The frequency and impact of admission hyperglycemia on short term outcome of acute stroke patients admitted to Tikur Anbessa teaching hospital, Addis Ababa, Ethiopia

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Abstract

Background:- Although acute stroke accompanied by hyperglycemia is often associated with worse prognosis, the relationship between hyperglycemia and stroke outcome has not been studied in Ethiopian patients. As better understanding of this potentially adverse influence on stroke outcome would provide guidance for stroke management and acute care. This study aimed to determine frequency of admission hyperglycemia and its impact on thirty day functional outcome and case fatality among acute stroke patients in an urban setting in Ethiopia. Methods:- From July to December 2016, we collected information on 103 consecutive first ever acute stroke patients admitted within 72 hours of symptom onset to Tertiary hospital in Ethiopia. We obtained demographic, clinical and neuro-imaging data including capillary blood glucose at admission. National Institute of Health Stroke Scale and modified Rankin Scale were used to assess the baseline stroke severity and the degree of disability at thirty day. Results:- A total of 103 first ever acute stroke patients were enrolled with, mean age = 55.5+ 15.3 years, 64.1% male, 65% under the age of 65 years, and 31.1% were farmers by occupation . Fifty one (49.5%) patients had a documented hyperglycemia at admission with median National Institute of Health Stroke Scale score of 14 and 3(2.9%) of them were later diagnosed with diabetes mellitus. The mean modified Rankin score at 30-day was 3.6 + 1.45 while 34 (79.1%) of hyperglycemic stroke survivors scored between 3 and 5. Older age >65 years ($p = 0.037$), admission hyperglycemia ($p = 0.04$) and stroke severity ($p <0.001$) were significantly correlated with poor functional outcome. Conclusions:- High blood glucose on admission was significantly associated with sever disability in acute stroke patients, independent of the presence of diabetes mellitus. By establishing the negative impact of admission hyperglycemia on the neurological outcome, this study suggests that achieving normal blood glucose in the early stages of stroke could have a favorable impact on improved neurological outcome and quality of life for stroke patients. The study provides a rationale for acute stroke management that addresses the potentially adverse consequences of hyperglycemia at the time of presentation in an urban Ethiopian setting.

Background

Stroke is the second most common cause of death, next to ischemic heart disease and the third leading cause of disability worldwide [1]. The 2013 Global burden of diseases (GBD) stroke burden estimates confirmed the significant increase in stroke burden in the world over the last two and half decades, especially in developing countries [1,2]. Often stroke is associated with significant morbidity and mortality, particularly in low and middle-income countries (LMICs) in sub-Saharan Africa (SSA) where the epidemiology is shifting to vascular disorders due to rapid urbanization, aging population, and life style changes [2].

Although stroke mortality and disability-adjusted life-years (DALYs) rates have declined over the decades, there were almost 25.7 million stroke survivors, 6.5 million deaths from stroke, 113 million DALYs due to stroke, and 10.3 million new strokes globally [2].

Stroke outcome is influenced by myriad of factors including stroke subtype, severity, predisposing factors, associated comorbidities, related complications, and availability of stroke care facilities [3]. Admission hyperglycemia is one of the potentially modifiable factors associated with adverse stroke outcome [4]. Several clinical and experimental studies have demonstrated that admission hyperglycemia has a deleterious effect on short term outcomes in acute stroke patients though some other studies have debated this [5-7]. Acute hyperglycemia in acute stroke is not always due to diabetes mellitus (DM) but may be due to stress response but the exact relationships as a cause or a consequence of more severe stroke remains controversial [8].

In spite of a higher percentage of in-hospital case fatality and severe neurologic deficit among stroke patients admitted to tertiary hospital in Ethiopia [9]. Little is known about the relationship between admission hyperglycemia and stroke outcomes in SSA, particularly in east Africa countries, where the number of neurologists is limited and access to stroke centers is negligible. There is no published study that has assessed the negative effect of high blood glucose on stroke patients' outcome in the region. There is rationale to conduct a study in the region to assess the prevalence of admission hyperglycemia in acute stroke patients and its impact on short term neurological recovery. Therefore, we hypothesize Ethiopian stroke patients admitted shortly after symptom onset will have higher blood glucose and it will negatively affect their short term functional recovery and increase the case fatality rate.

Methods

2.1 Study design

An institution based prospective, cross-sectional study was conducted at Tikur Anbessa Specialized Hospital (TASH) between July and December, 2016.

2.2 Study Setting

TASH is located in the capital Addis Ababa and it is the largest and the first tertiary level referral university teaching hospital with an estimated bed capacity over 700.It has an emergency unit, intensive care unit, neurology ward, clinical laboratory, and radiology department with a CT and MRI scan providing an integrated clinical service by highly trained radiologists, neurologists and emergency care physicians for the entire nation.

