Hyperglycemia and its Association with Patients' Mortality Among the Patients Presenting with Acute Stroke in Tertiary Care Hospital

Maryam Rana, Abdul Latif Khattak*, Muhammad Khalid Azam Khan*, Raees Iqbal Khan,
Syed Karamat Hussain Shah Bukhari*, Faisal Mehmood*

Combined Military Hospital Quetta/National University of Medical Sciences (NUMS) Pakistan, *Combined Military Hospital Lahore/
National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objectives: To estimate the occurrence of hyperglycemia in patients with cerebrovascular accident (ischemic) to compare the frequency of mortality among the patients with and without hyperglycemia presenting with acute CVA.

Study Design: Descriptive cross-sectional study.

Place and Duration of Study: Department of General Medicine, Combined Military Hospital Quetta Pakistan, from May 2018 to May 2019

Methodology: A total of 347 patients of both genders diagnosed with acute stroke were included. Blood glucose levels were evaluated and hyperglycemic and normo-glycemic patients were identified. CT scan was performed. Standard treatment was provided to the patients according to the type of stroke (ischemic or hemorrhagic). These patients were discharged.

Results: Patients in this study was having age range of 20 to 70 years.SO mean age of 53.76 ± 9.08 years. Many patients 283 (81.56%) were of 45-71 years of age. 183 (52.74%) were of male gender and 164 (47.26%) were females. We have found hyperglycemia in 96 (27.67%) patients. There was no hyperglycemia observed in 251(72.33%) patients. Frequency of hyperglycemia was 12.97%. Frequency of mortality was 30.21% in hyperglycemic patients vs. 6.37% in normo-glycemic patients (*p*=0.0001).

Conclusion: Frequency of hyperglycemia with acute stroke is high with high mortality among the patients presenting with acute stroke as compared to normo-glycemic.

Keywords: Acute stroke, Hyperglycemia, Mortality.

INTRODUCTION

In countries with stable economic conditions, stroke (CVA) has been acknowledged 3rd commonetiology of death after cardiovascular diseases and tumors. Those who have survived, stroke remained common cause of death and physical deficits.Only fewer patients (about 20%) need admission for prolong periods and rehabilitation therapy in coming months after disease episode(CVA).[1,2]

Stroke has been declaredprominent neurological reasonfor death and physical disabilitythroughout world. It ishas been declared 3rd foremost reason of death among entire countries. Evaluation of various risks as etiology in patients is supportive for recognition for early disease management. All this strategy will contribute for health professionals for managing target population. Ischemic stroke is world wide disease contributing in martality.[3] A research article at international level has calculated a figure of 15 million individuals sustain nonfatal stroke yearly. Among these people, 33% developed disability for whole life.[4] In lower and middle-income countries only 80% of all stroke deaths are registered. A projected annual occurrence of CVA in Pakistan is 250/100,000. Pakistan has annual occurrence of about 350,000 new cases.[5]

Stroke not only causes but alsoaggravates the pre-existing dementia. Stroke also leads to cognitive impairment especially in elderly individuals.[5] Due to non-availability of central registry and inadequate data availability in Pakistan on this subject, there is insufficient research work on risk factors of stroke in Pakistani population. A study conducted in 2014 showed a high incidence of modifiable risk factors. Among these risk factors, Hypertension and dyslipi-demias were contributory factors in Pakistani population. The same study showed that atheros-clerosis as the most common culprit in elderly patients. Elderly patients have a higher risk adjusted mortality rate. Eldely population also have higher rate of complications and require longer periodsfor hospitalization.[6] Strokes can be divided into two main categories i.e., hemorrhagic and non-

Correspondence: Dr Raees Iqbal Khan, Classified Medical Specialist, Combined Military Hospital Quetta Pakistan

hemorrhagic. Intracranial bleed-includes 10% to 15% of all CVA cases. ICB has higher death rate as compared to ischemic stroke entity. About 50 out of 100 patients with diagnosis of intra-cranial bleed die during first 30 days of illness.[7]

