



Research Article

Glycemic Status in Acute Stroke in Relation to its Severity and Outcome

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Abstract

The correlation of glycemic status to clinical severity and outcome of cerebrovascular accident (CVA) was studied in newly diagnosed CT/MRI proven cases of stroke. Total 200 patients were classified into euglycemia, stress hyperglycaemia and diabetic group based on the admission blood glucose, glycosylated haemoglobin (HbA1C) and past history of diabetes. The lesions (bleed/infarct) were classified into small, medium and large sized. Neurological assessment was done on admission using National Institute of Health Stroke Scale (NIHSS) score and the patients were followed up for 7 days to see the outcome. The maximum number of patients were between age groups of 61-70 constituting 39.5% of the total, with M: F 1.3:1, The incidence of hyperglycaemia was 58% and admission blood glucose ranged between 70-576 mg%. There were 35.5 % patients with diabetes, 22.5% with stress hyperglycemia and 42 % with euglycemia. Increased admission glucose was associated with severe presentation, high NIHSS scores and higher mortality among ischemic stroke. Admission blood glucose did not correlate with the severity and outcome in haemorrhagic stroke suggesting that admission blood glucose is not an independent predictor of severity and outcome in haemorrhagic stroke.

Keywords: *glycemic status, stress hyperglycaemia, diabetes, cerebrovascular accident, ischemic stroke, haemorrhagic stroke, HbA_{1C}, NIHSS.*

Introduction

Stroke or cerebrovascular accident is an abrupt onset of a neurological deficit lasting for more than 24hrs that is attributable to a focal vascular cause¹.

It is the third largest killer in India and world after coronary artery disease and cancer. It is the most common cause of disability and dependence. It accounts for atleast 50% of all neurological admission in general hospital¹.

A study by the world health organisation says that the incidence of stroke in India is around 130 per 100000 every year².

Diabetes is an independent risk factor for stroke and is associated with 1.8 to 6 fold increased risk compared with non diabetic subjects and worsens survival of patients with stroke³.

Hyperglycemia and stroke appear to be related in two ways. First incidence of stroke is known to be higher in diabetics than non diabetics. Second it has been suggested that even in non diabetics relatively mild degree of hyperglycemia early in stroke might increase infarct size and lead to poor prognosis.

Though first introduced 130 years ago, the concept of stress diabetes or stress hyperglycemia

has gained tremendous attention in recent years in view of the landmark articles by Van der Berghe and Colleagues in 2001. Stress hyperglycemia defined as hyperglycemia during acute process, mirrors the severity and outcome of critical illness. Hyperglycemia occurs in 60% of the cases with acute stroke and in 12.53% of them stress hyperglycemia is observed. Hyperglycemia predicts higher mortality and morbidity after acute stroke more so in patients without the prior history of diabetes^{4,5,6}. Hyperglycemia occurs in 20-40% of patients with stroke, and is associated with worse functional outcome, longer hospital stay, higher medical costs and an increased risk of death⁷.

Aims and Objectives

1. To find out the glycemic status on admission in patients of acute stroke (haemorrhagic and ischemic).
2. To correlate glycemic status of patients in acute stroke with relation to severity and outcome using the NIHSS score system

Materials And Methods

The observational study was carried out in V. S. S. Institute of Medical Science and Research, Burla from 2016 – 2018. 200 patients with stroke with consideration to the inclusion and exclusion criteria were included in the study.

Selection of patients

Inclusion criteria: Both male and female patients with age more than equal to 14yrs presenting with clinical features of acute stroke proven radiologically by CT/MRI within 72hrs of onset of stroke. Both haemorrhagic and ischemic stroke are included in the study

Exclusion criteria: Patients with previous neurological deficits, traumatic intracerebral bleed, TIA, CT scan showing old infarcts, known case of seizure disorders, cerebral venous thrombosis, presence of intracranial space occupying lesions, valvular heart disease and cardiac arrhythmias

Investigations

1. Hemoglobin %, Total leukocyte count, Differential Count, Erythrocyte Sedimentation Rate.
2. Random blood glucose/ Fasting blood glucose, Blood urea, Serum Creatinine, Serum Sodium, Serum Potassium.
3. HbA1c was assessed in patients
4. Fasting Lipid Profile
5. Urine routine examination and microscopy
6. CT Scan/MRI Scan of brain