2.3 Study population

The study population was all patients presenting to the emergency department with neurologic deficits suggestive of acute stroke and who fulfilled the inclusion criteria of age greater than 14 years, presentation within 72 hours of symptom onset, and confirmation of stroke diagnosis using emergency brain Computerize tomography scan. A non-fasting capillary blood sample was used to estimate the admission blood glucose (ABG) using a calibrated glucometer. Patients with Transient ischemic attack

(TIA), trauma related cerebral hemorrhage, prior neurologic deficit, unknown duration from symptom onset or CT scan, and who declined to give consent were excluded.

2.4 Sample size and sampling technique

The sample size was calculated using the single population proportion formula $n=Z^2*pq/d^2 = 164$ with estimated population proportion of 30% [10], α= 5% and d= 5%. During the study period, we performed a systematic enrollment of all first ever acute stroke patients consecutively who met the inclusion criteria and consented to participate in the study.

2.5 Data collection

The socio-demographic and clinical data were collected using structured questionnaire which was pre-tested on 8 acute stroke patients in a pilot study with complete response rate. We tried to avoid selection bias by randomly selecting the study population from the target population. At admission stroke severity was assessed by National Institute of Health Stroke Scale (NIHSS), well validated and commonly used measure of acute stroke-related neurologic deficit. NIHSS score was categorized into two: mild stroke (NIHSS score ≤ 14) and severe stroke (NIHSS score >14) [11]. In all patients, ABG was documented and hyperglycemia was defined as ABG level ≥140 mg/dl and normoglycemia as ABG <140mg/dl [12]. Known DM was diagnosed if patient was diagnosed with diabetes or taking antidiabetics drugs before stroke onset. If the ABG was >200 mg/dl and a repeat test after 8 hour of fasting showed ≥126 mg/dl, patients were defined as newly diagnosed DM[13].

2.6 Outcome

The modified Rankin scale (mRS) was used to describe the functional outcome at 30-day after stroke onset which may coincide with the hospital discharge and for those who were discharged earlier we followed them by telephone using standardized interview protocol. mRS is a six point scores which focuses on global disability including instrumental and basic activity of daily living (ADL).The mRS score was categorized into; favorable outcome (independence in ADL, scores range 0-2), and poor outcome (dependence in ADL, scores range 3-5). mRS score of 6 means dead and documented as case fatality [14].

2.7 Statistical analysis

The statistical analysis was performed using SPSS version 20.0 computer program. Descriptive statistics were summarized using the frequency and proportion table for categorical data with mean (standard deviation) or median (interquartile range) for continuous data. Dichotomous categorical variables were compared using the Pearson's Chi square test. Those factors that showed significant association were added for multivariate analysis. In multivariate analysis, age and baseline NIHSS score were added as covariates because they were accepted as independent predictors of stroke outcomes (15). Also interactions between hyperglycemia and history of diabetes were tested. A binary logistic regression

model was used with adjustment for possible confounders to calculate odds ratios with 95% confidence interval (CI). A *p* value of < 0.05 was considered statistically significant.

2.8 Ethics approval and consent to participate

Ethics approval was obtained from the Institutional Review Board (IRB) of College of Health Science in Addis Ababa University. All participants were asked to give written informed consent. For patients with depressed consciousness or severe aphasia, consent was obtained from their care takers. For participants aged 14-18 years an assent form was obtained from the parents or legal guardians. Confidentiality and anonymity of all patient data were kept throughout the study. The study was performed in accordance with the Declaration of Helsinki.

Results

We approached 110 consecutive stroke patients for the study and seven were excluded because of unknown stroke severity and baseline blood glucose level during their transfer from other hospitals. Therefore, a total of 103 first ever acute stroke patients were included for final analysis. Majorities (64.1%) were male and two-third (65%) was below the age of 65 years with mean age of 55.5 ± 15.3 years. The majority of our study participants were married (79.6%). Forty (38.8%) patients were illiterate and only one-third (36%) went to formal education. Among our participants, 32 (31.1%) were farmers by occupation. Demographic characteristics and clinical profiles for all admitted acute stroke patients are shown in Table 1. Based on CT scan finding, diagnoses of ischemic stroke and hemorrhagic stroke were made in 52 (50.5%) and 51 (49.5%) of the participants, respectively. The mean age (SD) for ischemic and hemorrhagic stroke is 58.28 (2.16) and 52.39 (2.04), respectively. Eight (7.8%) of our participants had been previously diagnosed with DM and they were already on oral hypoglycaemic agents. Out of the 7 patients who had a record of ABG >200mg/dl, three (2.9%) patients fulfilled the IDF diagnostic criteria for newly diagnosed diabetes mellitus. (Table 1)

3.2 *Admission hyperglycemia and clinical characteristics*

Almost half (49.5%) of our study participants were hyperglycaemic at time of admission and the mean ABG level in the normoglycemic and hyperglycemic groups was 119.9±13.0 mg/dl and 183.2±34.5 mg/dl, respectively. The majority (87.5%) of patients with prior history of DM were hyperglycemic at admission (Table 2).

The median NIHSS score for the hyperglycemic group was 14 (interquartile range [IQR] 10-19) and 11 (IQR 8-15) for the normoglycemic group. At bivariate analyses factors that were significantly associated with admission hyperglycemia were; past history of diabetes (p = 0.025), hemorrhagic type of stroke (p = 0.003), and severe stroke at admission (NIHSS scores >14) (p = 0.04) (Table 2).