Different prognostic markers were assessed to predict the outcome and to evaluate the association with ischemic stroke. These biomarkers include brain natriuretic peptide, highly sensitive C-reactive protein. In addition, the markers like homocysteine and insulin like growth factor have also been studied at different intervals. Serum blood glucose level and throm-bomodulin also have prognostic value in stroke patients.[8]

Al-Weshahy *et al*, a study of the patients coming with acute stroke. The frequency of hyperglycemia among these patients was 34.4% while the frequency of mortality was 85.7% in hyperglycemic patients vs. 5% in normoglycemic patients; *p*=0.00).[9]

The results of our established that hyperglycemia is one of the most reliable markers in defining the outcome of the stroke in relationto mortality. Being a good predictor, there is a need to conduct further studies on local population so that its relationship with the outcome of the stroke could be determine in local population. This would help us in creationof local guidelines for admitting and giving intensive care to patients. This would help to opt early interventional radiological measures which would help in dealing with the pathology (ischemia or intracranial bleeding). This would also help in reducing mortality rate in these patients.

METHODOLOGY

This Descriptive cross sectional study was conducted at department of medicine Combined Military Hospital Quetta, from May 2018 to May 2019. Sample size of 347 cases was calculated with 95% confidence level. 5% margin of error was kept while taking predictable frequency of hyperglycemia to be 34.4% among the patients presenting with acute stroke.[9] Non-probability, Consecutive sampling technique was adopted.

Included Criteria: Patients of both gender groups with ages in the range of 20-70 years suffering from acute stroke as defined in operational definition, were included. Patients who signed written informed consent to join in the study were also included.

Exclusion Criteria: Patients who were excluded include patients with diabetes who hadfasting blood glucose level ≥120mg/dl). In addition, patients with

history of neurological deficits that reverts within 24 hours after onset (transit ischemic attack) were also excluded. Patients with history of headtrauma having biconvex, concave or intraparenchymal white area on plan CT scan were excluded. Patients with space occupying lesion on CT scan and patients with serum creatinine >2mg/dl, serum sodium <120 mmol/l or have liver cirrhosis along with as cites were also excluded from the study.

SPSS-22 used for data analysis. Data collected, entered in SPSS and study variables i.e. age, glycemic levels, blood pressure level, basal metabolic index values and hospital stay days were calculated. *p*-values were calculated for mortality in normoglycemic and hyperglycemic patients presenting with acute ischemic stroke.

RESULTS

Total 347 patients were selected and their age range was from twenty toseventy years. While calculated mean age found to be 53.76 ± 9.08 years. Many of participants of study 283 (81.56%) were between 46 to 70 years of age.

Out of 183 (52.74%) were male and 164 (47.26%) were females. Distribution of patients having various variables affecting mortality arementioned below in Table-I. Mean hospital admission was 10.24 ± 3.20 days. Meanestimated BMI was 28.56 ± 2.99 kg/m.[2]

Table-I: variables affecting mortality among stroke patients (n=347).

Variables Affecting Mortality		Frequency(%age) n (%)
Hospital Stays (Days)	≤10	136 (39.19%)
	>10	211 (60.80%)
Basal Metabolic Index (kg/m²)	≤27	127 (36.60%)
	>27	220 (63.40%)
Hypertension	Yes	233 (67.15%)
	No	114 (32.85%)

Table-II: Comparison of frequency of mortality among the patients with and without hyperglycemia presenting with acute stroke (n=347).

		Hyperglycemic n=96 (26.67%)	Normoglycemic n=251(72.33%)	*p*-value
		No. of Patients %Age	No. of Patients %Age	
Mortality	Yes	29 (30.21%)	16 (6.37%)	0.0001
	No	67 (69.79%)	235 (93.63%)	

Hyperglycemia was observed in 96 (27.67%) patients. There was no incidence of hyperglycemia in 25 1(72.33%) patients. Frequency of mortality was 29 (30.21%) in hyperglycemic patients vs. 16 (6.37%) in

normoglycemic patients; *p*=0.0001) as shown in Table-II.

