ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Stress hyperglycemia as a prognostic indicator of the clinical outcome in patients with ischemic stroke

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Submission: 05-05-2024 Revision: 23-05-2024 Publication: 01-07-2024

ABSTRACT

Background: Stroke is gaining worldwide importance as the focus now shifts to non-communicable diseases. According to the World Health Organization, over 15 million people, equating to one in every 400 people, suffer stroke worldwide per year. There are many factors which affect the outcome of stroke – artery involved, size of the infarct, associated co-morbidities, age of the patient, collateral blood supply, and many more. Among those one of the factors proposed is stress hyperglycemia (SH). **Aims and Objectives:** The aims and objectives of the study are to identify the occurrence of SH in patients admitted with ischemic stroke and to assess the relation of SH in clinical outcomes in patients with ischemic stroke. **Materials and Methods:** The prospective study was conducted on patients admitted to medical college hospitals affiliated with VIMS, Ballari. All patients age more than 18 years presenting with acute-onset ischemic stroke were taken into the study, and GRBS was done at presentation and at every 6th hourly for 48 h to identify hyperglycemia. Hemoglobin A1c was done to rule out overt diabetes and previously undiagnosed diabetes mellitus. Clinical outcome and functional recovery using the modified ranking scale (MRS) were done at the time of admission, at discharge, and at every month for 3 months. **Results:** Out of 150 patients, 63 (42%) of them had SH. The majority of patients belong to 60–69 years age group. The mean age of patients with SH was 60.2 years and that of patients without SH was 57.75 years. MRS score at the time of admission and during follow-up was higher in SH patients than no SH patients ($P<0.001$). Patients with SH were more prone to urinary tract infection (n = 19 [SH]; n = 8 [no SH] $P<0.001$), bed sores (n = 10 [SH]; n = 18 [no SH] $P<0.008$), lower respiratory tract infection (n = 30 [SH]; n = 34 [no SH], $P=0.000$), and duration of hospital stay ($P=0.000$). Delay in presentation to a health facility after the onset of stroke symptoms was found to be a significant contributing factor in SH patients ($P<0.003$). **Conclusion:** The prevalence of SH in ischemic stroke is high. Patients with SH had longer duration of hospital stay, high mortality rate, higher incidence of complications, and poor functional recovery.

Key words: Stress hyperglycemia; Ischemic stroke; Prognosis; Functional recovery

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v15i7.65418

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

As early as 5th century stroke was acknowledged by Hippocrates, who termed stroke as "Apoplexy" which means struck down.[1,2] Stroke is gaining worldwide importance as the focus now shifts to non-communicable lifestyle diseases. According to the World Health Organization (WHO), over 15 million people, equating to one in every 400 people, suffer stroke worldwide per year. Of these, 5 million die and another 5 million are permanently disabled.[3] The definition of stroke (according to WHO criteria) is "rapidly developed clinical signs of focal (or global) disturbances of cerebral function lasting for more than 24 h, unless interruption by surgery or death, with no apparent cause other than a vascular origin."[4]

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India has been experiencing significant demographic, economic, and epidemiological transitions during the past 2 decades. These have resulted in an increase in life expectancy and consequently an increase in the aging population.[3] The cumulative incidence of stroke ranged from 105 to 152/100,000 persons per year, and the crude prevalence of stroke ranged from 44.29 to 559/100,000 persons in different parts of the country during the past decade. The incidence of stroke worldwide is 179 per 1,00,000 population.[4] There are many prognostic/contributing factor which affects the functional outcome such as infarct size, associated comorbidities, age of the patient, and sodium abnormalities. One of the proposed factors is stress hyperglycemia (SH) which is defined as a blood glucose level (BGL) above 200 mg% in previously non-diabetic patients at the time of presentation following a stressful event[5] or SH has been defined as hyperglycemia in previously euglycemic patients that correct once the acute process resolves.[3] It has been noted that hyperglycemia is common in stroke even in patients without a previous diagnosis of diabetes mellitus. It has been documented in two-thirds of all stroke patients and almost half of ischemic stroke patients.[4] Various studies have shown a direct relationship between the extent of SH and the severity and outcome of stroke, including mortality.[5] Hyperglycemia is due to greater release of "stress hormones" such as cortisol and norepinephrine which increases gluconeogenesis, glycogenolysis, decreased insulin utilization causing insulin resistance.[6]

Aims and objectives

1. To identify the occurrence of SH in patients admitted with ischemic stroke
2. To assess the relation of SH in clinical outcomes in patients with ischemic stroke.

