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Correlation Of Admission Day Plasma Glucose Levels In Patients With Acute Ischemic Stroke

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Abstract

Objective*: Acute stroke can lead to deviations in glucose metabolism which further can worsen outcomes in terms of residual disability as well as increased mortality. In patients with acute ischemic stroke and without a past history of diabetes mellitus (DM), prevalence of hyperglycemia is 30-40%. Sometimes hyperglycemia indicates previous obscure diabetes, but more commonly it is due to an acute stress response termed as stress hyperglycemia. In this study, we have explored whether functional outcomes in non-diabetic patients with ischemic stroke correlate with hyperglycemia or not.*

Materials and Methods*: This was a one year, prospective, observational study conducted from January to December 2021 in a tertiary health care centre on 200 patients presenting with first episode of acute ischemic stroke admitted in Medicine ward. Assessment of initial stroke severity was done in first 24 hours using the National institute of Health Stroke Scale (NIHSS) and assessment of the functional outcome was done after 1 month by using the Modified Rankin Scale(mRS). Admission plasma glucose levels were measured in all patients. HbA1C (%) was done when RBS was ≥200 mg/dl and diagnosis of diabetes mellitus was established using WHO criteria.*

Results*: In our study, it was observed that cut off of admission plasma glucose levels more than 155mg/dl (as interpreted by receiver operating characteristic curve) was associated with a higher NIHSS and mRS score when adjusted for age, sex, co-morbidities, body mass index, alcohol and smoking,. Mean NIHSS was worse, 16.8 in hyperglycemics as compared to 9.45 in normoglycemics ($p<0.0001$) and mean mRS was 3.88 in hyperglycemic group as compared to 2.06 in other group($p<0.0001$), higher scores indicating more severe disease in both scales. 36.4% mortality was seen in hyperglycemic group as compared to 7.83 in other group ($p< 0.0001$). Rate of new onset DM was 5.59% in hyperglycemics.*

Conclusion*: In our study, patients with hyperglycemia as defined by admission plasma glucose levels >155mg/dl had poorer outcomes as compared to normoglycemics in terms of severity of stroke at admission, residual disability at 1 month follow up and mortality.*

Keywords*: Hyperglycemia, stroke, modified Rankin Scale, NIHSS score*

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I. Introduction

Stroke is defined as the rapidly developing clinical symptoms and/or signs of local or global disturbance of cerebral functions, with symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.[1] Stroke continue to exist as a major global health problem as it is the second most common cause of death and the third most common cause of death and disability combined as expressed by disability-adjusted life-years lost (DALYs).[2] The burden of stroke has increased substantially in terms of the absolute number of cases from 1990 to 2019. There has been increase of 70.0% in incident strokes, 102.0% in prevalent strokes, 43.0% in deaths from stroke, and 143.0% in DALYs. Major bulk of the global stroke burden (86.0% of deaths and 89.0% of DALYs) belong to lower-income and lower-middle-income countries (LMIC).[3]

Crude incidence of stroke in India ranges from 108 to 172/100,000 people per year, crude prevalence from 26 to 757/100,000 people per year and one-month case fatality rates from 18% to 42%.[4] India is currently witnessing an epidemic of stroke due to existing non-traditional risk factors like alcohol and tobacco and also due to insufficient support needed for control of common modifiable risk factors like atherogenic lipid profile, diabetes, low haemoglobin, hypertension, and poor public awareness. Considering all these issues, it is of utmost

importance to evaluate risk factors, region-specific issues, epidemiology, management and outcome of stroke in India, so as to decrease the prevalence and to improve outcomes of stroke.[5]

Various recent studies have suggested that hyperglycemia is found frequently in ischemic stroke patients and is responsible for an increased risk of mortality and poor clinical outcomes.[6] Relationship between hyperglycemia and stroke is two-way. DM itself is a key risk factor for stroke and from other point of view, hyperglycemia in stroke can lead to poor outcomes and increased mortality. A recent study has shown an independent association of hyperglycaemia with poorer functional outcomes and higher mortality with a total increase of 12.9% within the first 48 h. These studies also show that outcomes are worse in non- diabetics as compared to diabetic patients.[7] Cut off value of hyperglycemia has been taken differently in different studies and we don't know what cut off value of plasma glucose will hold true for our population. Therefore it was planned to find out this cut off by measuring various plasma glucose levels in our population and correlate these values with outcomes in patients with acute ischemic stroke.

