|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
PubMed (National Library of Medicine ID: 101738825)
Index Copernicus Value 2018: 75.71
Original Research Article Volume 3, Issue 9; September: 2019; Page No. 94-100

STUDY OF ALTERED GLUCOSE LEVELS IN CASES OF ACUTE ISCHEMIC STROKE AND ITS EFFECT ON PROGNOSIS

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Article Info: Received 11 August 2019; Accepted 14 September. 2019
DOI: https://doi.org/10.32553/ijmbs.v3i9.540
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Conflict of interest: No conflict of interest.

Abstract

Introduction

Globally about 20 million people suffer from stroke each year. Stroke is a medical condition in which poor blood flow to the brain results in cell death. The risk factors causing stroke are high blood pressure, high blood, tobacco smoking, obesity cholesterol, diabetes mellitus and previous Transient Ischemic Attack (TIA).

Objectives: To determine the association of stress hyperglycemia at admission with outcome of acute ischemic stroke

Materials and Methods: A study was done at Thiruvalla, Kerala for a period of one year. All new cases of cerebral infarction admitted comprised of 70 cases, 35 each in Euglycemia and Stress hyperglycemia group who were classified at the time of admission based on random blood glucose estimation with the features of stroke. All necessary investigations for the work-up of case required were done. Glasgow Outcome Score for the assessment of recovery in patients was scored, based on National Institute of Health Stroke Scale (NIHSS) on day 1, at the time of discharge and then again on day 30 to assess the clinical outcome. Standard descriptive statistics were used to report the data. Fisher's exact test and Students t test were used to compare the two groups. Binary logistic regression analysis was done.

Result: Patients with stress hyperglycemia were found to have increased NIHSS scores on admission and this was more prominent at time of discharge on compared to euglycemic group. Poor recovery was associated with small and medium infarct size in stress hyperglycemia. However, prognosis worsened if size of infarct increased in both groups.

Conclusion: Adequate control of blood glucose levels should be maintained immediately during admission and during follow-up to improve prognosis.

Keywords: Stroke, Glucose levels, Prognosis

Introduction:

Stroke is defined as abrupt onset of a neurological deficit that is attributable to a vascular cause, is one of the major cause of death worldwide.[1] Various risk factors are known to increase the liability of stroke and its outcome, of which the most important being diabetes, hypertension, smoking and dyslipidemia.[2]

Stroke is a dreaded disease because of the devastating disability it leaves behind. Various studies have shown that nearly one third of stroke patients die within three weeks of onset and 48% die within a year. This warrants an early and proper management of acute stroke which in turn requires an accurate diagnosis of the pathological type of stroke. Stroke may be of ischemic or hemorrhage type and distinguishing between the two is a prerequisite for management.[2]

John Jacob Werter (1620-95), Swiss physician was probably the first to suggest that apoplexy was caused by disease of blood vessel in the brain. The first person to lay the principles of circulation was William Harvey (1578-1657). In 1664, Thomas Willis described the circle of Wills. Subsequently, Brunner (1653-1727) identified the significance of aneurysm, of the vessel of the brain in the causation of the subarachnoid haemorrhage (Walton, 1956). This was followed by extensive study by Morgagini (1682-1771) and Jean Martin Charcot (1825-1893). 1978).British physicist Godfrey Hounsfield (1972) introduced computerized axial tomography technique into neuro-radiology which resulted in award of

Nobel Prize in 1979. This lead to more precise categorization of ischemic V/s hemorrhagic CVA.[3]