The infarct/bleed size was classified into small, medium and large sized lesion on the CT. The small size were $<3\text{cm}^2$ (A), medium sized were $3-6\text{cm}^2$ (B), and large sized lesions were $>6\text{cm}^2$ (C). Patients with stroke were classified into ischemic and haemorrhagic type radiologically by CT Scan/MRI. The stroke severity was assessed by the NIH Stroke Scale (NIHSS). All patients in both types of stroke were followed in hospital for 7 days to see the outcome whether they were discharged or died.

Patients were classified into

- Euglycemics (FPG $<100\text{mg/dl}$, HbA_{1c} $<5.6\%$, RBS $<140\text{mg/dl}$)
- Stress hyperglycemics (FPG $>100\text{mg/dl}$, RBS $>140\text{mg/dl}$, HbA_{1c} $<5.6\%$)
- diabetics (FPG >126 , 2hr PPG/RBS >200 , HbA_{1c} $>6.5\%$)

Results

Table 1: Sex Distribution of Cases

Sex	No.	Percentage
Male	116	58%
Female	84	42%
Total	200	100%

In this study group, 58% of the cases were males and 42 % were females. There was a male preponderance with male: female ratio of 1.3:1

Table 2: Age Distribution (n =200)

Age (years)	Number	Percentage
21-30	2	1.0
31-40	5	2.5
41-50	31	15.5
51-60	32	16.0
61-70	79	39.5
71-80	41	20.5
>80	10	5.0
Total	200	100.0

The mean age of the patients in the study group was 63.81 + 12.62 years. Maximum number of patients belonged to age groups 61-70 years and 71-80 years. Minimum age in the group was 25 years and maximum being 89 years.

Table 3: Distribution of Ischemic and Haemorrhagic Stroke (n=200)

Ischemic and haemorrhagic stroke	No.	Percentage
Infarct	168	84%
Haemorrhage	32	16%
Total	100	100%

In the study group, 16 % cases had haemorrhagic stroke while 84 % cases had ischemic stroke. The number of ischemic stroke outweighed those of haemorrhagic stroke with ischemic to haemorrhagic ratio of 5.25:1. Among the patients with ischemic stroke 52% had cortical(57% involving the MCA territory,28% involving the ACA territory and 15% in PCA territory) ,20% had lacunar type,10% had striatocapsular and 18% had brainstem/cerebellar type stroke.

Table 4: Glycemic Status of the study group (n=200)

Glycemic Status	No.	Percentage
Euglycemia	84	42%
Stress hyperglycemia	45	22.5%
Diabetes	71	35.5%
Total	200	100%

In the study group, 35.5 % had diabetes, 22.5 % had stress hyperglycemia and 42 % were euglycemics.

Table 5: Distribution of Stroke Pattern in Euglycemics, Stress Hyperglycemic and Diabetics

GLYCEMIC STATUS	HAEMORRRHAGE N=32		INFARCT N=168	
	Number	Percentage	Number	Percentage
euglycemia	14	43.8	70	41.7
Stress hyperglycemia	7	21.9	38	22.6
diabetes	11	34.4	60	35.7
Total	32	100	168	100

In the study group, among the patients with haemorrhagic stroke 34.4 % were diabetics, 43.8 % were euglycemics and 21.9 % had stress hyperglycemia. In the study group, among the patients with ischemic stroke 35.7 % were diabetics, 41.7 % were euglycemics and 22.6 % had stress hyperglycemia.

Table 6: Comparison of size of ICH with Glycemic Status

GLYCEMIC STATUS	SIZE OF LESION			TOTAL
	SMALL (<3cm ²)	MEDIUM (3-6cm ²)	LARGE (>6cm ²)	
EUGLYCEMIA	2	7	5	14
STRESS HYPERGLYCEMIA	4	2	1	7
DIABETES	5	3	3	11
TOTAL	11	12	9	32
P>0.05				

In the study group, 34.37 % lesions on brain imaging (hemorrhage) were small (A), medium (B) and large (C) sized lesion accounted for 37.5% and 28.12% respectively. The above table shows that out of 32 patients of ICH,14(43.75%) were euglycemics, 7(25%) were stress hyperglycemics and 11(34.37%) were diabetics. The medium sized (58.33%) and large sized lesions (55.55%) were seen more in euglycemics while small sized lesions(81.81%) were seen in diabetics.