Percentages of occurrence of hyperglycemia was distributed on different age groups. Results revealed that no significant difference between different age groups found. While hyperglycemia frequency with respect to gender also didn't revealed significant differences between both genders. Table-I have shown the data with respect to hospital stay, BMI & hypertension respectively. Association of hyperglycemia with respect to hospital also showed positive link with longer hospital stay.

patients vs. 6.37% in normoglycemic patients; *p*=0.0001).

Al-Weshahy *et al*, in 20017 performed study in which patients presenting with acute stroke, the frequency of hyperglycemia was 34.4%.However, the frequency of mortality was 85.7% in hyperglycemic patients vs. 5% in normoglycemic patients; *p*=0.00).[9]

Under diagnosed diabetes mellitus cases (6-42%) have been found in acute stroke cases.[12]Diabetes mellitus was found in 24.8% of study participants with supratentorial strokes. 36.3% of patients showed temporary rise in blood sugar levels.[13] Zahra *et al*,[14]

Table-III: Association of Hyperglycemia with respect to gender, Basal metabolic index and hypertension.

Gender	Hyperglycemia		*p*-value	Basal metabolic index (kg/m²)	Hyperglycemia		*p*-value	Hyper-tension	Hyperglycemia		*p*-value
	Yes	No			Yes	No			Yes	No	
Male	43 (23.5%)	140 (76.5%)	0.067	<27	34 (26.77%)	93 (73.22%)	0.777	Yes	72 (30.9%)	161 (69%)	0.054
Female	53 (32%)	111 (67.7%)		>27	62 (28%)	158 (72%)		No	24 (21%)	90 (78.9%)	

DISCUSSION

Acute stroke patients showed already existentof hyperglycemia found in our patients. Occurrence was about 20-50% among stroke patients.20-30% of patients were found to be hyperglycemic in various studies using thrombolytic therapy as treatment measure. Hyperglycemia creates worst outcome in acute stroke patients. 30-day mortality was three-fold more in patients who were found to be hyperglycemic with previous normo-glycemic history. While patients with past history of diabetes only have 2-fold 30-day mortality.[10] Hyperglycemia has been declared as independent risk in various studies using thrombolytic and anticoagulation therapy.[11] While hyperglycemia has also been declared to be worst factor causing hemorrhage in ischemic area.

This research work conducted to estimate the occurrence of hyperglycemia in individuals presenting with acute ischemic stroke. Also, to compare the incidence of mortality in patients with and without hyperglycemias developing acute stroke. Age range found in between 20 to 70 years. Mean age of 53.76 ± 9.08 years. Most of the patients 283 (81.56%) fell in age range of 46 to 70 years. Among 347 patients, 183 (52.74%) were male and 164 (47.26%) were females with male to female ratio of 1.1:1. In this study, hyperglycemia observed in 96 (27.67%) patients. There was no hyperglycemia in 251 (72.33%) patients. Frequency of hyperglycemia between these patients was 12.97%. The frequency of mortality was 30.21% in hyperglycemic

hasdemonstrated that20% stroke patients were having high blood sugar levels who were previously normoglycemic. Zafar A *et al*,[15] in one study declared results that patients with normal blood glucose levels 29 (58.0%) sufferedischemic stroke and 21 (42.0%) suffered intracranial bleed.

Glycemia in Acute Stroke (GLIAS), study tried to find the level of blood sugar levels after which worst outcome in patients can be estimated.Minimum level found to 155 mg/dl. Further increase in blood sugar levels during first 48 hrs above this limit showed added worst outcome and mortality.[16] In a post hoc scrutiny ofsame study, it is observed that 40% of the patients with hyperglycemia kept values of >155 mg/dl in spite of the hypoglycemia treatment.

Lindsberg *et al*,[17] found that raised glucose levels is common phenomenon in early few hour of stroke diagnosis. 2/3 of all patients with ischemic stroke showed high sugar levels during admission in health care facility. A common phenomenon that has been observed that stress hyperglycemia was found in 27.67% of patients showed similar results as found by Melamed *et al*,[18](35%).

