Original Article

Glycaemic Status In Acute Ischaemic Stroke And Its Relation To Severity And Outcome

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DOI: 10.47750/pnr.2023.14.S02.224

Abstract

The aim of this study was to investigate the glycemic status in patients with acute ischemic stroke and its association with stroke severity and outcome. A total of [number of patients] patients were enrolled and their blood glucose levels were measured upon admission to the hospital. The severity of the stroke was assessed using [standard scale or method]. The outcome of the stroke was evaluated at [time period or discharge] using [outcome measure]. The results showed that high glucose levels were significantly correlated with increased stroke severity and poor outcome. The findings suggest that glycemic control should be an important part of the management strategy for acute ischemic stroke patients. Further large-scale studies are needed to confirm these findings and determine the optimal target glucose range in this population.

Introduction

Stroke is the second leading cause of death worldwide. Among all the neurological diseases it ranks first in the frequency of importance. [1] It is an important cause of premature death and disability in low-income and middle-income countries like India. [1,2] 80 % of stroke is ischemic, rest are hemorrhagic. [1] Diabetes mellitus by virtue of its microvascular and macrovascular complications plays a major role in the genesis of stroke. The incidence of stroke is higher in diabetics as compared to non-diabetics. [3] Stress hyperglycemia in the early course of stroke is associated with a range of adverse effects like increased infection rates, independent of another prognostic factor, abnormal immune function and hemodynamic and electro cardiac abnormalities, and greater morbidity and mortality in acute ischemic stroke. [3,4] With this background the present study was carried out to study the clinical profile of cerebral infarction in relation to glycemic status at presentation, to find out the infarct size on CT in relation to glycemic status and to observe the clinical recovery during the first seven days in the hospital in accordance with National Institute of Health Stroke Scale.

Materials and methods

The study is a prospective study conducted in S.C.B. medical college and hospital and was carried out in 100 patients of either gender with first cerebrovascular accident and with the clinical features of acute stroke proven radiologically by CT/MRI within 72 hours of the onset of stroke. Patients with a previous history of stroke, intracerebral hemorrhage, traumatic stroke, transient ischemic attacks, space-occupying lesions in CT, cerebral venous thrombosis, and known

cases of seizure disorders were excluded. The included cases were followed up over a period of one year. Random testing of blood glucose was done at the time of presentation at casualty along with detailed history and neurological and systemic examination, with the application of NIHSS. Once the diagnosis was confirmed, patients were enrolled in the study after obtaining written informed consent. All routine and specialized investigations were done as per the hospital protocol. The ethical clearance was obtained from the institutional ethics committee.

Study definitions:

Depending on the admission RBS, FBS and PPBS, Hba1c, and past history of diabetes, the patients are classified as euglycaemic (FBS < 100 mg/dl, RBS < 140 mg/dl, Hba1c < 5.6%), stress hyperglycaemic (RBS ≥140 mg/dl, Hba1c <5.6%, no prior history of diabetes), diabetes (FBS ≥ 126 mg/dl, RBS/PPBS ≥200 mg/dl, Hba1c ≥ 6.5%) and pre-diabetic (FBS-100-125 mg/dl, RBS/PPBS – 140-199 mg/dl, Hba1c- 5.7-6.4%). The infarct was classified depending on their size on CT. Small size - <5mm in diameter, < 2 adjacent CT slices, Medium size –5-10 mm in diameter, > 2 CT slices, Large size - >10 mm in diameter, involving large vascular territory. A repeat assessment was done on day 7 of clinical illness using the NIHSS scale.

Results

The mean age of the patients in the study group was 55.6 years. The maximum number of patients with cerebral infarction belonged to age groups 46-60 years and 61-75 years. In this study, 52% of the cases were males and 48% were females. There was a male preponderance with a male: female ratio of 1.08:1. In the study group, 36 % had diabetes, 24 % had stress hyperglycemia, 16 % were prediabetic and 24% were euglycemic. 40.4% of the male patients had diabetes, 28.8% were euglycemic, 17.3% were stress hyperglycemia and 13.5% were prediabetic whereas 31.3% % of the female patients had diabetes, 18.8% were euglycemic, 31.3% were stress hyperglycemic and 18.8% were pre-diabetic. The mean glucose in the euglycemic group was 115 ± 15.13 mg/dl, the stress hyperglycemic group was 209.16 ± 51.69 mg/dl, in the prediabetic group was 168.75 ± 16.86 mg/dl and in the diabetic group was 295.39 ± 85.33 mg/dl. 36% of the infarcts were medium-sized and seen on more than 2 CT slices. The small and large-sized infarcts accounted for 32% of each. **[Table 1]**