Table 7: Comparison of size of infarct with Glycemic Status

GLYCEMIC STATUS	SIZE OF LESION			Total
	SMALL (<3cm ²)	MEDIUM (3-6cm ²)	LARGE (>6cm ²)	
EUGLYCEMIA	18	38	14	70
STRESS HYPERGLYCEMIA	12	14	12	38
DIABETES	10	18	32	60
TOTAL	40	70	58	168

P<0.05

In the study group, 23.8% lesions on brain imaging (infarct) were small (A), medium (B) and large (C) sized lesion accounted for 41.66 % and 34.52 % respectively. The above table shows that out of 168 infarct patients 70(41.66%) were euglycemics, 38(22.61%) were stress hyperglycemics and 60(35.71%) were diabetics. The small sized lesions (45%) and medium sized lesions(54.28%) were seen more in euglycemics and the large sized lesions(55.17%) were seen more in diabetic and it is statistically significant.

Table 8: Admission Blood Sugar(BSL)/Random Blood Glucose according to Glycemic Status

GLYCEMIC STATUS	ADMISSION BSL
EUGLYCEMIA	109.28±6.93
STRESS HYPERGLYCEMIA	174.93±21.46
DIABETES	302.01±359.16

The admission blood glucose in the study group ranged from 95-500 mg %. Mean admission blood glucose in diabetics was 302.01±359.16, shows a skewed distribution, in euglycemics was 109.28±6.93 and in stress hyperglycemia was 174.93 ± 21.46.

Table 9: HbA_{1C} According to Glycemic Status

GLYCEMIC STATUS	HbA _{1C}
EUGLYCEMIA	4.23±0.36
STRESS HYPERGLYCEMIA	4.70±0.37
DIABETES	7.92±1.23

The HbA_{1C} in study group ranged from 3.2-12 with mean of 5.65 ± 1.87. Mean HbA_{1C} in diabetic group was 7.92 ± 1.23, in euglycemia was 4.23 ± 0.36 and in stress hyperglycemia was 4.70 ± 0.37

Table 10: Comparison of Glycemic Status with NIHSS in Infarct

GLYCEMIC STATUS	NO. OF CASES	NIHSS
EUGLYCEMIA	70	10.33±2.68
STRESS HYPERGLYCEMIA	38	13.68±3.30
DIABETES	60	19.38±6.66

The NIHSS score in the study group ranged from 5-39 with mean NIHSS score of 14.15±5.90. Among the euglycemic group mean NIHSS score of 10.33±2.68 was observed while in the stress hyperglycemic and diabetic group the NIHSS score was 13.68±3.30 and 19.38±6.66 respectively. The NIHSS score increases as the the glycemic spectrum changes from euglycemia to diabetes, indicating worsening severity of stroke with change in the glycemic status from euglycemia to diabetes.

Table 11: Comparison of Glycemic Status with NIHSS in ICH

GLYCEMIC STATUS	NO. OF CASES	NIHSS
EUGLYCEMIA	14	11.86±2.50
STRESS HYPERGLYCEMIA	7	12.14±3.13
DIABETES	11	15.73± 6.77

Among the euglycemic group mean NIHSS score of 11.86±2.50 was observed while in the stress hyperglycemic and diabetic group the NIHSS score was 12.14±3.13 and 15.73± 6.77 respectively. Though the NIHSS score increases as the the glycemic spectrum changes from euglycemia to diabetes, the difference was not found to be statistically significant.

Table 12: Comparison of HbA_{1C} and Stroke Severity in Infarct

HbA _{1C}	NO. OF PATIENTS	NIHSS
<6.5	108	11.51± 3.32
≥6.5	60	19.38± 6.66

In the above table it shows that patients with HbA_{1C} less than 6.5 had mean NIHSS score of 11.51± 3.32 and patients with HbA_{1C} greater than equal to 6.5 had mean NIHSS score of 19.38± 6.66. Patients with HbA_{1C} ≥ 6.5 had higher NIHSS

score. The F value is 104.547 and is statistically significant. Thus HbA_{1C} affects the severity of ischemic stroke.

