Original Article

Stress Hyperglycemia as a Prognostic Marker in Acute Ischemic Stroke

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ABSTRACT

Background : Stress hyperglycemia is transient elevation of the blood glucose due to the stress of acute illness. The present study was carried out to know the association of stroke with hyperglycemia and its impact on hospital outcome.

Method : Total 150 CT Scan proved patients of acute ischemic stroke were enrolled in the study. Patients were evaluated for glycemic status on admission Those who had random blood glucose (RBG) > 140 mg/dl was taken as hyperglycemia and grouped into group A -71, (47.33%) and those who had RBG < 140 mg/dl were grouped into group B - 79 (52.67%).The prevalence of hyperglycemia in stroke was found out and various parameters were compared between two groups.

Results : Prevalence of hyperglycemia in our study was found out to be (47.33%).NIHSS score was compared between two groups. Higher score is associated with more impairment of neurological function. Mean NIHSS score in group A on admission was 17.72 ± 3.86 and on discharge was10.42 ± 3.93. In group B, NIHSS score on admission was 12.95 ± 2.65 and on discharge was 4.36 ± 1.66.The mean GCS score in Group A was 6.11+ 2.74 and Group B was7.78 + 2.70.It means that the level of consciousness was better in normoglycaemic patients. Mean duration of hospital stay in group A and group B was 4.61 ± 1.88 and 3.86 ± 1.49 respectively, which is statistically highly significant. Functional recovery was better in normoglycaemic patients compared to hyperglycemic patients. The mortality was more in group A (40.84%) than group B (10.12%).

Conclusion : Admission hyperglycemia is associated with increased duration of in hospital stay, late functional recovery and increase mortality.

Key-words : Stress **Hyperglycemia,** Normoglycaemic Stroke, NIHSS score(National institute of health stroke scale), GCS score (Glasgow coma scale)

Introduction :

Stroke is a major health problem globally. It is the secondmost common cause of death and fourth leading cause of morbidity or disability worldwide[1]. World Health Organization (WHO) defines stroke as rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting for more than 24 hours or leading to death, with no apparent cause other than that of vascular origin[2]. Ischemic stroke accounts for 50-80%, hemorrhagic stroke accounts for 7-27% and subarachnoid hemorrhage accounts 1%-7% of total stroke cases.

Many factors affect the prognosis in patients with stroke like older age, temperature >38°C, GCS on admission, NIHSS on admission, hyponatremia and hypoglycemia. Stress hyperglycemia is also common in patients with acute stroke, occurring in up to 60% of patients[3,4]. Admission hyperglycemia predicts higher mortality and morbidity after acutestroke independently of other adverse prognostic factors, mentioned above[5].

Stress hyperglycemia is directly toxic to the ischemic brain. Accumulation of lactate and intracellular acidosis in the ischemic brain promotes and accelerates ischemic injury by enhancing lipid peroxidation and free radical formation, and impairing mitochondrial function[6,7]. These neurotoxic effects may be particularly important in the ischemic penumbra where neurons are injured but still viable. Hyperglycemia facilitates the development of cellular acidosis in the ischemic penumbra and results in a greater infarct volume, thus promoting the recruitment of potentially salvageable neurons into the infarction[8].

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Received on 20th December 2019 Accepted on 28th December 2019

Stress hyperglycemia may be a marker of the extent of ischemic damage in patients with stroke, patients with severe or fatal strokes may develop hyperglycemia because of greater release of "stress hormones" such as cortisol and norepinephrine. Stress hyperglycemia is of pathophysiological significance in patients with stroke and is not simply an epiphenomenon of the stress response to stroke[9]. Hence the present study was carried out to know whether stress hyperglycemia can be a prognostic marker in patients of acute ischemic stroke.

Methodology :

The present cross-sectional observational study was conducted in 150 cases of acute ischemic stroke, admitted in medicine wards and intensive care units at Government Medical college Nagpur, from November 2016 to November 2018.The study was approved by ethical committee of the hospital. Informed consent was taken from all participants or from their close relatives. All CT proved cases of acute ischaemic stroke, more than 18 yrs. of age and with normal HbA1c levels were included in our study. Patients with age < 18 years, patients of hemorrhagic stroke, known diabetics, and patients with deranged HbA1C level were excluded from the study.

Detailed clinical history was recorded with particular reference to temporal profile of the stroke including history of risk factors like hypertension, smoking, diabetes mellitus, old cerebrovascular episode, alcoholism. The physical examination with special emphasis on neurological examination was done. Acute ischaemic stroke was confirmed by computed tomography scan of brain features. Clinical and lab assessment (serum sodium levels, random blood sugar, renal function test, liver function test, lipid profile and HbA1c) was done.