MATERIALS AND METHODS

The prospective study was conducted on patients admitted to medical college hospitals affiliated with Vijayanagar Institute of Medical Sciences, Ballari, from November 2016 to October 2018.

Inclusion criteria

Patients admitted during the study period presenting with new onset of ischemic stroke with GRBS more than 200 mg% and with hemoglobin A1c (HbA1c) <6.5% were included in the study.

Exclusion criteria

Known cases of diabetes mellitus, patients with HbA1c values >6.5%, patients with subarachnoid hemorrhage, transient ischemic attack, other causes of focal neurological deficits, patients with hemorrhagic stroke, history of stroke, patients administered hyperglycemic (DNS/5% dextrose/25% dextrose) agents from peripheral health facility, patients on steroids therapy, age <18 years, and patients not giving their consent for the study were excluded from the study.

Study tools

Detailed pro forma to record the serial number, age, sex, presenting complaints, time in the presentation to the health facility, the presence of co-existent co-morbidities, family history of stroke, family history of diabetes, personal history of smoking, alcohol consumption, vitals, and detail clinical examination for each patient.

Investigations done

Random BGL every 8th hourly for the first 24 h, HbA1c, computed tomography (CT) scan brain (plain or contrast), magnetic resonance imaging (MRI) scan if required, renal function test, liver function test, and serum electrolytes.

Case definition

(1) Ischemic stroke: Sudden onset of focal neurological deficit lasting for more than 24 h due to cerebral vascular occlusion by thrombus or embolus
(2) SH: Random blood glucose sugar values more than 200 mg% in a previously non-diabetic patient as evidenced by normal HbA1c levels.

After obtaining a detailed history, a complete general physical examination, and a systemic examination, the patient's GRBS at the time of admission and every 8th hourly for the first 48 h of admission was measured. HbA1c is done for the first blood sample. Clinical outcome was measured in the form of the severity of stroke at the time of admission (by modified ranking scale [MRS] score), infarct size in CT scan, duration of hospital stay, recovery at the time of discharge or death (during the hospital stay or during follow-up) and patients were being followed up at the end of every 1st month, 2nd months, and 3rd months of discharge, during which patients were assessed for function recovery by MRS, development of any complications (such as hemorrhagic transformation, incidence of infection-urinary tract infection [UTI], pneumonia, bed sores, aspiration).

Statistical analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min–Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. Results were also recorded as frequencies and P-values. P<0.05 was taken as the criteria of significance

for all purposes. The Chi-square/Fisher's exact test has been used to find the significance of study parameters on a categorical scale between two and more groups.

RESULTS

Out of 150 patients in the study population, 63 (42%) of them had SH and the remaining 87 (58%) patients had no SH. The maximum number of patients belongs to the 60–69-year age group. The mean age of patients with SH was between 60.2 years and that of patients without SH was 57.75 years (P<0.07). In the study population, 65.3% (n=98) were males and 34.7% (n=52) patients were females. SH was found in 42 males and 21 females (P=0.777) which is not significant. Out of 150 patients studied, 115 of them presented to the hospital within 24 h of the onset of stroke symptoms (among them, 40 patients had SH) whereas 27 of them presented between 24 and 48 h of the onset of symptoms (19 of them had SH). The remaining eight of them presented to the hospital beyond 48 h of onset of stroke symptoms (four patients had SH) (P<0.003). Hence, the delay in presentation to a health facility after the onset of stroke symptoms is significantly associated with SH. The various factors associated among patients with SH and among patients with no SH are described in Table 1.