Diabetes mellitus is well established independent risk factor for ischemic stroke with an overall risk of 2.5 times higher than non- diabetic patients[4], and this is associated with greater in- hospital mortality and morbidity both ischemic stroke cases and intracerebral hemorrhage. Hyperglycemia is common among patients with acute stroke, occurring in up to 60% of patients overall and approximately 12-53% of acute stroke patients without prior diagnosis of diabetes. The adverse effect of hyperglycemia is possibly due to anaerobic metabolism of glucose, worsening the intracellular and extracellular acidosis. Hyperglycemia is common in patients with acute stroke, occurring in up to 60% of patients overall and approximately 12- 53% of acute stroke patients without prior diagnosis of diabetes.[5]Hyperglycaemia in both diabetic and non- diabetic (stress hyperglycemia) patients is associated with poor prognosis both in terms of mortality and functional recovery, irrespective of patient's age, severity of condition or stroke sub-type.[4] It is found that scrupulous control of blood glucose might reduce the risk of cerebral infarction. Thus stress- induced hyperglycemia may be modifiable risk factor for brain damage.[6]

The issue of hyperglycemia in patients with acute stroke continues to generate a lot of debate. Hence the present study is undertaken to determine the effects of hyperglycemia on the severity, morbidity and mortality in patients with cerebral infarction during their hospital stay and at the end of 30 days wherever feasible.

MATERIALS AND METHODS

Longitudinal observational study was done at Pushpagiri Institute of Medical sciences Thiruvalla during the period December 2016- December 2017. Sample size was calculated based on assumption of bad outcome of 40% among euglycemia group with an odds ratio of 4 in stress hyperglycemia group sample size of group with 35 each (n=70) at 95% confidence and 80% power . The present study comprised of 70 cases, 35 each in Euglycemia and stress hyperglycemia group who were classified at the time of admission based on random blood glucose estimation with the features of stroke. Inclusion Criteria where all new cases of cerebral infarction admitted to the hospital , Thiruvalla during the period December 2016- December 2017 and Exclusion Criteria where Previous history of stroke - Transient ischemic attacks - Hemorrhagic stroke – Cerebellar / Brain stem infarction - Known cases of Space Occupying Lesions - Cerebral Venous Thrombosis.

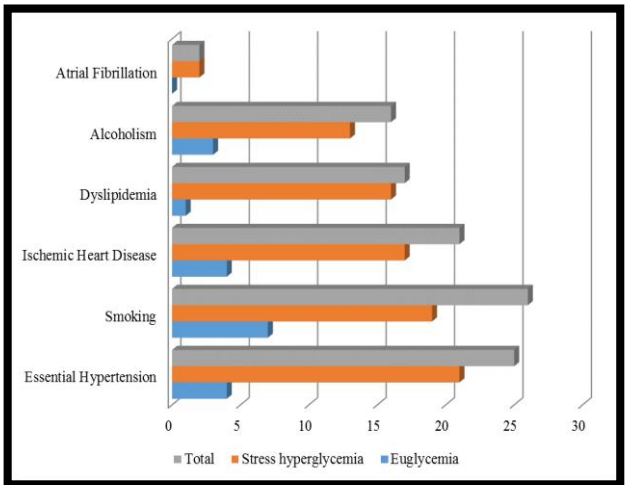
Patients were selected based on the inclusion criteria after thorough clinical examination on presentation of case in emergency room. Random blood glucose levels were done within 24 hours of hospital admission along with all necessary investigations for the work-up of case required was done. Investigations included Blood examination**,** Hemoglobin**,** Total leukocyte count , Differential leukocyte count ,Erythrocyte Sedimentation Rate **,**Platelet count **,**PT/INR , Urine routine-Albumin, Sugar, Microscopy, CT scan brain (plain) / MRI. Random Blood Sugar within 24 hours of hospital admission (Fasting Blood Sugar , Postprandial Blood Sugar), HbA1c levels, ECG , Fasting lipid profile, Fundoscopy ,Serum electrolytes, blood urea and serum creatinine, 2 D Echo (if needed), Glasgow Outcome Score for the assessment of recovery.