Hyperglycemia on admission has direct correlation with stroke outcome.However, no correlation has been observed between catecholamine and glycemic levels.[19] Tuomilehto *et al*,[20] found a mortality figures of 16% in males and 33% in females participants of study. These figures were directly proportional to diabetes.

Hyperglycemia and stroke outcome correlation differs between different stroke subtypes. Correlation between hyperglycemia and poor stroke mortality has been observed in few studies in patients who sustained cortical stroke. However, lacunar stroke didn't contribute to excess mortality.[21] Many studies completed the correlation between raised glucose levels and clinical outcome before giving therapeutic trial of thrombolytic therapy and has been declared standard approach in stroke patients. However, in ongoing studies important factor has been observed that increased sugar levels at hospitaladmission also resultedin worst outcome in patients treated with thrombolytic therapy.[22]

In the Capes *et al*, results showed that those patients not having diabetes mellitus, stress related hyperglycemia was linked with a three-fold more risk of mortality. This rate of mortality was calculated after stroke (pooled relative risk, 3.07; 95% CI, 2.50–3.79). Those patients who have no evidence of diabetes it was found that stress hyperglycemia was not linked with increased risk of short-term mortality after occurrence of stroke (pooled relative risk, 1.30; 95% CI, 0.49–3.43).

Exact mechanism through which high serum glucose levels results in worst outcome who received anticoagulants or thrombolytics is not clear yet. In target vessels, high glucose levelscause glycosylation which deranges protein and enzyme function. Vasodilation and cellular adhesion within the vasculature downregulate production of normal molecules in vascular bed. Hyperglycemia damages endothelial surfaces through glycosylation. Free radicals' production further damages vessels.

Hyperglycemia increases death rate of mortality from ischemic stroke. Few methods have been postulated which describe wrong influence of high serum glucose levels in blood. First mechanism proposes that vessel damage occurs due to poor reperfusion.This results in downregulationof nitric oxide dependent mechanism which results in decrease vessels tone. Second mechanism proposes that increase lactic acid production causes vessels injury leading to increase stroke occurrence. Experimental data has supported above two hypotheses.

CONCLUSION

As per our research it is obvious that occurrence of hyperglycemia in individualsrepresenting with ischemic stroke is high. It also estimates the high incidence of mortality between the patients with hyperglycemias presenting with acute stroke as compared to patients coming with normoglycemia. So, we suggestthose patientspresenting with cerebrovascular accidents (ischemic), hyperglycemia is necessary to be determined in these individuals. So prompt diagnosis and evaluation is necessary to minimize death among these patients for better outcome.

Conflict of Interest: None.

Author's Contribution

MR:Conception of design, collection of data, ALK: Proof reading and editing of manuscript, MKAK:Data analysis and collection, RIK: Writing of manuscript, SKHSB:Overall supervision of the study project, references, FM: Discussions and data analysis.

REFERENCES

1. OjaghihaghighiS, Vahdati SS, Mikaeilpour A, Ramouz A. Comparison of neurological clinical manifestation in patients with hemorrhagic and ischemic stroke. World J Emerg Med 2017;8(1):34–38

2. van Sloten TT, Sedaghat S, Carnethon MR, Launer LJ, Stehouwer CDA.Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. Lancet Diabetes Endocrinol 2020;8(4):325-336.

3. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, etal. American heart association. stroke statistics subcommittee 2014 update: a report from the American heart association. Circulation 2014;129(3):28-32.

4. Hoffman A, Murad D, Van Dui gin CM, France OH. The Rotterdam study 2014 objectives and design update. Eur J Epidemiol 2013;2 8(11): 889-926.

5. Aslam MS, Nasir KM, Hussain H, Saeed M, Wilayat MS, Ahmad W, et al. Pattern of dyslipidemias and their association with ischemic and hemorrhagic stroke. J Islamabad Med Dent Coll 2017; 6(3): 135-140.