All the patients were divided into two groups according to random blood glucose (RBG) on admission, group A included patient who were having blood sugar > 140 mg/dl, group B having blood sugar levels < 140 mg/dl. Functional neurological recovery in group A and group B was assessed with the help of NIHSS score on admission and on discharge. GCS score was also calculated on admission and on discharge. Various parameters were compared between two groups.

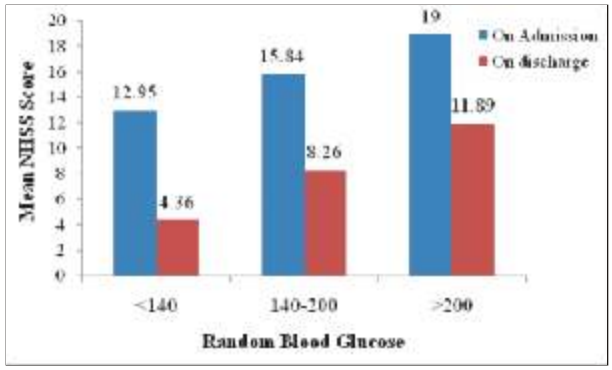
Statistical analysis :

Continuous variables were presented as mean ± SD and categorical variables were expressed in frequency and percentages. Continuous variables were compared between stress hyperglycemia group A and normoglycemic group B patients and also between survival and mortality by independent t-test. Categorical variables compared by performing a chi-sq test for small numbers, Fisher exact test as used wherever applicable. The entire tests were two-sided. $p < 0.05$ was considered as statically significance. Statistical software STATA version 14.0 was used for data analysis.

Observations and Results :

Total 150 patients were included in our study. They were divided according to blood sugar level on admission. Group A included those having hyperglycaemia, and group B included those patients in whom the blood sugar levels were normal. Out of 150 stroke patients 71 (47.33%) were having admission hyperglycemia and 79 (52.67%) were normoglycemic.

Figure 1 : **Correlation of RBG values and NIHSS Score in patients**



Three groups were made according to RBG on admission (1st group - RBG < 140 mg/dl, 2nd - RBG 140-200 mg/dl and 3rd - RBG > 200 mg/dl) and compared with NIHSS score on admission and on discharge, ***(Figure 1).*** NIHSS score in group A on admission was 17.72 ± 3.86 and on discharge was10.42 ± 3.93. In group B NIHSS score of

Table 1 : **Age and sex distribution of patients in group A and group B**

Age in Years	No. of patients	Group A		Group B	
		Male	Female	Male	Female
31-40	11 (7.3%)	2	2	4	3
41-50	25 (16.7%)	4	4	13	4
51-60	36 (24.0%)	11	6	14	5
61-70	56 (37.3%)	15	15	13	13
71-80	19 (12.7%)	7	2	4	6
>80	03 (2.0%)	2	1	0	0
Total	150 (100%)	41	30	48	31
Mean age	60.06 ± 11.47	61.6 ± 10.54	62.90 ± 11.26	60.29 ± 12.47	56.54 ± 10.95
Range	31-84	38-62	34-84	31-76	31-75

Total 150 patients of acute ischemic stroke were included in the study, among them 89 (59.3%) were males and 61 (40.7%) were females. The mean age of all the patients studied was 60.06 ± 11.47 years. Maximum numbers of patients were in the age group of 61-70 years (37.3%).

admission was 12.95±2.65 and on discharge was 4.36 ±1.66. Higher score signifies poor outcome or slow recovery and increased mortality.

Table 2 : **GCS Score in patients of acute ischaemic stroke**

GCS	No. of Patients	Group-A	Group-B	p-value
<5	32	26 (81.25%)	6 (18.75)	Chi2= 19.6849 <0.001, HS
5-10	100	40 (40%)	60 (60%)	
11-15	18	5 (27.77%)	13 (72.22%)	

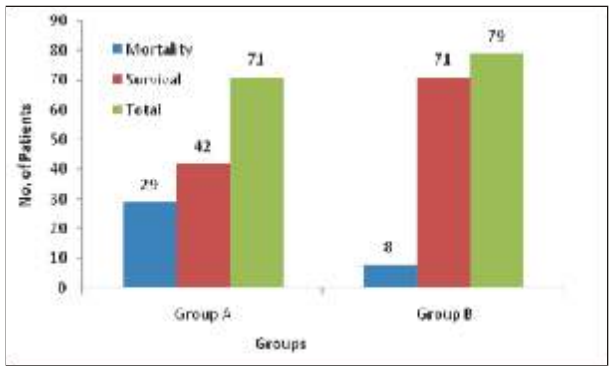
Mean GCS in patients having admission hyperglycemia was 6.11 ± 2.74, mean GCS in patients with normoglycemia was 7.78 ± 2.70. Hyperglycemia was more commonly seen to be associated in patients with lower GCS values. The statistical difference was found to be significant (p = 0.0003) which suggests that fall in GCS is proportionate to the degree of severity of hyperglycemia.