II. Material And Methods

This was a one-year, prospective, observational study conducted from January to December 2021 on patients presenting with first episode of acute ischemic stroke. This study was duly approved by the institutional ethics committee which operates through ICH-GCP/ICMR/New Drugs and Clinical Trial Rules-2019. Patients of age between 18-75 years with diagnosis of acute infarct made by computed tomography (CT)/magnetic resonance imaging (MRI) presenting within 7 days were included in the study. Patients with transient ischemic attack (TIA), hemorrhagic stroke, recurrent stroke, pre-existing diabetes mellitus, administration of dextrose before measuring plasma glucose level, pre-existing physical disability or known neurological disease, on steroids/any other drug known to increase plasma glucose levels were excluded from the study. Informed consent was obtained from all participants/attendants in case the participant was unable to provide consent or understand the procedure due to his/her medical condition. Detailed history and clinical examination was carried out in all the subjects. Demographic profile of all patients was recorded and their risk factors were evaluated. All patients were subjected to routine investigations which consist of serum levels of hemoglobin, total leukocyte count, creatinine, urea, albumin, fasting glucose, lipid profile, calcium, electrocardiography etc. At admission, first NCCT (Non-Contrast Computerized Tomography) head was done to exclude patients with hemorrhagic stroke. In patients having a normal CT scan, MRI brain was done for further elaboration. According to TOAST classification, stroke was categorised into large artery atherosclerosis, cardio-embolic, small vessel occlusion, stroke of other determined and undetermined etiology.[8]

Admission day plasma glucose levels were measured in all patients within first 2 hours by venous plasma estimation. HbA1C was done when RBS was ≥200 mg/dl and diagnosis of diabetes mellitus was established using WHO criteria. At admission, severity of stroke was evaluated in first 24 hours by applying NIHSS score (National institute of Health Stroke Scale)[9,10]. According to symptoms and on the basis of NIHSS score, patients were classified into the following five categories as:

0= No stroke
1-4= Minor stroke
5-15= Moderate stroke
16-20= Moderate to severe stroke
21-42= Severe stroke

On follow up after 1 month, patients were contacted in person or telephonically also if they could not come to the hospital. The functional outcome was evaluated by applying Modified Rankin Scale(mRS)[11]. The mRS score varies from 0 that is no residual disability to 6 which means death.

mRS≤2 = favourable or good outcome
mRS≥3 = poor outcome.

Diabetes, HTN, atrial fibrillation (AF), coronary artery disease (CAD) and dyslipidemia were specified as certain covariates per standard definitions.

Sample Size

On the basis of the proportion, the minimum sample size required to achieve a confidence interval of 95% and a power of 80% will be estimated and a non-response rate of 5% will be assumed and the final sample size will be obtained. $p< 0.05$ will be considered statistically significant. According to Donghua Mi et al., prevalence of ischemic stroke in non-diabetic patients was found to be 59.3%.[12]

Using this, Sample size (N) was calculated by using following formula:

P = prevalence from previous studies= 59.3
Q = 100-p =40.7
d = absolute error or precision (6-20%)
Thus N = $4PQ/d^2$ = 4×59.3×40.7/7.1×7.1=191.5

Considering 5% drop out the sample size will be 191.5+9.5 = 200 approx. Thus total no of patients for study will be 200.

Statistical Analysis

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (interquartile range). The following statistical tests were applied for the results:

1. The association of the variables which were quantitative in nature were analysed using Independent t test.
2. The association of the variables which were qualitative in nature were analysed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used.
3. Spearman rank correlation coefficient was used for correlation of MKAQ scale with MMAS8.
4. Multivariate logistic regression was used to find out significant factors affecting hyperglycemia.
5. Pearson correlation coefficient was used for correlation of admission plasma glucose with NIHSS during stay, mRS at 1 month and HbA1C (%) and correlation of NIHSS during stay with mRS at 1 month.
6. Receiver operating characteristic curve was used to find cut off point, sensitivity, specificity, positive predictive value and negative predictive value of admission plasma glucose to predict poor prognosis.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 21.0. For statistical significance, p value of less than 0.05 was considered statistically significant.

III. Results

Initially 238 patients were enrolled but many were excluded because of incomplete data especially mRS after 1 month (response rate 77.5%) and finally 200 patients were included. Maximum number of patients 75(37.50%) belonged to age group 66 to 75 years. Maximum age was 75 year and minimum being 35 years. Mean age(years) of study subjects was 59.33 ± 10.7. Out of 200, 138(69.00%) patients were males and 62(31.00%) patients were females. Among the common risk factors for stroke, the most common was dyslipidemia 144 (72.00%) followed by hypertension 137(68.50%), atrial fibrillation 49(24.50%) and chronic kidney disease 40(20.00%). Coronary artery disease was present in 28 out of 200 patients (14.00%). Majority 84(42.00%) of patients were smokers and 67 out of 200 patients (33.50%) were alcoholics. In majority 65(32.50%) of patients, stroke type was large artery disease followed by cardioembolic 50(25.00%), small vessel occlusion 43(21.50%) and undetermined etiology 33(16.50%). Only 9 out of 200 patients (4.50%) belonged to other known cause category. Baseline characteristics of study participants are summarized in Table 1.