Table 13: Comparison of HbA_{1C} and severity of Haemorrhagic Stroke

HbA _{1C}	NO. OF PATIENTS	NIHSS
<6.5	21	11.95±2.65
≥6.5	11	15.73±6.77

In the above table it shows that patients with HbA_{1C} less than 6.5 had mean NIHSS score of 11.95±2.65 and patients with HbA_{1C} greater than equal to 6.5 had mean NIHSS score of 15.73±6.77. Patients with HbA_{1C} ≥ 6.5 had higher NIHSS score. The F value is 5.151 and is statistically significant. Thus HbA_{1C} affects the severity of haemorrhagic stroke.

Table 14: Comparison of Admission Blood Glucose, HbA_{1C} and NIHSS with Size of Infarct

INFARCT SIZE	RBS	HbA _{1C}	NIHSS
SMALL	139.70±38.00	4.93±1.29	9.35±2.52
MEDIUM	198.64±370.85	5.29±1.64	13.03±4.08
LARGE	234.76±98.29	6.64±2.21	19.31±6.27

ANOVA Table				
			F	Sig.
RBS SIZE OF LESION	Between Groups	(Combined)	1.978	.141
	Within Groups			
	Total			
HbA _{1C} SIZE OF LESION	Between Groups	(Combined)	12.817	.000
	Within Groups			
	Total			
NIHSS SIZE OF LESION	Between Groups	(Combined)	66.558	.000
	Within Groups			
	Total			

The correlation with size of infarct was found to be significant in two groups i.e HbA_{1C} and NIHSS. The correlation between size of infarct and mean RBS was not found to be significant because of the large variation in the values of the RBS.

Table 15: Comparison of Admission Blood Glucose/Random Blood Glucose, HbA_{1C} and NIHSS with Size of ICH

BLEED SIZE	RBS	HbA _{1C}	NIHSS
SMALL	163.45±36.78	5.56±1.50	10.27±1.42
MEDIUM	153.33±53.12	5.27±1.35	12.92±3.37
LARGE	194.22±119.42	5.88±2.25	17.33±6.20

ANOVA Table				
			F	Sig.
RBS SIZE OF LESION	Between Groups	(Combined)	1.978	.141
	Within Groups			
	Total			
HbA _{1C} SIZE OF LESION	Between Groups	(Combined)	12.817	.000
	Within Groups			
	Total			
NIHSS SIZE OF LESION	Between Groups	(Combined)	66.558	.000
	Within Groups			
	Total			

The correlation with size of haemorrhage was found to be significant in two groups i.e HbA_{1C} and NIHSS. The correlation between size of ICH and mean RBS was not found to be significant because of the large variation in the values of the RBS.

Table 16: Comparison of Admission Blood Glucose /Random Blood Glucose with Outcome in Ischemic Stroke

	OUTCOME ON 7 TH DAY		Total	P<0.05
	Alive	Dead		
EUGLYCEMIA	68	2	70	
STRESS HYPERGLYCEMIA	29	9	38	
DIABETES	37	23	60	
TOTAL	134	34	168	

The table above shows that out of 34 patients who died 5.88% were euglycemics, 26.47% were stress hyperglycemics and 67.65% were diabetes and it was found to be statistically significant. Mortality increased with increase in the admission blood glucose level in ischemic stroke.

Table 17: Comparison of Admission Blood Glucose /Random Blood Glucose with Outcome in Haemorrhagic Stroke

	OUTCOME ON 7 th DAY		Total	p>0.05
	alive	dead		
EUGLYCEMIA	12	2	14	
STRESS HYPERGLYCEMIA	4	3	7	
DIABETES	8	3	11	
TOTAL	24	8	32	

The table above shows that out of 8 patients who died 25% were euglycemics, 37.5% were stress hyperglycemics and 37.5% were diabetes. Although more death occurred in the stress hyperglycemia and diabetes group in haemorrhagic stroke, the above result was not found to be statistically significant.