The small-sized infarcts were seen more in the euglycemic group, medium-sized infarcts in the stress hyperglycemic group and prediabetic group, and large-sized infarcts more in the diabetes group. In the euglycaemic group, small-size infarcts comprise 40.6% whereas large infarcts comprise 9.4%. In the diabetes group, small infarcts comprise 25% and large infarcts comprise of 56.3%.The euglycemic group has a lesser baseline NIHSS score as compared to other groups whereas the diabetic group has a higher baseline NIHSS score. This is suggestive of higher clinical severity in the diabetes group even in smaller size infarcts. **[Table 2]** Also, the baseline NIHSS score in the prediabetic and stress hyperglycemic group for small-size infarcts is higher as compared to the euglycemic group. So, the baseline NIHSS score increases with an increase in glycaemic status indicating higher clinical severity with higher glucose levels. The progression of NIHSS scores on follow-up till day 7 shows a gradual decline in all three glycaemic groups in small-size infarcts. However, there is a slower progression in NIHSS score in the stress hyperglycaemic group as compared to the normoglycemic group indicating slower clinical recovery. There is a progressive increase in baseline NIHSS score with an increase in glycaemic status in medium-size infarcts. In large-size infarcts, there is a higher baseline NIHSS score in both diabetes and stress hyperglycaemic groups. This indicates higher clinical severity in the diabetes and stress hyperglycaemic group. There is a progressive increase in NIHSS score with an increase in glycaemic status in large-size infarcts. On follow-up of these patients till day 7, there is a gradual decline in NIHSS score in all the three glycaemic groups with the stress hyperglycaemic group showing a little slower decline as compared to the diabetes group. This is suggestive of slower clinical recovery in the stress hyperglycaemic group as compared to the diabetes group. The baseline NIHSS score corresponds to the infarct size in the study group. There is a gradual increase in NIHSS score with infarct size. On follow-up of the patients on day 7 there is a decrease in NIHSS score in all size infarcts. The baseline NIHSS scores increase as the glycemic status changes from euglycemia to diabetes, indicating increasing clinical severity of stroke with a change in the glycemic status from euglycemia to diabetes. The diabetes

group has a higher baseline NIHSS score among the glycemic groups. The stress hyperglycemia group has a slow progression of score from baseline on follow-up till day 7. This slower change in the scores indicates slow recovery on day 7 of hospitalization. This slow progression is noted for all infarct sizes in stress hyperglycemia. No statistical significance is seen in the follow-up scores in both the stress hyperglycemia and diabetes group. **[Table 3]**

The admission blood glucose and HbA1C correlated well with the infarct size. Higher blood glucose levels and higher HbA1C had large-size infarcts as compared to small-size infarcts with lower admission blood glucose and HbA1C. Higher blood glucose levels at admission are associated with larger infarct size and also higher NIHSS scores at presentation. Small-size infarcts are associated with lesser admission blood glucose and lesser NIHSS score which is statistically significant. Large-size infarcts are associated with higher blood glucose levels at admission and higher NIHSS score. However, no statistical correlation is found in the case of large-size infarcts. This indicates that an increase in blood glucose levels at admission is associated with an increase in infarct size and an increase in the clinical severity of stroke. Infarct size correlated well with the HbA1C. Small-size infarcts are associated with lesser HbA1C and lesser NIHSS score at presentation whereas large-size infarcts are associated with higher HbA1C and higher NIHSS at presentation. This indicates higher clinical severity and higher infarct size in the case of uncontrolled diabetes. **[Table 4, 5]**

There are no deaths in euglycaemic, stress hyperglycaemic, and prediabetic groups. In the diabetes group, there is a death of 12.5% of study group subjects indicating bad clinical outcomes in diabetes patients. In medium size infarct group, death in the diabetes group is 20%, in the prediabetic group is 12.5% and in the stress hyperglycaemic group is 9.1%. This is suggestive of worse clinical outcomes in the hyperglycaemic group as compared to the normoglycaemic group. **[Table 6]**

Discussion

The study was conducted at a tertiary care hospital in Cuttack. 100 patients with acute cerebral infarction proven by computed tomography met the inclusion criteria for the study. The age group of the patients ranged from 30-100 years with a mean age of 55.6 years, and the maximum number of cases were between the age group of 46-75 years (78%) This finding was comparable to Guillermo et.al; where the mean age was 59$\pm$ 4 years.5 In the UKPDS study, it was noted that advancing age was an important risk factor for stroke.8

In the study group, 52% were male and 48% were female patients. There was a male preponderance with a male: female ratio of 1.08:1. Although the UKPDS study noted male sex as an important risk factor for stroke.8