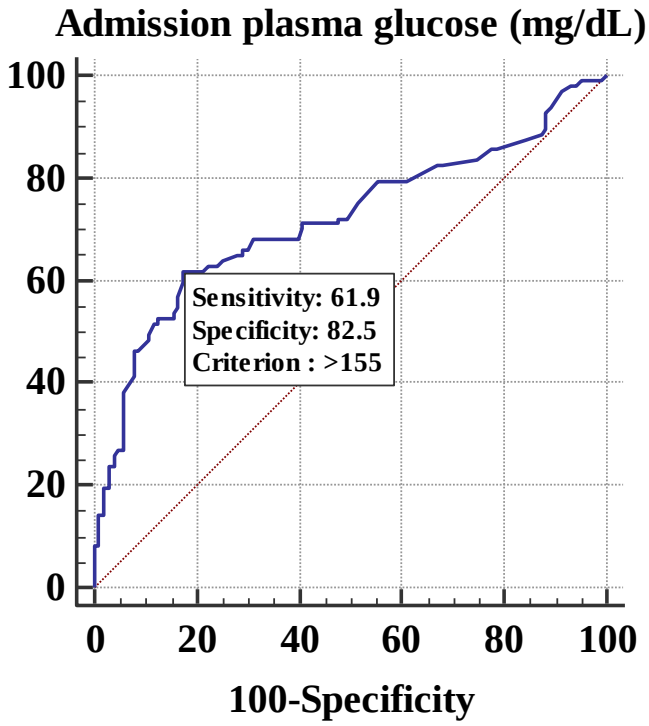
Table 1: Baseline characteristics of study population

Age(years)	**Frequency**	**Percentage**
35 to 45 years	19	9.50%
46 to 55 years	52	26.00%
56 to 65 years	54	27.00%
66 to 75 years	75	37.50%
Gender		
Female	62	31.00%
Male	138	69.00%
Total	200	100.00%
Co-morbidities		
Hypertension	137	68.50%
Coronary artery disease	28	14.00%
Atrial fibrillation	49	24.50%
Chronic kidney disease	40	20.00%
Dyslipidemia	144	72.00%
Personal history		
Alcohol	67	33.50%
Smoker	84	42.00%
Stroke types		
Undetermined etiology	33	16.50%
Cardioembolic	50	25.00%
Large artery disease	65	32.50%
Small vessel occlusion	43	21.50%
Other known cause	9	4.50%

The cut off value of admission plasma glucose level above which poor outcomes (in terms of mRS score greater than 2 and NIHSS score less than 5) was observed was found to be 155mg/dl, as shown in figure 1. So admission plasma glucose more than 155mg/dl at admission was considered as hyperglycemia in our study.

Receiver operating characteristic curve was used to find cut off point, sensitivity, specificity, positive predictive value and negative predictive value of admission plasma glucose to predict poor prognosis. Admission plasma glucose levels at a cut off > 155 mg/dl showed a significantly good discrimination power for increased mortality and morbidity. [13]

Figure1:-Receiver operating characteristic curve of admission day plasma glucose to predict poor prognosis



Hyperglycemia was present in 85 out of 200 patients (42.50%) and absent in 115(57.50%) patients, as shown in table 2. Total 11 out of 200 patients (5.50%) had diabetes mellitus. The severity of stroke was determined based on NIHSS scale. Mean value of NIHSS at admission was 12.58 ± 7.39. Mean NIHSS at admission in patients with hyperglycemia was 16.8 ± 7.22 which was significantly higher as compared to patients without hyperglycemia 9.45 ± 5.8 (p value <.0001). Mean value of mRS of study subjects after one month of presentation at our centre was 2.84 ± 2.14. Mean mRS score at 1 month in patients with hyperglycemia was 3.88 ± 2.1 which was significantly higher as compared to patients without hyperglycemia (2.06 ± 1.83) (p value <.0001) (table 3)

Table 2:-Distribution of hyperglycemia in study subjects

Hyperglycemia	Frequency	Percentage
Absent	115	57.50%
Present	85	42.50%
Total	200	100.00%

Table 3:-Association of NIHSS at admission and mRS scores at one month with hyperglycemia