Table 18: Comparison of HbA_{1C} and Outcome in Ischemic Stroke

HbA _{1C}	OUTCOME ON 7 th DAY		Total
	ALIVE	DEAD	
HbA _{1C} <6.5	97	11	108
HbA _{1C} >6.5	37	23	60
Total	134	34	168
P<0.05			

The above table shows that out of 134 cases of infarct that were discharged 72.38% had HbA_{1C} <6.5 and 27.61% had HbA_{1C} >6.5. Among those who died 32.35% had HbA_{1C} <6.5 and 67.65% had HbA_{1C} >6.5. Patients with higher HbA_{1C} had higher mortality rate in ischemic stroke and it was found to be statistically significant.

Table 19: Comparison of HbA_{1C} and Outcome in Haemorrhagic Stroke

HbA _{1C}	OUTCOME ON 7 th DAY		Total
	ALIVE	DEAD	
HbA _{1C} <6.5	16	5	21
HbA _{1C} >6.5	8	3	11
Total	24	8	32
P>0.05			

The above table shows that out of 24 cases of haemorrhage that were discharged 66.66% had HbA_{1C} <6.5 and 33.33% had HbA_{1C} >6.5. Among those who died 62.5% had HbA_{1C} <6.5 and 37.5%

had HbA_{1C} >6.5. HbA_{1C} value did not correlate with mortality in haemorrhagic stroke and it was not found to be statistically significant.

Discussion

The maximum number of patients were between age groups of 61-70 constituting 39.5% of the total, next highest was in age group of 71-80 years constituting 20.5% of the total. It was noted that advancing age was an important risk factor for stroke. This is in accordance with observation of K Ghanachandra Singh et al, 2014, Agarwal et al, 1976, SS Mishra et al, 1962 and also Dalal et al, 1968⁸. But according to Bonita R et al stroke incidence rate rises exponentially with increasing age with 100 fold increase in the rates from about 3/10,000 population in the 3rd and 4th decade to almost 300 in 8th and 9th decade⁹. The peak seen in later life might be due to higher life expectancies of western populations.

In the study it was found that the patients with the impaired glycaemic status i.e stress hyperglycemia and diabetes had the higher incidence of both ischemic (58.3%) and haemorrhagic stroke (56.3%). Among haemorrhagic lesions the medium sized (58.33%) and large sized lesions (55.55%) were seen more in euglycemics while small sized lesions (81.81%) were seen in diabetics. There is no relation between size of haemorrhage and glycaemic status. Mankovsky et al, 1996 also states that diabetes mellitus is a risk factor for ischemic but not haemorrhagic stroke.¹⁰ it was observed the infarct size increased with progressive worsening in glycaemic status, our finding are consistent with various studies (Mehta's Bair et al) who have reported increase infarct size in hyperglycemia¹¹.

The clinical severity of stroke was measured using the National Institute of Health Stroke Scale (NIHSS). The NIHSS score increased with increase in the size of infarct. The NIHSS score for small, medium and large sized lesions were 9.35±2.52, 13.03±4.08 and 19.31±6.27 respectively. The NIHSS score for euglycemics, stress hyperglycemics and diabetes were

10.33 \pm 2.68, 13.68 \pm 3.30 and 19.38 \pm 6.66 respectively. Admission blood glucose correlated well with the NIHSS score in all the three glycemic groups. These findings are comparable to Johnson et al. where infarct volume was a significant predictor of NIHSS score.¹² An increase in admission blood glucose on presentation was associated with higher NIHSS score indicating the severe clinical presentation of the stroke¹³. Patients with HbA_{1C} \geq 6.5 had higher NIHSS score. Thus HbA_{1C} affects the severity of ischemic stroke and was found to be statistically significant. These findings corroborate with the study performed by Sunanda et al, 2016 who also found higher HbA_{1C} levels affected stroke severity and functional outcome.¹⁴

