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A study on incidence of stress hyperglycemia in acute ischemic stroke in non-diabetic patients and its prognostic significance

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ABSTRACT

Background: Hyperglycemia detected during acute illness-like ischemic stroke is associated with adverse outcomes more than in normoglycemic patients. However,very limited data regarding stress hyperglycemia and its prognostic value are available for our Indian population. **Aims and Objectives:** This study was aimed at comparing the stress hyperglycemic and normoglycemic patients in terms of mortality and functional recovery during 28 days follow-up assessed by the Barthel index for Activities of Daily Living. **Materials and Methods:** Adult non-diabetic patients with ischemic stroke were assessed for random venous blood glucose and HbA1c levels and divided into two groups: Patients with hyperglycemia and normoglycemia. The Barthel Index for Activities of Daily Living was used to compare mortality and functional recovery on the day of admission, day 3, and day 28 after stroke. **Results:** Mortality over the 28 days follow-up was significantly higher in hyperglycemic patients (45% vs. 20%,P=0.02). The Barthel Index score on admission (day 0) was 8.75±7.41 among stress hyperglycemic patient whereas it was13.54±11.12 among normoglycemic patient, which was significantly different (P=0.028). Similarly, day 3 (18.89±6.08 vs. 23.26±13.05, P<0.05) and day 28 scores (83.24±7.49 vs. 84.55±12.84, P=0.039) were significantly better in normoglycemic patients. **Conclusion:** The mortality rate was much higher and functional recovery was much poorer in stress hyperglycemic patients. Further studies should be directed toward determining complications in long-term follow-up related to stress hyperglycemia and the effects of management on patient outcome.

Key words: Stress hyperglycemia; Acute ischemic stroke; Barthel index; Prognostic value

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INTRODUCTION

A stroke, or cerebrovascular accident, is defined as the abrupt onset of a neurologic deficit that is attributable to a focal vascular cause Cerebral ischemia is caused by a reduction in blood flow that lasts longer than several seconds(10 s).[1,2] Among all the neurological diseases of adult life, strokes clearly rank first in frequency and importance. Stroke is the second leading cause of death worldwide and accounted for 6.2 million deaths in 2011.[2] The mortality rate of stroke in the acute phase is as high as 20% and it remains higher for several years after the acute event in stroke patients than in the general population.[3] Ischemic strokes account for more than 80% of total stroke events.[4] Even in the absence of a prior diagnosis of diabetes mellitus, a high proportion of patients may develop hyperglycemia following an acute stress such as a stroke or myocardial infarction (MI). Diabetes mellitus remains an independent risk factor for stroke and coronary heart disease. The increased risk of recurrent stroke due to diabetes ranges from 2.1 to 5.6 times that of non-diabetic patients and is

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independent of glucose control during the inter stroke period.[5]

The prevalence of previously recognized diabetes mellitus in acute stroke patients is only 8–20% whereas approximately one-third of all patients with diabetes have undiagnosed diabetes.[6] More evidence is now available to demonstrate how hyperglycemia and insulin resistance exacerbate brain injury and induce cell lysis.[7-9]

Post-stroke hyperglycemia during hospital admission, in patients who are not known to have pre-existing diabetes mellitus, is associated with adverse clinical outcomes.[10,11] Hyperglycemia after stroke increases during the first 12 hand then decreases or establishes within 1to a few weeks. Prolonged stress hyperglycemia in ischemic stroke patients increases the risk of in-hospital 28-day mortality, especially in non-diabetic patients.[12] However,there are very limited data regarding this in our population.

Aims and objectives

This study was done to determine the frequency of stress-induced hyperglycemia in patients who were admitted within 48 hours of the occurrence of an ischemic stroke and to find out if there was any difference between patients who had stress hyperglycemia and patients who did not in terms of short-term hospital stay mortality and 28-day follow-up functional recovery assessed by Barthel Index for Activities of Daily Living.

MATERIALS AND METHODS

This study was a prospective, comparative study in non-diabetic adult patients with clinical features of acute stroke with a CT (computed tomogram) scan of the brain suggestive of ischemic stroke. Patients with diabetes mellitus/whose admission time HbA1c was >6.5%, patients with transient ischemic attacks, hemorrhagic stroke, cerebellar/brain stem infarction, space occupying lesions in the brain, or with cerebral venous thrombosis were excluded from the study. The study was conducted between December 2019 and March 2022.

Study technique

After the selection of patients based on the inclusion criteria from general medicine ward, venous blood was drawn from patients and sent in vial with sodium fluoride coating for random plasma glucose on the day of hospital admission. Blood for glycosylated hemoglobin (HbA1C) was sent in an EDTA vial simultaneously. HbA1C measured by the high-performance liquid chromatography method.