NIHSS score at admission	Patients with hyperglycemia(n=85)	Patients without hyperglycemia(n=115)	Total	P value
Mean ± SD	16.8 ± 7.22	9.45 ± 5.8	12.58 ± 7.39	<.0001‡
mRS score at 1 month	**Patients with hyperglycemia(n=85)**	**Patients without hyperglycemia (n=115)**	**Total**	**P value**
0	7 (8.24%)	30 (26.09%)	37 (18.50%)	<.0001†
1	9 (10.59%)	17 (14.78%)	26 (13%)	
2	8 (9.41%)	32 (27.83%)	40 (20%)	
3	11 (12.94%)	11 (9.57%)	22 (11%)	
4	9 (10.59%)	11 (9.57%)	20 (10%)	

5	10 (11.76%)	5 (4.35%)	15 (7.50%)	
6	31 (36.47%)	9 (7.83%)	40 (20%)	
Mean ± SD	3.88 ± 2.1	2.06 ± 1.83	2.84 ± 2.14	<.0001‡

Out of 200 patients, 40 patients could not survive (mRS 6) (20% motality rate). Among these 40 patients, 35(87.50%) patients were males and 5(12.50%) patients were females. In majority 34(85.00%) of patients, NIHSS at admission was >14. NIHSS at admission was ≤ 14 in only 6 out of 40 patients (15.00%). In majority 31(77.50%) of died patients, hyperglycemia was present and 7 out of 40 patients (17.50%) had diabetes mellitus (table 4).

Table 4 :- Distribution of characteristics of patients who died

Characteristics of patients who died	Frequency	Percentage
Gender		
Female	5	12.50%
Male	35	87.50%
NIHSS at admission		
≤14	6	15.00%
>14	34	85.00%
Hyperglycemia	31	77.50%
Diabetes mellitus	7	17.50%

Thus, our study showed that there was a significant association between hyperglycemia, higher NIHSS and mortality when adjusted for age, sex, co-morbidities, body mass index, alcohol and smoking. Significant positive correlation was seen between admission plasma glucose (mg/dL) with NIHSS during stay, mRS at 1 month, HbA1C(%) with correlation coefficient of 0.52, 0.459, 0.465 respectively (Table 5). Significant positive correlation was seen between NIHSS at admission with mRS at 1month with correlation coefficient of 0.717 (Table 6).

Table 5:-Correlation of admission plasma glucose with NIHSS at admission, mRS at 1 month

Variables	NIHSS at admission	mRS at 1 month
Admission plasma glucose		
Pearson correlation coefficient	0.520	0.459
P value	<0.0001	<0.0001

Table 6:-Correlation of NIHSS at admission with mRS at 1 month.

Variables	mRS at 1 month
NIHSS at admission	
Pearson correlation coefficient	0.717
P value	<0.0001

IV. Discussion

Out of total 200 patients, 138(69.00%) were males and 62(31.00%) were females (male: female = 2.22:1). Globally, stroke is more prevalent in men than women. One of the vital risk factors for stroke is male gender because cigarette smoking, ischemic heart disease, peripheral artery disease are more prevalent amidst males. Women have lesser incidence of stroke as compared to men because of low blood pressure levels, genetic factors, positive effects of estrogen on the cerebral circulation. Various stroke studies from India showed that male to female ratio varied from 2:1to 3:1.[2,14]

In our study, we have included patients of acute ischemic stroke without history of pre-existing Diabetes mellitus. Mean random admission plasma glucose was 143.12 ± 76.49 mg/dL and hyperglycemia defined as admission day plasma glucose levels more than 155mg/dl was present in 85 out of 200 patients (42.50%). On further evaluation, on the basis of HbA1c done it was found that only 11 out of 200 patients (5.50%) had diabetes mellitus (HbA1c > 6.0%). Thus 42.5 % patients were hyperglycemics out of which only 5.50% were diabetics. Various studies conducted worldwide have pointed towards the fact that hyperglycemia is prevalent in patients of acute stroke independent of their diabetic status. SK marulaiah et al. conducted a study in patients of acute ischemic stroke to identify the association of admission hyperglycemia with outcomes. 56% patients had hyperglycemia and in 92% of these patients, it was attributed to stress related hyperglycemia.[15] A recent study has also shown that hyperglycemia can occur in critically ill patients including stroke because of acute stress response typically called stress related hyperglycemia due to stimulation of the hypothalamic–pituitary–adrenal (HPA) axis which causes stimulation of the sympathetic autonomic nervous system leading to accelerated release of

catecholamines and increased levels of serum glucocorticoids including cortisol. An appropriate activation of the hypothalamic–pituitary–adrenal axis leading to hypercortisolism is vital for acute provision of energy and short-term survival but in long term can lead to increased morbidity and mortality. High cortisol levels indicate more severe stress whereas low levels of cortisol point to an inability to sufficiently respond to stress termed as relative adrenal failure. [16,17]

