroke subtypes. Finally, the follow up of the patients was limited to three months. Studies with longer follow up periods are required in future.

Conclusion

Stress hyperglycemia in patients with acute ischaemic stroke has been a known risk factor associated with poor clinical outcomes. The findings of the present study adds to the literature and provides prospectively collected data about the short-term functional outcome in stroke patients with stress hyperglycemia. This would help inform the physicians about the importance of hyperglycemia in stroke patients so that a reasonable outcome assessment can be conveyed to the attendants of the patients. Also achieving normal glucose levels in diabetics is equally important. Future randomized studies are required to understand the involved mechanisms and support the findings of the present study.

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Conflict of interest: None

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