The glycemic status in the study group revealed 36% diabetes, 24% with stress hyperglycemia, 16% were prediabetic and 24% were euglycemia patients. Stress hyperglycemia in this study was defined by admission glucose > 140mg% and normal HBA_1C. Capes et.al in a systematic review noted that cutoffs to define hyperglycemia ranged from 108 mg/dL to 180 mg/ dL (6 to 10 mmol/L) in previous studies.7 The incidence of hyperglycemia (admission glucose >140 mg) in this study was 75 %. This is comparable to various studies (Gray et.al, Guillermo et.al, Candelise et.al) where the admission hyperglycemia ranged from 29-36%. 5,6,7,8

Among the study subjects, there was a higher percentage of diabetes in males (40.4%) and a higher percentage of stress hyperglycemia in female patients (31.3%) Hart et.al and Jhanghorbani et.al found a stronger association between hyperglycemia and stroke in women than in men. 9,10

The admission blood glucose ranged from 88-470 mg% in the study group, 76 of the total 100 patients (76%) had admission glucose in the hyperglycemic range i.e. >140 mg%. The admission glucose in the stress hyperglycemia group ranged from 140- 330mg % (n=24). The size of the infarct was measured on CT as small, medium, and large-sized infarcts and was validated by two radiologists separately. This categorization of infarcts was similar to a study done by Haobam et.al.16 The stress hyperglycemia and prediabetic group had a higher percentage of medium-sized

infarcts and the diabetes group had a higher percentage of large-sized infarcts. Thus, it was observed that there was an increase in infarct size with an increase in glycemic status. Our findings are consistent with various studies (Mehta. S et al, Haobam et al) which have reported an increase in infarct size with hyperglycemia.[11,12]

The clinical severity of the stroke was measured using the National institute of health stroke scale (NIHSS) and monitored during the hospitalization till day 7. The NIHSS score increased with an increase in the size of the infarct. The admission blood glucose correlated well with the NIHSS score in all three glycemic groups. These findings are comparable to Johnston et.al where infarct volume was a significant predictor of NIHSS score.[13]

An increase in admission blood glucose on presentation was associated with a higher NIHSS score indicating higher clinical severity of the stroke. Our findings are comparable to a study by Lee et.al that found that more severe stroke and higher mortality are associated with increased blood glucose at presentation with stress hyperglycemia associated with increasing severity of stroke irrespective of stroke size.[15] Nina et.al noted higher admission severity scores in hyperglycemic patients and opined that admission hyperglycemia was an independent predictor of mortality even after controlling for disease severity.[14]

Our study demonstrates admission hyperglycemia as a bad prognostic marker. Many studies (Capes et.al, Weir et.al, Bruno et.al, Kiers et.al, Guillermo et.al, Sarkar et.al, Lee et al, etc.) have demonstrated the ill effects of admission hyperglycemia. [5,6,15,16,17,19,20]

There was a progressive increase in the NIHSS score across all groups irrespective of the infarct size as the glycemic status changed from euglycemia to diabetes. This correlates well with Wouters et al which suggested that higher baseline NIHSS scores are associated with poor clinical outcomes.[21] The decrease in the NIHSS score from baseline on follow-up on the 7^{th} day was taken as a sign of improvement or recovery. Non-progression in the scores from the day of admission or slow progression was taken as a slow or non-recovery and bad prognostic sign. These findings were comparable to Adams et.al who noticed a decrease in the likelihood of survival by 24% and; an excellent outcome at 7 days for an additional increase in the baseline score.[22] Stress hyperglycemic patients had statistically significant slow progression in scores for all age groups, in both medium and large-size infarct groups($p<0.001$) indicating slower clinical recovery. Overall, hyperglycemia on presentation was associated with larger infarct size and poor recovery compared to normoglycemic individuals. Bruno et.al noticed poor recovery in their patients admitted with hyperglycemia[18.] Capes et.al observed that stress hyperglycemia upon hospital admission was associated with poor functional recovery[6] Both admission glucose and HbA_1C correlated well with infarct size. Lower HbA_1C was associated with a smaller infarct size while poorly controlled diabetics suffered a severe stroke with a larger infarct size which was statistically significant($p<0.05$). Admission blood glucose correlated well with the infarct size and it was found to be statistically significant($p<0.05$). Higher admission blood glucose levels were associated with an increase in infarct size and an increase in NIHSS score indicating higher clinical severity. This finding correlated well with the findings of Lee et al. [15]

Hemiplegia, cranial nerve dysfunction mainly VII CN, altered sensorium, language disturbances, and sensory symptoms were common presenting symptoms. The common co-morbid conditions in the study group were hypertension, ischemic heart disease, and dyslipidemia. The other conditions included valvular heart disease (mitral stenosis), smoking, and chronic alcohol abuse. These are comparable to studies on risk factors in stroke.[23,24] Pneumonia was the commonest complication. Nina et.al noticed hypertension (78%) and congestive cardiac failure (14%) in their study.[14] Dalal noted hypertension as one of the most important risk factors in the Indian scenario. [25]

There were 12.5% deaths in the diabetic group in the case of small-size infarcts whereas there were no deaths in other groups. But there were no deaths in the euglycaemic group. In the case of large-size deaths, there was an increase in the number of deaths with an increase in the glycaemic status but the maximum number of deaths were in the stress hyperglycaemic group (37.5%). This was in accordance with K Ghanachandra Singh et al[26] and Wouters A et al [21]

Limitations of the study

The sample size was small. The treatment of hyperglycemia was not standardized. The study did not address the question of whether treatment of hyperglycemia would reduce the morbidity and mortality associated with hyperglycemia. The patients had only limited hospital follow-up, better long-term correlation would have been possible had these patients been followed after discharge.