A detailed history and physical examination of the patients were done simultaneously at the time of admission and put on the patient's information sheet. Two groups of patients were found based on HbA1C –

1. Undiagnosed diabetes patients were diagnosed when HbA1C was at or more than6.5%.
2. Non-diabetic patients defined as having no prior history of diabetes and normal HbA1c (<6.5%).

Among these two groups, only non-diabetic patients were considered for the study. Stress hyperglycemia was defined as admission time random venous blood glucose >180 mg% (>10mmol/L)nd HbA1c <6.5%.

Two groups of patients were found based on stress hyperglycemia:

A. Patients with stress hyperglycemia and
B. Patients without stress hyperglycemia.

These two groups of patients were compared in terms of mortality and functional recovery on the day of admission, on day3 after admission, and again on day 28 (wherever feasible) after stroke at (outpatient department) follow-up using Barthel Index Activities of Daily Living.[12-14] Barthel Index questionnaire was given to the patients or patient party and their answers were put down on Barthel Index form to calculate total score ranging from 0 to 100 [Table 1].

Ethical considerations

Ethical clearance was obtained from the Institutional Ethical Committee. All procedures were conducted in accordance with the 1965 Declaration of Helsinki and its later amendments.

Statistical analysis

The data were entered into a Microsoft Excel spreadsheet and then analyzed using SPSS 24.0 and Graph Pad Prism version 5. Data for numerical variables were summarized as mean and standard deviation, while categorical variables were summarized as frequency and percentages. Two-sample t-tests for a difference in mean involving independent samples or unpaired samples. One-way analysis of variance was used to compare means of three or more samples for numerical

Table 1: Barthel index scoring

Score	Interpretation
80–100	Independent
60–79	Minimally dependent
40–59	Partially dependent
20–39	Very dependent
<20	Totally dependent

data (using the F distribution). P<0.05 was considered statistically significant.

RESULTS

About 50% of the patients were at or above 60 years of age, mean age of the study population was 62±4.6 years. Around two-third of the patients were male and more than 80% of patients were hypertensive. Nearly half of the population were smoker and around 20% had addiction to alcohol. Table 2 presents the socio-demographic characteristics of the study participants.

Table 3 shows that 21.7% of patients had hyperglycemia on checking blood glucose value immediately after admission.

Table 2: Baseline characteristics of study population

Characteristics	Values
Age of patients (in years)	
<40	02 (2.1%)
40–59	44 (47.8%)
>60	46 (50.0%)
Mean age±SD (in years)	62.28±4.6
Gender	
Female	32 (34%)
Male	60 (66%)
Hypertension	
Yes	78 (84.7%)
No	14 (15.3%)
Atrial fibrillation	
Yes	15 (16.3%)
No	77 (83.7%)
Addiction habits	
Smoking	
Yes	40 (43.4%)
No	52 (56.5%)
Alcoholism	
Yes	22 (23%)
No	70 (77%)

Table 3: Distribution of stress hyperglycemia among study population

Stress Hyperglycemia	Number of patients (%)
Present	20 (21.7)
Not present	72 (78.3)
Total	92 (100%)

Over in the period of 28 days of follow-up, 24 patients died and among them patients with stress-related hyperglycemia contributed around 38% of cases. On separate analysis, 45% of patients with stress hyperglycemia died in comparison to only 20% of the normoglycemic group. The difference was statistically significant (P=0.02). Table 4 shows the distribution of mortality.

Barthel index score patterns

For all of the study patients, mean Barthel index score was calculated on days 0, 3, and 28 after stroke. The mean score on day 0 was 12.50±10.574 (Mean±S.D), on day 3, 22.32±12.010 (Mean±S.D), and on day 28, it was 84.25±11.775 (Mean±S.D). The difference in mean Barthel index score was statistically significant (P<0.001).

The Barthel index score on admission (day 0) was 8.75±7.41 among stress hyperglycemic patients whereas it was 13.54±11.12 among normoglycemic patients. This difference was statistically significant (P=0.028). Similarly, day 3 score (18.89±6.08 vs. 23.26±13.05, P<0.05) and day 28 scores (83.24±7.49 vs. 84.55±12.84, P=0.039) were significantly different between stress hyperglycemic and normoglycemic patients (Table 5).

DISCUSSION

Hyperglycemia detected during acute illness is associated with adverse outcomes. Among patients without known diabetes admitted to hospitals with MI, stroke, pneumonia, and exacerbation of chronic obstructive pulmonary disease, higher blood glucose levels are associated with in-hospital and late mortality, intensive care unit admission, prolonged length of hospital stay, and discharge to long-term nursing.[10]

In our study, initially, 100 patients were taken among which eight patients were diagnosed as diabetic whose diabetic status was unknown and thus excluded from the study. Rest of the 92 patients were assessed for mortality and Barthel Index score was calculated for them on days0, 3, and 28 on follow-up (Table 3).