Patients was scored, based on National Institute of Health Stroke Scale (NIHSS) on day 1, at the time of discharge and then again on day 30 to assess the clinical outcome. The outcome is classified as favorable and not favorable based on NIHSS score (<25 or >25).Outcome measurement was calculated as Diabetic status was assigned on the basis of history of diabetes or treatment with hypoglycemic agents or elevated HbA1c or persistent/ marked hyperglycemia. Stress hyperglycemia was defined as admission blood glucose > 140 mg% and normal HbA1c.Infarct size on MRI scan brain < 3 cm^2 is small, 3-5 cm^2 is moderate and > 5 cm^2 was considered as large infarct. NIHSS score was quantified as less than 5 indicates mild neurologic impairment, 5- 15 indicates moderate, 15-25 indicates severe and score more than 25 indicates very severe neurologic impairment. NIHSS will be grouped favorable when score is < 25 and not favorable when score is > 25 .Standard descriptive statistics were used to report the data. Fisher's exact test and Students t test were used to compare the two groups. Binary logistic regression analysis was done, which adjust co-morbidities affecting the outcome. (NIHSS score favorable or not favorable)

RESULTS

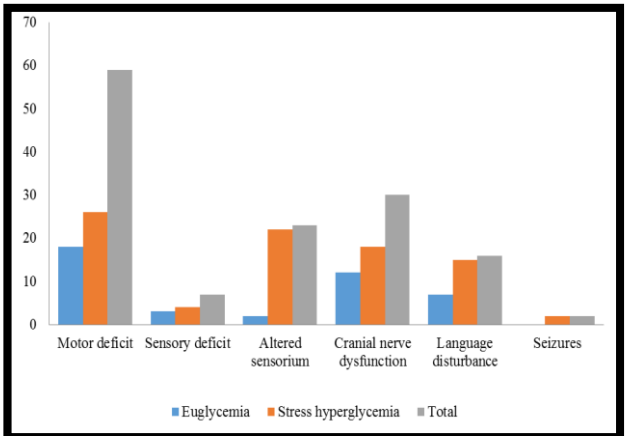
The study sample varied from 28 years to 80 years and maximum number of cases reported was in the age group of 51 to 60 years followed by 71 to 80

years of age .Male cases reported were nearly 69 % and 31 % of the cases were female indicating a male predominance. The present study comprised of 70 cases, 35 each in Euglycemia and stress hyperglycemia group who were classified at the time of admission based on random blood glucose estimation with the features of stroke.



Graph 1: Risk factors reported in study group

Essential hypertension was more in Stress hyperglycemia group whereas smoking were seen more in Euglycemic group .As a whole, risk factor was in descending pattern with highest risk for Essential Hypertension, Smoking, Ischemic Heart Disease, Dyslipidemia, Alcoholism and Atrial Fibrillation.



Graph No.2: Clinical Presentation reported in study group

The most common mode of clinical presentation as shown in our study is motor deficits followed by cranial nerve involvement, cranial nerve dysfunction and altered sensorium followed language deficit and sensory deficit.

Based on observation of size of infarct we had fairly equal distribution of cases classified as small, medium and large size of infarct. *Classification of cases based on infarct size on CT/MRI imaging where as follows* - medium >3cm^2 to <5cm^2 (33.33%), large >5 cm^2 (30.67%), small <3cm^2 (29.33%). *Classification of cases based on infarct size and Euglycemic status on CT/MRI imaging were as followed* - large >5 cm^2 21 (60%), medium >3cm^2 to <5cm^2 (29%) and small <3cm^2(11%).

Table 1: NIHSS Score on admission at discharge and after 30 days by glycemic status and size of infarct