Conclusion

Hyperglycemia was a common finding in patients with acute cerebral infarction with or without a history of diabetes. The admission random blood glucose and NIHSS score correlated with clinical severity. Patients with hyperglycemia in acute cerebral infarction had increased severity with high NIHSS scores on admission, irrespective of infarct size. Stress hyperglycemic had a high percentage of medium-sized infarcts, while diabetics had a high percentage of large-sized infarcts and had poor recovery on NIHSS scores for both medium and large-sized infarcts from the baseline score. Hyperglycemia on presentation was associated with larger infarct size and poor recovery in diabetes mellitus. Both admission glucose and HbA_1C correlated well with infarct size in diabetes. Poorly controlled diabetes mellitus had large infarct size and high NIHSS. An increase in glycaemic status was associated with an increase in the number of deaths.

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Table 1: Clinico demographic characteristic of patients in acute ischemic stroke (N= 100)

Clinico- Demographic Parameter	**Value**
Age (number of patients)	
30-45	18
46-60	40
61-75	38
76-90	3
>90	1
Gender (number of patients)	
Male	52
female	48
Glycemic status at admission (number of patients)	
Euglucemic (Male vs Female)	15,9
Stress hypeglycemia (Male vs Female)	9,15
Pre-diabetic (Male vs Female)	7,9
Diabetic (Male vs Female)	21,15
Blood glucose at admission mg/dl (mean±SD)	
Euglucemic	115±15.13
Stress hypeglycemia	209±51.69
Pre-diabetic	168.75±16.86
Diabetic	295.38±85.33
Infarct size (number of patients)	
Small	32
Medium	36
Large	32

Table 2: Infarct size and baseline mean NIHSS score of patients in acute ischemic stroke

Infarct size	NIHSS 0	NIHSS 3	NIHSS 7
Small	14.40 ± 6.78	10.46 ± 5.20	8.12 ± 3.99
Medium	21.80 ± 7.21	17.19 ± 8.06	13.31 ± 6.45
Large	29.75 ± 4.28	25.90 ± 5.60	20.84 ± 3.54

Table 3: Baseline, follow up AT DAY 7 and change from baseline NIHSS score in various glycemic groups of patients in acute ischemic stroke

Glycaemic index	NIHSS 0	NIHSS 3	NIHSS 7
Euglycemic	13.41 ± 6.07	10.33 ± 5.79	7.78 ± 3.97
Stress hypertension	22.70 ± 8.41	17.87 ± 9.26	12.80 ± 5.53
Pre diabetic	17.56 ± 5.17	14.06 ± 6.16	10.07 ± 3.19
Diabetic	29.16 ± 4.66	24.42 ± 6.44	20.09 ± 5.70

Table 4: Mean blood glucose, HbA1C and infarct size at admission of patients in acute ischemic stroke

Infarct size	Small	Medium	Large	P value
Blood glucose level at Day 0	176.15± 73.40	195.47 ± 83.90	263.75 ± 99.70	0.0001
HbA1c	5.71 ± 1.25	6.18 ± 1.77	7.40 ± 1.85	0.001

Table 5: Infarct size, Admission RBS and NIHSS score at presentation of patients in acute ischemic stroke

Infarct Size	Blood glucose at admission	NIHSS SCORE at day 0	Pearson correlation coefficient	P value
Small	176.15 ± 73.40	14.40 ± 6.78	0.777	0.0001
Medium	195.47 ± 83.90	21.80 ± 7.21	0.795	0.0001
Large	263.75 ±99.73	29.75 ± 4.28	0.337	0.059

Table 6: Infarct size, glycemic status and survival of patients in acute ischemic stroke

Infarct Size	Glycemic Status	Survival n (%)
Small	**Euglycemic**	13(100)

	Stress hyperglycaemic	5(100)
	Pre diabetic	6(100)
	Diabetic	7(87.5)
Medium	**Euglycemic**	8(100)
	Stress hyperglycaemic	10(90.9)
	Pre diabetic	6(85.7)
	Diabetic	8(80)
Large	**Euglycemic**	2(66.7)
	Stress hyperglycaemic	5(62.5)
	Pre diabetic	2(66.7)
	Diabetic	14(77.8)