In our study, an increasing trend in NIHSS has been noticed with increasing admission blood glucose levels suggestive of increasing severity of stroke. Study by Hanna A. El-Gendy et al. showed that high random blood sugar (RBS) on admission positively correlates with higher median duration of hospital stay and higher median NIHSS score ($p < 0.001$).[13] This was similar to our study in which there is a positive correlation between NIHSS score and hyperglycemia. In our study good functional outcome at 1 month was seen in 51.5% patients and poor functional outcome in 48.5 % of patients while 20% patients died by the end of 1 month. Mortality rate was similar to a study by DAS P. C. et al. [18]

Blood glucose levels in patients with poor functional outcomes was significantly higher than those with good outcomes as per mRS score at 1 month. Among patients who died, hyperglycemia was significantly associated with mRS score (Pearson correlation=0.459, $p<0.000$). This was in agreement with a Keith W. Muir et al. study which suggested that hyperglycaemia had a positive association with mortality and poorer functional outcome independently with a complete increase of 12.9% within the first 48 h (95% CI 9.2–16.7).[7] A study by **S**tead LG et al. showed that remarkably higher stroke severity and more functional impairment was observed in patients with hyperglycemia than those with normoglycemia. Mortality at 90 days was 2.3 times higher in hyperglycemics as compared to normoglycemics ($P < 0.001$).[19]

The biological mechanism explaining the association how hyperglycemia affects outcomes in ischemic stroke independently, after adjusting for other confounding factors such as age, alcohol, smoking ,comorbidities and stroke severity is most likely due to hyperglycemia induced aggravated cerebral damage.[20,21] Increase in reactive oxygen species (ROS) production during the initial onset of hypoxia and reoxygenation is considered to be one of the most important mechanism responsible for hyperglycemia induced aggravated cerebral damage.[22,23] Hyperglycemia has potential to create an imbalance in ion homeostasis and shift to anaerobic metabolism in cells causing cell death. Also it has been found in some studies that hyperglycemia can directly activate coagulation by accelerating the production of thrombin–antithrombin complexes and thus can be correlated with constant occlusion in ischemic stroke even in patients treated with rtPa (recombinant tissue plasminogen activator).[24,25] It is also a risk factor for BBB (blood brain barrier) injury because of augmented inflammatory responses resulting in increase in cerebral edema and hemorrhagic transformation.[26,27] .

Although many studies have found a significant relationship between hyperglycemia and poor functional outcomes in stroke, safety and efficacy of tight glycemic control (tGC) is still a topic of debate. On one hand some trials have described that insulin has a neuroprotective effect and tGC can be beneficial but on the other hand some recent trials has shown that use of tGC can be very challenging in these patients and can accelerate the chances of hypoglycemia leading to a poor clinical outcomes.[28] The landmark leuven clinical trials were done to study about tGC in patients with stroke. Goal of the trial was to keep blood glucose levels less than 6.1 mmol/L.[29] This trial concluded that iCU (intensive care unit) patients who were treated with tGC had better favourable outcomes as compared to patients not treated with tGC. The landmark Glucose Insulin in Stroke Trial (GIST-UK), was done to study about tGC. It was concluded that there was no noteworthy distinction in mortality at 90 days between ischemic stroke patients who received tight glycemic control and who received routine care.[30]

V. Limitations

1. This study was conducted in a government set up and due to resource limitation and non-availability of HbA1c in hospital, it was only done in patients having RBS ≥200 mg/dl to reduce the financial burden on mostly poor patients. Also the probability of Diabetes Mellitus was higher when RBS was ≥200 mg/dl.
2. Most of the patients could not reach hospital within window period of thrombolysis and those who reached could not undergo thrombolysis due to multiple reasons like affordability issues in view of non-availability of thrombolytic agents (Tenecteplase and Reteplase) in hospital and as per past experience many patients did not prefer thrombolysis because of explained risks. Therefore patients undergoing thrombolysis (far & few) were not included.
3. Non-availability of mechanical thrombectomy in hospital.
4. Blood glucose monitoring was not done on follow up after 1 month.

VI. Conclusion

Admission hyperglycemia is an independent risk factor responsible for poor outcomes in ischemic stroke after adjusting for other risk factors like dyslipidemia, hypertension, atrial fibrillation etc. Higher plasma glucose levels were correlated with NIHSS and mRS clinical scoring systems.

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