Thirty four out of 150 patients in the study population admitted with ischemic stroke died during the course of their hospital stay, out of these, 23 (67.65%) had SH (P=0.001). Six patients were lost to follow-up for reasons not determined in the study which is significant. The duration of hospital stay and its association with SH are described in Figure 1.

The Modified Rank Score of ischemic stroke patients during our study period is given in Table 2.

A comparison between the MRS score of patients with SH and no SH is given in Figure 2.

The MRS was assessed at the time of admission, at the time of discharge, and the end of the 1st, 2nd, and 3rd months of follow-up. The patients who presented with SH had a poorer MRS score at the time of presentation to the health facility, at the time of discharge from hospital as well as during the follow-up for 3 months, P=0.001 that was significant statistically. Hence, SH significantly affects the patient with ischemic stroke at the onset of the illness as well as it was related to slow and poor functional recoveries on long-term follow-up.

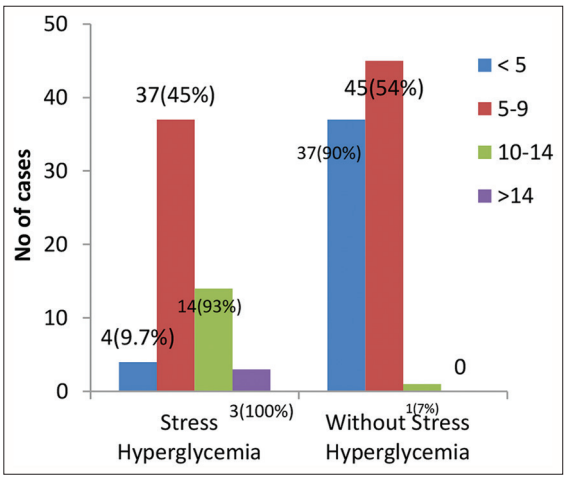

Figure 1: Duration of hospital stay and its association with stress hyperglycemia

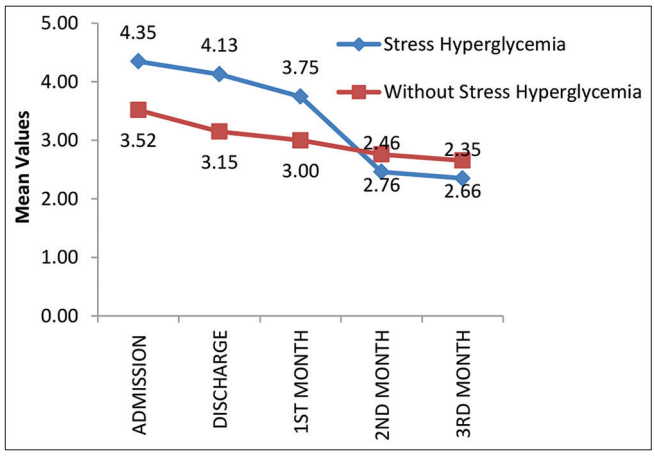

Figure 2: Comparison between modified ranking scale score of patients with stress hyperglycemia and no stress hyperglycemia

DISCUSSION

In the present study, the maximum number of patients belongs to the 60–69-year age group. The mean age of patients with SH was between 60.2 years and that of patients without SH was 57.75 years (P<0.07). According to Basu et al.,[7] (median age 60 years, mean age=60±13 years, range 25–88 years), there was no significant association between age group and occurrence of SH.

The majority of the patients were males which constitutes 65.3% (98 patients). Williams et al.,[8] study showed a preponderance of women among admitted hyperglycemia patients with acute stroke, this study reveals that a male preponderance may be due to the skewed number of male-to-female ratio in the study sample.