Admission blood glucose and HbA_{1C} had positive correlation with NIHSS score in all the three groups. Although size of the infarct increased with increasing mean admission blood glucose level and HbA_{1C}, there was positive correlation only between HbA_{1C} and size of the infarct. The association between mean admission blood sugar level and size of the infarct was not found to be statistically significant because of the large variation in the values of the random blood glucose. Our study demonstrates admission hyperglycemia as a bad prognostic marker. Helgason, 1988 had stated that both acute and chronic hyperglycemia are associated with increased edema and infarct size¹⁵. Many studies (Candecise et al, Weir et al, Bruno et al, Sarkar et al) have demonstrated the ill effects of admission hyperglycemia on ischemic stroke^{16,17}

The NIHSS score increased with increase in the size of bleed. The NIHSS score for small, medium and large sized lesions were 10.27 \pm 1.42, 12.92 \pm 3.37 and 17.33 \pm 6.21 respectively. The NIHSS score for euglycemics, stress hyperglycemics and diabetes were 11.86 \pm 2.50, 12.14 \pm 3.13 and 15.73 \pm 6.77 respectively. Though the NIHSS score increases as the glycemic spectrum changes from euglycemia to diabetes, the difference was not found to be statistically significant. This is in

accordance with the study conducted by Lakshman I et al Front Neurol. 2018 who also found that admission blood glucose level was not an independent predictor of severity of stroke in haemorrhagic stroke¹⁸. Patients with HbA_{1C} \geq 6.5 had higher NIHSS score. Thus HbA_{1C} affects the severity of haemorrhagic stroke and was found to be statistically significant. There was positive correlation only between HbA_{1C} and size of the bleed. The association between mean admission blood sugar level and size of the bleed was not found to be statistically significant. This suggests that stress hyperglycemia does not affect the size of haemorrhagic stroke.¹⁸

When Chi-square test was used to prove the association of increased mortality with higher blood glucose level among ischemic stroke, this association was found to be statistically significant (P<0.05). Mortality increased with increase in the admission blood glucose level in ischemic stroke. The association between HbA_{1C} and outcome in ischemic stroke patients was also found to be statistically significant. This is in accordance with several studies carried out (K Ghanachandra Singh et al, 2014, Kes VB et al. Ann Saudi med. 2007 Sep-Oct, Ahmed Al-Weshahy et al, 2017, Candelise 1995, Kiers et al 1992). Our study findings contradict with the study of Power et al, 1988 who concluded that HbA_{1C} is less closely related to fatality suggesting that the relatively high blood glucose level at onset of stroke are not due to previously undiagnosed diabetes mellitus but are at least partly related to the stress of acute illness¹⁹. Hyperglycemia causes impaired autoregulation of cerebral blood flow in diabetes resulting in cerebral oedema²⁰; patients with stroke and hyperglycemia had higher lactate content in their ischemic brain. Recovery of cerebral ATP generation following cerebral ischaemia is impaired when the ischaemia occurs in the setting of hyperglycemia.

When Chi-square test was used to prove the association of increased mortality with higher blood glucose level in haemorrhagic stroke, this association was not found to be statistically

significant ($P>0.05$). Although more death occurred in the stress hyperglycemia and diabetes group in haemorrhagic stroke, the above result was not found to be statistically significant. Lakshman I et al Front Neurol.2018 also found that admission blood glucose level was not an independent predictor of mortality in haemorrhagic stroke¹⁸. The association between HbA_{1C} and outcome in haemorrhagic stroke patients was also not found to be statistically significant. HbA_{1C} level does not affect the outcome in terms of mortality in patients with haemorrhagic stroke. Masaru Sakarai et al, 2013 also did not get a significant association between HbA_{1C} and outcome in haemorrhagic stroke.²¹

Conclusion

Hyperglycemia was a common finding in patients with acute stroke with or without history of diabetes. The admission/random blood glucose and NIHSS scores correlated with clinical severity in ischemic stroke. Patients with impaired glycemic status in acute ischemic stroke had increased severity with high NIHSS scores on admission irrespective of the size of the lesion. Hyperglycemia should be considered as a marker for poor clinical outcome and worse prognosis following an acute ischemic stroke.

Admission blood glucose did not correlate with the severity and outcome in haemorrhagic stroke suggesting that admission blood glucose is not an independent predictor of severity and mortality in haemorrhagic stroke. Further studies need to be carried out to confirm with this finding.

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