Table 4: Distribution of mortality among the two groups of patients

Group	Parameters			Total	P-value
	Death				
	Day 0	Day 3	Day 28		
Stress hyperglycemia (n=20)	01	06	02	09 (45%)	0.02
Normoglycemia (n=72)	00	07	08	15 (20%)	
Total (n=92)	01	13	10	24 (26%)	

Table 5: Comparison of mean Barthel Index score between stress hyperglycemia versus normoglycemic patient

Barthel Index Score	Stress Hyperglycemia	Normoglycemia	P-value
	Mean (±SD)	Mean (±SD)	
At day 0	8.75±7.41	13.54±11.12	0.028
At day 3	18.89±6.08	23.26±13.05	0.047
After day 28	83.24±7.49	84.55±12.84	0.039

In our study, we defined stress hyperglycemia as RBS >180 mg/dl.We found that 20 (21.7%) patients had stress hyperglycemia among 92 study patients.

Among 20 patients with stress hyperglycemia, 9(45%) died in comparison to 15(20%) among 72 normoglycemic patients. The mortality among stress hyperglycemic patients was significantly higher than other group (P=0.02) reflecting the trend of the previous studies (Table 4).

In a meta-analysis of 31 studies published between 1966 and 2000, Capes et al., found that hyperglycemia is associated with 3-fold increased risk of short-term mortality, an increased hemorrhagic transformation rate and poor functional recovery of stroke patients compared to euglycemic patients.[10,15]

Sarkar et al., in their study on the effect of glycemia on stroke outcome in 450 patients during 2002–2004, found that the mortality within 4 weeks of stroke was higher in ischemic and hemorrhagic stroke patients with hyperglycemia (either known diabetic or stress hyperglycemia).[13]

In this study, the Barthel Index score on admission (day 0) was 8.75±7.41 (Mean±S.D) among stress hyperglycemia patient whereas 13.54±11.12 (Mean±S.D) among normoglycemic patient which was statistically significant with P=0.028. Similarly, the difference of day 3 score and final follow-up score on day 28 between stress-hyperglycemic and normoglycemic patients was also statistically significant with P<0.05 (Table 5).In this study, it was observed that functional recovery, as measured by Barthel Index, is much better in normoglycemic patients in short-term follow-up (28days) and hospital stay, whereas it is much worse in stress hyperglycemic patient.

Yadav et al., in 2004, studied 50 patients with acute stroke to assess the role of glycemic status on clinical profile and outcome of stroke. They found that hyperglycemia was an important risk factor for stroke and there was a correlation between deranged glucose metabolism, size, severity, and poor stoke outcome.[16]

Several explanations may account for the observed association between hyperglycemia and poor prognosis after ischemic stroke.

First, hyperglycemia may be directly toxic to the ischemic brain. Although the mechanism is not fully understood, accumulation of lactate and intracellular acidosis in the ischemic brain (produced through anaerobic cerebral glucose metabolism) may contribute.[17-21] These neurotoxic effects may be particularly important in the ischemic penumbra (the region of brain tissue surrounding the core of infarcted tissue where neurons are injured but still viable).[21] Second, hyperglycemic patients are relatively deficient in insulin leading to both reduced peripheral uptake of glucose and increased circulating free fatty acids which have been shown to promote calcium overload and arrhythmias.[22,23]

Third**,** patients without a diagnosis of diabetes who develop stress hyperglycemia are likely to have dysglycemia or undiagnosed diabetes when not stressed. Patients with dysglycemia or undiagnosed diabetes have a higher risk of vascular disease than patients with normal blood glucose level.[24-27] Furthermore, even non-diabetic hyperglycemia is linked to endothelial dysfunction**,** which is another possible mechanism of cerebrovascular disease in these patients.[28]

Fourth, hyperglycemia may disrupt the blood–brain barrier and promote hemorrhagic infarct conversion.[29,30]

Limitations of the study

There are certain limitations in this study –first, the sample size was very small and it was a single-institutional study, so the study results cannot be extrapolated on general population. Second, long-term follow-up was not done to assess functional recovery later. Moreover, location and size of ischemic stroke were not considered for functional recovery in this study.

CONCLUSION

Mortality rate is much higher and functional recovery was not well enough in stress hyperglycemic patients. These patients can constitute a high-risk group requiring close monitoring of blood sugars and thus preventing complications. Further studies should be directed toward determining complications in long-term follow-up related to stress hyperglycemia and the effects of management on patient outcome.

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Author's Contribution:
HR- Concept and design of the study, preparation of the first draft of manuscript; **SD-** Data collection and statistical analysis, reviewed the manuscript; **AK-** Concept and coordination, prepared the manuscript; **LB-** Literature review, interpretation of results, and reviewed the manuscript; **SKP-** Did the literature review, intellectual contribution, and final editing of the manuscript.

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