In the present study, 42% of the patients were found to have SH. In a study conducted by Basu et al.,[7] 21% of patients who were

Table 1: Various factors associated in patients with stress hyperglycemia and no stress hyperglycemia

Variables	Stress hyperglycemia	No stress hyperglycemias	P-value
Family history of stroke			
Yes (13)	7 (8.7%)	6	0.33
No (137)	56	81	
Family history of diabetes mellitus			
Yes (22)	7	15	0.295
No (128)	56	72	
History of coexisted hypertension			
Yes (69)	31	38	0.53
No (81)	32	49	
Coexisted coronary artery disease			
Yes (9)	3	6	0.430
No (141)	60	81	
History of valvular heart disease			
Yes (3)	1	2	0.620
No (147)	62	85	
History of atrial fibrillation			
Yes (3)	1	2	0.620
No (147)	62	85	
History of smoking			
Yes (72)	38	34	0.01
No (78)	25	53	
History of alcohol consumption			
Yes (66)	35	31	0.01
No (84)	28	56	
UTI			
Yes (27)	19	8	0.001
No (123)	44	79	
LRTI			
Yes (64)	30	34	0.000
No (53)	33	53	
Bed sores			
Yes (28)	18	10	0.008
No (122)	45	77	
Hemorrhagic transformation			
Yes (0)	0	0	-
No (150)	63	87	
Vascular territory			
MCA (128)	56	72	0.575
PCA (16)	5	11	
ACA (6)	2	4	
Death			
Yes (34)	23	11	0.001
No (116)	40	76	

UTI: Urinary tract infection, LRTI: Lower respiratory tract infection, MCA: Middle cerebral artery, PCA: Posterior cerebral artery, ACA: Anterior cerebral artery

Table 2: Modified ranking score of patients

MRS	Stress hyperglycemia		Without stress hyperglycemia		Unpaired t-test		
	Mean	Standard deviation	Mean	Standard deviation	t-value	P-value	Significance
AT admission	4.35	0.63	3.52	0.94	6.117	0.000	HS
AT discharge	4.13	0.81	3.15	0.95	6.617	0.000	HS
AT 1st month	3.75	1.37	3.00	1.05	3.786	0.000	HS
AT 2nd month	2.46	1.93	2.76	1.14	-1.18	0.239	NS
AT 3rd month	2.35	2.00	2.66	1.42	-1.095	0.275	NS

HS: High significance, NS: No significance, MRS: Modified ranking scale

not known diabetic were found to be hyperglycemic though their HbA1c level was normal. In a study conducted by Toni et al.,[9] SH is present in 20–40% of patients with acute ischemic stroke, regardless of history of diabetes mellitus. Melamed[10] showed that hyperglycemia was present in 28% of patients. In study conducted by Capes et al.,[11] stress hyperglycaemia occurred in 20-50% of ischemic stroke patients.

The majority of the patients in the study time of presentation to hospital was <24 h. In the present study,

76% of the patients reported within 24h of onset of symptoms of stroke; 18% of them presented 24-48 hours and 5.4% of patients presented >48 hours after the onset of symptoms. In a study conducted by Basu et al.,[7] 40% reported within 24 h. Among the study group, there was no significant association between SH and a family history of stroke, diabetes; however, in a study conducted by Rehman et al.,[12] it was noted that patients with SH had greater incidence of diabetes mellitus in first-degree relatives than patients with euglycemia. Out of 67 patients, SH 35 [52%] had a family history of diabetes and out of 173 euglycemia patients, 10 [5.7%] had a family history of diabetes, P<0.001).

In our study, among 150 patients in a study population, 69 (46%) of them had co-existed hypertension. 31 (44.9%) out of 69 had SH and the remaining 32 (46.1%) of the patients did not have SH. P<0.503 was not significant. In a study conducted by Basu et al.,[7] there was no significant association between systemic hypertension and the occurrence of SH. In a meta-analysis of a large volume of clinical trial data from the Virtual International Stroke Trials Archive, a history of hypertension was seen to be predictive of post-stroke hyperglycemia within 48 h of stroke.