Glycemic Status& Infarct size	n	Mean±SD on admission	Mean ± SD at discharge	Mean ± SD at 30 days
Infarct size: SMALL<3cm^2				
Euglycemia	18	9.95 ± 6.8	4.65 ± 1.35	2.63± 0.35
Stress hyperglycemia	4	15.38 ± 1.8	9.27 ± 1.73	6.58± 1.65
		t=1.57(p=0.13)	t=5.9(p=0.001)*	t=11(p=0.001)*
Infarct size: MEDIUM>3cm^2 to <5cm^2				
Euglycemia	15	12.68 ± 2.52	8.21 ± 1.56	5.36± 1.02
Stress hyperglycemia	10	14.94 ± 3.91	11.67 ± 3.04	8.32± 2.35
		t=1.74(p=0.09)	t=3.7(p=0.001)*	t=23(p=0.001)*
Infarct size: LARGE>5 cm^2				
Euglycemia	2	21.51 ± 1.81	11.25 ± 1.89	9.35± 1.35
Stress hyperglycemia	21	26.56 ± 5.37	17.72 ± 6.55	11.66± 4.35
		t=1.29(p=0.21)	t=1.36(p=0.18)	t=0.7(p=0.45)

As shown in Table No.1 the mean scores of NIHSS on the day of admission, at the time of discharge and after 30 days based on the severity of condition considering the size of infarct radiological. The difference in the mean scores at the time of discharge and after 30 days was significantly different in stress hyperglycemia group when the infarct size was small and medium in euglycemic group. Whereas when the size of infarct increased the score difference in both the groups was not statistically significant.

Table 2: Comparison of blood glucose and HbA1c correlation with NIHSS score based on size of infarct in Euglycemia

Infarct size		Euglycemia				
		RBS	HbA1c	NIHSS on admission	NIHSS at discharge	NIHSS at 30 days
	n	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Small <3cm^2	18	131.05 ±8.26	4.15±0.43	9.95 ± 6.8	4.65 ± 1.35	2.63± 0.35
Medium >3cm^2 to <5cm^2	15	137.58±2.78	4.1 3±0.63	12.68 ± 2.52	8.21 ± 1.56	5.36± 1.02
Large >5 cm^2	2	136.86±1.36	4.12±0.31	21.51 ± 1.81	11.25 ± 1.89	9.35± 1.35
		F=1.87 P=0.17	F=1.07 P=0.95	F=4.76 P=0.015*	F=35 P=0.0001*	F=38 P=0.0001*

***-Statistically significant**

On comparison of mean random blood sugar level and Hb A1c levels in group of euglycemic with the NIHSS score we found after one way ANOVA the difference in random blood glucose and mean Hb A1c levels did not differ much among the different size of infarct but the NIHSS score when observed among the different groups it had a significance difference suggesting NIHSS score correlating with the size of infarct as displayed in Table No.2

Similarly in table No.3 the comparison was in the stress hyperglycemia group which indicated random blood sugar levels were significantly different with the severity of the condition or random glucose levels were increased in cases with increased size of infarct which was statistically significant but the same difference was not presented with Hb A1c levels. The NIHSS score as observed in euglycemic score were similar trend in stress hyperglycemica group with significant difference among the different infarct size

Table 3: Comparison of blood glucose and Hb A1c correlation with NIHSS score based on size of infarct in Stress hyperglycemia

Infarct size		Stress hyperglycemia				
		RBS	HbA1c	NIHSS on admission	NIHSS at discharge	NIHSS at 30 days
	n	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Small <3cm^2	4	171.16±15.42	4.63±0.44	15.38 ± 1.8	9.27 ± 1.73	6.58± 1.65
Medium >3cm^2 to<5cm^2	10	208.97±21.32	5.01±0.94	14.94 ± 3.91	11.67 ± 3.04	8.32± 2.35
Large >5 cm^2	21	318.87±19.35	5.38±1.38	26.56 ± 5.37	17.72 ± 6.55	11.66± 4.35
		F=164 P=0.0001*	F=0.82 P=0.57	F=24 P=0.0001*	F=35 P=0.0001*	F=4.85 P=0.01*

Table 4: Glasgow Outcome Score based on glycemic status

Glasgow outcome score	Euglycemia (%)	Stress hyperglycaemia (%)	Total
1. Death	0	0	0
2.Persistent vegetative state	2 (5.7%)	5 (14.4%)	7
3. Severe disability	4 (11.3%)	8 (22.8%)	10
4. Moderate disability	7 (20%)	10 (28.6%)	15
5. Low disability	22 (63%)	12 (34.2%)	38

Table No.4 displayed the Glasgow outcome score based on glycemic status though no death were reported in our study, we observed the glycemic status had impact outcome of the disease with severe

disability reporting in the stress hyperglycemia group and low disability being dominant in the group of euglycemia.