Table 3 : **Correlation of stress hyperglycemia with mean duration of hospital stay**

RBG	No. of Patients	Mean hospital stay	P-value
< 140 mg/dl	79	3.86 ± 1.49	0.0223
140-200 mg/dl	32	4.5 ± 1.81	
> 200 mg/ dl	39	4.71 ± 1.95	

Mean duration of hospital stay in group A and group B was 4.61 ± 1.88 and 3.86 ± 1.49 day respectively, (p=0.0067). Three groups were made according to RBG on admission. After statistical analysis hyperglycemia was found to significantly increase the length of hospital stay in stroke patients, (p=0.0223).

Figure 2 : **Outcome in patients of acute ischaemic stroke**



Out of 71 patients with hyperglycemia in acute stroke, 29 patients (40.84%) died whereas in non-hyperglycemic group of 79 patients, 8 patients (10.12%) expired, ***(Figure 2).*** After statistical analysis, the p-value was found to be < 0.001; which suggested there was a strong significant association between hyperglycemia with the outcome of stroke.

Table 4 : **Correlation of RBG levels and mortality in acute ischemic stroke**

RBG in mg/dl	No. of Patients	Mortality	P-value
<140 mg/dl	79	8 (10.1%)	<0.001, HS
140-200 mg/dl	32	9 (28.1%)	
>200 mg/dl	39	20 (51.3%)	

When RBG levels on admission were compared with the mortality, it was found that that mortality was lowest in group with RBG > 140 to 200 mg/dl (10.1%), the group of patients with RBG 140 mg/dl-200 mg/dl mortality was (28.1%) and highest mortality was (51.3%) in group of RBG on admission > 200 mg/dl. As RBG on admission increased, mortality also increased. The relation of increasing value of admission RBG and its prognosis, it was found out to be highly significant with p value of < 0.001.

In our study the factors which were found to be highly significant were Increased Mean RBG, presence of fever, raised systolic BP, raised total cholesterol, low HDL, high LDL, old history of systemic hypertension, low GCS score,mean duration of hospital stay, NIHSS score on admission and NIHSS on discharge.

Age, raised diastolic blood pressure, raised triglyceride, old history of Cerebrovascular episode, history of smoking were compared between two groups of acute ischaemic stroke patients, and found to be significantly associated with stress hyperglycemia.

Whereas no significant association with gender, pulse rate, serum sodium level and history of alcoholism was found.

Table 5 : **Comparison of all study parameters between Group-A and Group-B.**

Parameter	Group-A	Group-B	p-value
Mean Age in years	62.35 ±10.90	58.01 ± 11.64	0.0202, S
Gender M/F	41 M 30 F	48 M 31 F	0.708,NS
Mean Pulse rate	86.14 ±16.10	85.31 ± 16.16	0.7552, NS
Mean SBP	152.25±19.21	143.79 ± 16.03	0.0039, HS
Mean DBP	92.39 ± 13.46	88.22 ± 9.96	0.0318, S
Mean RBG	205.32 ± 39.65	114.15± 13.48	<0.0001, HS
Fever present	30(42.25%)	15(18.98%)	0.002,HS
Mean Triglycerides	169.22 ± 65.92	143.87 ± 54.30	0.0108, S
Mean Total cholesterol	238.04±73.01	201.26 ±52.19	0.0005, HS
Mean HDL	40.95 ± 7.15	47.21 ± 5.23	<0.0001, HS
Mean LDL	136.94 ± 28.97	117.34 ± 27.78	0.0003, HS
History of Hypertension present	58(81.61%)	49(62.02%)	0.008, HS
History of Old CVE present	13(18.30%)	5(6.32%)	0.024, S
History of Smoking present	28(39.43%)	16(20.25%)	0.0100, S
History of Alcoholism present	18(25.35%)	21(26.58%)	0.864, NS
Mean SerumSodium	134.22 ±9.26	135.48±8.27	0.3819, NS
GCS score	6.11± 2.74	7.78 ± 2.70	0.0003, HS
Mean Duration of hospital stay (days)	4.61 ±1.88	3.86 ± 1.49	0.0067, HS
Mean NIHSS score on admission	17.72 ± 3.86	12.95 ±2.65	<0.0001, HS
Mean NIHSS on discharge	10.42 ±3.93	4.36 ±1.66	<0.0001, HS

Discussion :

In the present study, age and gender distribution of patients reflects that the late middle-aged (51-70 years) group of patients and male population were more prone to develop stroke. This finding may be due to hormonal protection from cardiovascular and cerebrovascular diseases of female population before menopause and also because males are more prone to risk factors for stroke like smoking and alcoholism. The overall prevalence of hyperglycemia in acute stroke was found to be 47.33% (71 cases) which is comparable with other studies[10-13]. These studies are also suggestive of fact that male population is more prone for cerebrovascular episodes and most of the patients were in the age group of 51-70 years.