The most common area of ischemic stroke was in the middle cerebral artery (MCA) territory found in 128 patients out of 150 patients. The P-value for their association was 0.576 which is not significant. However, the incidence of SH with MCA territory stroke is high though their association is not statistically significant. The patients who presented with SH had a poorer MRS score at the time of presentation to the health facility as compared with those without SH and it was statistically significant. Even at the time of discharge from the hospital as well as during the follow-up for 3 months, there was a significant difference in the MRS scoring of patients with and without SH with a P=0.001. According to Baird et al.,[13] mean CGMS glucose and mean BGL glucose correlated with infarct volume change between acute and sub-acute diffusion-weighted MRI (r=0.60, P=0.01), acute and outcome MRI (r=0.56, P=0.01), outcome National Institutes of Health Stroke Scale (NIHSS; r=0.53, P=0.02), and outcome MRS (mRS; r=0.53, P=0.02). Acute and final infarct volume change and outcome NIHSS and mRS were significantly higher in patients with mean CGMS or mean BGL glucose 7 mmol/L. Multiple regression analysis indicated that both mean CGMS and BGL glucose levels of 7 mmol/L were independently associated with increased final infarct volume change. He concluded that persistent hyperglycemia on serial glucose monitoring is an independent determinant of infarct expansion and is associated with worse functional outcomes.

In our study, 67.65% of the deaths were among SH with a significant P<0.001. According to Kes et al.,[4] the unadjusted relative risk (RR) of in-hospital mortality within 28 days in ischemic stroke in patients with MBGL >6.1–8.0 mmol/L (121–144 mg/dL) at admission and after 72 h was 1.83 (95% CI, 0.41–5.5) for non-diabetic patients and 1.13 (95% CI, 0.78–4.5) for diabetic patients. Non-diabetic patients with hyperglycemia had a 1.7 times higher RR of in-hospital 28-day mortality than patients with diabetes. According to Capes et al.,[11] in non-diabetic patients with stroke, the risk for in-hospital or 30-day all-cause mortality (short-term mortality) was 3-fold greater in patients with SH than in those without it (RR 3.07, 95% CI 2.5–3.79).

In our study, there was a statistically significance association between the occurrence of SH in stroke patients and the subsequent development of UTI, respiratory tract infection, and bed sores (P=0.0001), and the mean value for the duration of hospital stay of patients with SH was 8.62 days with a median value of 8 days and that of patients without SH was 4.83 with a median value of 5 days. Applying an unpaired t-test, the P-value for the difference in the mean and median duration of hospital stay for those with and without SH was found to be <0.000 which is highly significant. Hence, patients having SH have a longer duration of hospital stay which is statistically significant when compared to those without SH. According to Khuda Bux Mangrio et al.,[14] patients with SH, the survivors have delayed recovery and poor prognosis but patients without SH have a rapid recovery and good prognosis, respectively. They concluded that SH in acute ischemic stroke patients increases the duration of hospital stay and short-term mortality and long-term morbidity. Thus, SH in ischemic stroke patients acts as a poor prognostic indicator of the clinical and functional outcome.

Limitations of the study

The limitation of our study was smaller population size and follow up was done for only 3 months.

CONCLUSION

From the results of the current study, we found that SH is frequently found in acute ischemic stroke. We also found that patients with SH had high MRS at the time of admission and during follow-up, longer duration of stay in the hospital, higher mortality rate, poorer clinical and functional recovery (more dependent lifestyle), and more complications (UTI, lower respiratory tract infection, bed sores), when compared to patients with no SH. The time at which the patient's first presentation to the hospital, i.e., delayed presentation was more associated with SH.

Thus, we could suggest that SH can be used as a marker of stroke severity predictor or in the stroke outcome. We would suggest early identifying and promptly controlling high blood sugar in patients with acute ischemic stroke to improve the functional recovery of the patient.

ACKNOWLEDGMENT

I sincerely thank all staff in the Department of General Medicine, VIMS Ballari.

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Authors' Contributions:
LV- Concept, protocol, sample collection, analysis, manuscript preparation, data analysis, statistical analysis, interpretation, and literature survey; **SJ-** Guiding and supporting the process of the study, design of the study, review of result analysis and interpretation, and review of the manuscript.

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Source of Support: Nil, **Conflicts of Interest:** None declared.