DISCUSSION

Stroke is a becoming a common clinical problem in present context due to rise in metabolic abnormalities and changing behavioral patterns. Elevated blood glucose is common in the early phase of stroke. The prevalence of hyperglycemia, defined as blood glucose level > 108 mg/dL, has been observed in two thirds of all ischemic stroke subtypes on admission and in at least 50% in each subtype including lacunar strokes[7]. Much experimental evidence is in support that hyperglycemia has adverse effects on tissue outcome and present study is attempt in that direction.

The present study comprised of 70 cases, 35 each in Euglycemia and stress hyperglycemia group who were classified at the time of admission based on random blood glucose estimation with the features of stroke. The age group of patients spanned from 26 years to 80 years with mean age of 54.6 ± 14.64 years and maximum distribution of cases were reported in sixth decade. Our results are in conjunction with UKPDS study reported advancing age as important risk factor for stroke. Sarkar RN et al., [6] reported mean age group of 51.2 years and Kamel et al., [67] in reporting 58.8 ± 10.1 years as the mean age of stroke in Indian population and our study results are in the range of the other Indian study population. Our study showed 69% male and 31% female with male to female ration of 2.3:1 which is different from other similar studies indicating male preponderance like Kushner et al.,[8] reporting 1.7:1.5 and Hvyarinen M et al.,[9] reporting 1.12:1 male to female ratio.

33% of cases had identified risk factor of essential hypertension in our study which is comparatively lower than the proportion as present by Sarkar RN et al., [6] 47.6% and Kamel et al., [10] reporting 48% of the non diabetic patients presenting with stroke suffering from hypertension Nearly 30% of the cases had risk factor identifies as ischemic heart disease which is almost similar to Kamel et al., [10] reporting as 28% in non-diabetic stroke patients. Other important risk factor identified were smoking nearly 34% and alcohol consumption 22% of the cases which is similar to study reporting smoking association with 37% and alcohol consumption 31% by Megherbi SE et al. [11]

Clinical presentation of pattern was predominantly as motor deficits in 79% of cases followed by cranial nerve involvement in 40% of cases closely followed by altered sensorium in nearly 31% of cases. Language disorders was associated in 21% of cases and sensory component involvement was only in 9% of cases and 3% of cases had seizures. Similar profile of presentations were reported by Wolf PA et al., [12]

Stress hyperglycemia had altered lipid parameters with significantly higher triglycerides and lower high density lipoproteins. Total cholesterol and low density lipoproteins were also elevated on compared to euglycemic group but not significantly which are similar to the results obtained by Kamel et al., [10] Classification of cases based on size of the infarct on CT scan imaging was as small (<3mm^2), medium (>3mm^2 to <5mm^2) and large (>5mm^2). In present study infarct of small size accounted for 29.33% and medium size infarct were reported around 33.33% and 30.67% of cases were reported with large size infarct. The trends observed in euglycemic was maximum cases belonged to small size infarct (51%) followed by medium size infarct (43%) and only 6% cases were having infarct of large size. In comparison the stress hyperglycemia group reported maximum number of cases with large size infarct (60%) followed by medium size infarct (29%) and only 11% had small size of infarct on CT imaging. As reported by Mehta et al, .[13] the size of infarct was worst with the increasing glycemic status concluding increased infarct size with hyperglycemia

The clinical severity of stroke was also assessed using the NIHSS stroke scale at the time of admission and followed the scale score at the time of discharge and after 30 days of admission. On comparison of the mean NIHSS stroke scale between stress hyperglycemia and euglycemia based on the size of infarct. At the time of admission mean score in small size infarct of euglycemic group was 9.95 ± 6.8 and in stress hyperglycemia 15.38 ± 1.8. in the same group the mean scores of NIHSS at the time of discharge and after 30 days was statistically significant between euglycemia and stress hyperglycemia suggesting a better recovery and improvement of scores in euglycemic group as compared to stress hyperglycemia