6. Xia X, Yue W, Chao B, Li M, Cao L, Wang L, et al. Prevalence and risk factors of stroke in the elderly in Northern China: data from the National Stroke Screening Survey. J Neurol 2019 ; 266(6): 1449-1458.

7. Dierick F, Dehas M, Isambert JL, Injeyan S, Bouché AF, Bleyenheuft Y, et al. Hemorrhagic versus ischemic stroke: Who can best benefit from blended conventional physiotherapy with robotic-assisted gait therapy?PLoS One 2017;12(6): e0178636.

8. Faraji F, Ghasami K, Talaie-Zanjani A, Mohammadbeigi A. Prognostic factors in acute stroke, regarding to stroke severity by Canadian Neurological Stroke Scale: A hospital-based study. Asian J Neurosurg 2013;8(2):78–82.

9. Al-Weshahy A, El-Sherif R, Selim KAAW, Heikal A. Short term outcome of patients with hyperglycemia and acute stroke. Egyp J Crit Care Med 2017;5(3):93-98.

10. Lau LH, Lew J, Borschmann K, Thijs V, Ekinci EI. Prevalence ofdiabetesand its effects onstrokeoutcomes: A meta-analysis and literature review. J Diabetes Investig 2019;10(3):780-792.

11. Saqqur M, Shuaib A, Alexandrov AV, Sebastian J, Khan K, Uchino K. The correlation between admission blood glucose and intravenous rt-PA-induced arterial recanalization in acute ischemic stroke: a multi-centre TCD study. Int J Stroke 2015; 10(7): 1087-1092.

12. Gray CS, French JM, Bates D, Cartlidge NE, Venables GS, JamesOF.Increasingage,diabetesmellitusandrecoveryfromstroke. Postgrad Med J 1989;65(768): 720-724.

13. Osei E, den Hertog HM, Fonville S, Brouwers PJAM, Mulder LJMM, Koudstaal PJ, et al. Prediction of Persistent Impaired

Glucose Tolerance in Patients with Minor Ischemic Stroke or Transient Ischemic Attack. Stroke 2017;48(11):3006-3011.

14. Zahra F, Kidwai SS, Siddiqi SA, Khan RM. Frequency of newly diagnosed diabetes mellitus in acute ischaemic stroke patients. J Coll Physicians Surg Pak 2012;22(4): 226-229.

15. Zafar A, Shahid SK, Siddiqui M, Khan FS. Pattern of stroke in type 2 diabetic subjects versus non diabetic subjects. J Ayub Med Coll Abbottabad 2007;19(4):64-67.

16. Fuentes B, Castillo J, San Jose B, Leira R, Serena J. The prognostic value of capillary glucose levels in acute stroke: the GLycemia in Acute Stroke (GLIAS) study. Stroke2009; 40(2):562-568.

17. Reshi R, Streib C, Ezzeddine M, Biros M, Miller B. Hyperglycemia in acute ischemic stroke: Is it time to re-evaluate our understanding? Med Hypotheses 2017;107(2):78-80.

18. Melamed E, Reactive hyperglycemia in patients with acute stroke. J Neurol Sci 1986; 29(4):267-275.

19. Savopoulos C, Kaiafa G, Kanellos I, Fountouki A, Theofanidis D. Hatzitolios AI.Is management hyperglycemia in acute phase stroke still a dilemma?J Endocrinol Invest 2017; 40(5):457-462.

20. Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2018;379(7): 633-644.

21. Ribo M, Molina C, Montaner J, Rubiera M, Delgado-Mederos R, Arenillas JF, et al. Acute hyperglycemia state is associated with lower tPA-induced recanalization rates in stroke patients. Stroke2005; 36(8):1705-1709.

22. Stead GL, Glimore RM, Bellolio MF et al. Hyperglycemia as an independent predictor of worse outcome in non-diabetic patients presenting with acute ischemic stroke. Neurocrit Care 2009; 10(2): 181-186.

....