All the patients were assessed with NIHSS stroke scale; three categories were made according to NIHSS. NIHSS score was compared between group A and group B, we found that 15 patients of group A were having NIHSS score in the range of 1-15, while 42 patients in group B were in range of 1-15.In the range of 16-30, number of patients in group A was 53, whereas in group B was 37. In range of NIHSS more than 30 all 3 patients were from group A. These observations suggest that group A consisted of patients with bad prognosis as more the NIHSS score, worse is the prognosis or slow recovery and increased mortality. Similar observation reported in study done by Prasad et al[11].

The existing study found that as the RBG on admission increased, NIHSS score increased which is bad prognostic marker. NIHSS score was compared also on discharge between two groups; which showed that as RBG level increased, functional recovery decreased. Admission hyperglycemia came to be highly significant factor related to late recovery and increased morbidity in acute ischemic stroke patients. Functional recovery compared by difference of NIHSS score on admission and on discharge, more the difference better is the outcome. In current study admission hyperglycemia is strongly associated with poor functional recovery in acute ischemic stroke patients. These results are comparable with the study conducted by Prasad et al[11].

Severe hyperglycemia was more commonly seen to be associated in patients with lower GCS values. The statistical difference was found to be significant which means that low GCS score is proportionate to the degree of severity of hyperglycemia. Higher the value of hyperglycemia, lower is the GCS score. This observation is indicative of bad prognosis in stress hyperglycemia.

When it comes to prediction of an unfavorable outcome, the current study's results correspond to those reported by Idrovo et al[14], the NIHSS score and the GCS predicted an unfavorable outcome. There were no significant differences for the predictive power of the two scoring methods. The NIHSS score had a higher predictive power than the GCS scale on first day and third day of admission. The two scores showed more accurate prediction when done at 72 h than at 24 h. As time passes, the prognostic value of impairment severity becomes clearer. If deficits do not subside or improve after a few days, prognostication becomes more accurate. The NIHSS is robust between days 2 and 9 to predict outcome[15,16].

Mean duration of hospital stay was more in hyperglycemic patients than in normal sugar levels group. When comparing duration of hospital stay and various groups of RBG, it was found that as admission RBG increased, recovery decreased and duration of hospital stay increased. After statistical analysis hyperglycemia was found to significantly increase the length of hospital stay in stroke patients. This is comparable with study done by Gorshtein et al[17] and Evans and Dhatariya[18].

The mortality was more in group A (29 patients) than group B (8 patients). Mortality was lowest in group of RBG in whom RBG level on admission was less than 140 mg/dl (10.1%).The group of patients with RBG 140 mg/dl - 200 mg/dl mortality was (28.1%) and highest mortality (51.3%) was in group of RBG on admission > 200 mg/dl. Thus as RBG on admission increased, mortality also increased in study groups. Thus, there was a strong significant association of hyperglycemia with the outcome of stroke. These outcomes are similar to study carried out by Gorshtein et al[17] and Basu et al[19].

In present study we observed that, increased mean RBG, fever, high systolic BP, raised total cholesterol, decreased HDL, increased LDL, old history of systemic hypertension, low GCS score, increased mean duration of hospital stay, high NIHSS score on admission and high NIHSS on discharge are the parameters highly significant with stress hyperglycemia and their association adds to bad prognosis. However, age more than 60, raised diastolic blood pressure, raised triglycerides, old history of CVE, history of smoking, are significant factors associated with stress hyperglycemia, whereas we didn't find any significant association with gender, pulse rate, serum sodium level and history of alcoholism.

There are some limitations of the study which include sample size of the study that may not be an appropriate representative of the population. This study was single centered and a short-term study; future studies will require a multi-centric approach involving more number of patients for an extended duration of time to establish the exact relationship of different clinico-pathological types of acute stroke with hyperglycemia.

Conclusion :

Hyperglycemia of different magnitude has been associated with acute ischemic stroke. Late middle aged 51-70 year patients are more prone to cerebrovascular episodes and admission hyperglycemia. Admission hyperglycemia is associated with increased duration of "in hospital stay", late functional recovery and increased morbidity and mortality. NIHSS score and GCS score also can be used as a prognostic indicator in acute ischaemic stroke patients. Fever, dyslipidemia, hypertension, smoking, old history of cerebrovascular episode, age more than 60 years are associated with stress hyperglycemia and associated bad prognosis.

The present study suggested that the admission blood sugar level helps in prognostication and can be easily done by Glucometer which is an easily available investigation in all institutes. However larger clinical studies and trials are required to support this postulation.

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