Similar trends of results were obtained in the group of infarct size being medium where NIHSS score at the time of discharge and after 30 days of stroke were statistically significant between stress

hyperglycemia and euglycemic group suggesting poor or slow recovery in stress hyperglycemia in cases with infarct size being medium (3 cm^2 to 5 cm^2). In the group of infarct size being large (> 5 cm^2) noted a difference in NIHSS score between stress hyperglycemia and euglycemia was not significant either at time of admission or at the time of discharge and after 30 days of admission suggesting in cases of large size infarct prognosis was poor irrespective of glycemic state.

Our results are not in conjunction with Gentile NT et.al, [14] who noted that hyperglycemia was associated with higher admission severity score. But was in agreement the admission hyperglycemia was an independent predictor of morbidity even after controlling the disease severity. Similar results were obtained by Sarkar R N et.al, [6] and Bruno A et.al, [15] who showed that hyperglycemia predicts poor outcome.

Capes S E et.al,[4] have reported a 3–fold increased risk in mortality in post stroke hyperglycemia, summarizing nine studies of varying population in non-diabetic patients similarly Hyvarinen M et.al,[9] confirmed in their study that hyperglycemia is a independent predictor of stroke mortality. Poppe AY et.al, [16] found that the strongest predictor of poor outcome and death was persistent hyperglycemia at baseline and at 24hours. Yong M et, al, [17] in study of non-diabetic patients with persistent hyperglycemia had shown the worst prognosis assessed by neurological improvement, functional outcome, mortality and hemorrhagic transformation.

Random blood glucose level and Hb A1C levels were correlated with infarct size and NIHSS score at the time of admission and similarly at the time of discharge and 30 days after stroke episode. In stress hyperglycemia the random blood sugar levels to the size of infarct were significantly different. In comparison to euglycemic group based on infarct size and random blood of glucose levels were not statistically significant. Similarly Hb A1C levels in both groups of euglycemia and stress hyperglycemia were not statistically significant. Higher blood glucose cases had larger size infarcts and thus more severe stroke similar to Cox NH et al,[18] reporting that hyperglycemia in conjunction with normal HbA1c, which probably represents a 'stress' response, is associated with poor prognosis for recovery from stroke.

Glasgow outcome score based on glycemic status observed the glycemic status had significant impact on outcome of the disease with severe disability reporting in the stress hyperglycemia group and low disability being reported in group of euglycemia.

This evidence supports that acutely elevated, predominantly stress-related hyperglycemia is associated with poor outcomes such as dependent state or other complications. Through several different biochemical mechanisms, elevated glucose in the setting of cerebrovascular insults probably accelerates the course of ischemic injury, also in the boundary regions with milder perfusion deficit. However, restoration of normoglycemia as soon as possible should be encouraged, although conclusive evidence of decreased risk with this approach is lacking. Especially the nondiabetic patients may be at risk of further brain damage if hyperglycemia prevails.

CONCLUSION

Stroke was more common in the age group of 50-60 years and male preponderance was noted in ratio of 2:1 for females. Two groups each of 35 euglycemia and stress hyperglycemia based on blood glucose levels at the time of admission was considered. Stress hyperglycemia defined as admission blood glucose > 140 mg% and normal HbA1c level. Admission blood glucose levels, HbA1c levels and NIHSS scores were compared with infarct size as small, medium and large based on CT findings. Patients with stress hyperglycemia were found to have increased NIHSS scores on admission and this was more prominent at time of discharge on compared to euglycemic group. Poor recovery was associated with small and medium infarct size in stress hyperglycemia. However, prognosis worsened if size of infarct increased in both groups .Preventive measures to be adopted for rigid control of blood glucose levels immediately during admission and during follow-up improves outcome.

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