3.3 *Thirty day functional outcome and case fatality*

In our study, the mean mRS score by day 30 was 3.6 ± 1.45 and 91 (88.3%) of the patients survived till thirteenth day. Poor functional outcomes were presented in more than two-third (70.3%) of the stroke survivors, while 29.7% had a mRS score between 1 and 2, indicative of good functional recovery (Table 3).

Multivariate linear logistic regression analysis was used to examine association between different clinical and laboratory parameters and 30-day functional outcome of stroke survivors. There were significant correlations between: older age (> 65 years) (p = 0.037), hyperglycemia on admission (p = 0.04) and stroke severity by NIHSS score > 14 (p <0.001) with poor functional recovery (mRS score 3 – 5) at day 30 among stroke survivors. (Table 3)

By the 30th-day of follow up, 12 patients had died (11.7%). On multivariate logistic regression analysis, factors that were significantly associated with 30 day case fatality were: older age (≥65 years) (p = 0.04), hemorrhagic stroke subtype (p = 0.013) and stroke severity at admission (NIHSS score >14) (p = 0.001). Although 8 (66.7%) of the death was documented in the hyperglycemic group there was no statistically significant association and also past history of diabetes did not show any association with 30 day case fatality. (Table 4)

Discussion

The majority of our participants were males, and they were relatively younger with mean age of 55.5 years, which was comparable to recent study in a tertiary teaching hospital from northern Ethiopia [15] and other Sub-Saharan countries like Kenya [16] and Nigeria [17] but it is lower than the median age of stroke victims in western countries, which is 73 years [18].

We also found that the ratio of ischemic to hemorrhagic stroke to be 1.02, which was similar to other studies from northern [15], and southern [19] parts of Ethiopia , 1.72 and 1.01 respectively. The relative equal proportion of ischemic and hemorrhagic stroke in our study and other hospital studies in Ethiopia is possibly related to the study setting where most minor ischemic strokes and TIA's were treated at local health centers by general practitioners and spontaneous resolution of minor clinical symptoms also avoid referrals to hospitals.

In our study we observed almost half of the participants had a documented hyperglycemia during admission and many of them had also a severe stroke. This observation is consistent with several other studies in which the reported prevalence of admission hyperglycemia in acute stroke varied from 20 to 50% depending on the study design (prospective versus retrospective), the cut off value for hyperglycemia and stroke subtype [20-21]. However when we compare our findings with the study done by Ogunrin and his colleagues, using the same hyperglycemic definition, they reported a lower prevalence rate at 28% which was attributed to the retrospective design of their study that might have affected the results as only 100 of their 163 cases had blood glucose estimated on admission [22].

Diabetes mellitus is a well-recognized risk factor for stroke and the frequency of diabetes in our study was 10.7%, of which one forth was newly diagnosed at time of current stroke admission. This finding is slightly higher than the prevalence of DM across different localities of Ethiopia, 0.3% to 7.0% [23].Another interesting finding in our study is majority of patients who had previous history of DM were in the hyperglycemic group, while 3 (6.8%) of the patients who had a significantly higher ABG (>200mg/dl) with no prior history of diabetes were later diagnosed with DM. Similarly L.S. Williams and his colleagues reported 18% of their patients with hyperglycemia had no prior evidence of diabetes, of these 11% were newly diagnosed with diabetes during their admission for stroke [24]. This finding suggests, the importance of screening acute stroke patients for hyperglycemia and for those with very high blood glucose level, a confirmatory test like glycosylated hemoglobin (HgA1c) or repeated FBS is indicated to early identify and treat this modifiable but significant risk factor of stroke.

Regarding the stroke severity based on NIHSS score, the median NIHSS score (Table 2) was 14 and 11for the hyperglycemic and normoglycemic groups, respectively whish was comparable to the report from Nigerian study, in which the median NIHSS score was 14 and 8 for a similar group of patients [25]. There are several explanations for the negative association between hyperglycemia and poor functional outcomes in stroke survivor including direct toxic effect of high blood glucose to ischemic neurons [26], also it aggravates the cellular acidosis and may disrupt blood-brain barriers which increases infarct volume and hemorrhagic transformation [27].

In our study, the short term functional outcome measured by 30-day mRS score was significantly higher (mRS ≥3) in the hyperglycemic patients as compared to the normoglycemic ones, which is consistent to a report from Chinese study where hyperglycemia was identified as an independent risk factor for poor functional outcome (assessed with mRS≥3) at 30 and 90 days after the stroke onset [28]. Another factor that is significantly associated with poor functional outcome at day 30 was the stroke severity at admission on NIHSS score, which is comparable to the result of hospital based study from India, where the 30 and 90 day functional outcomes were poor among the diabetics and stress hyperglycemic groups who also had a higher score of NIHSS at admission [29].

The case fatality rate at 30-day was significantly higher among those with hemorrhagic stroke, younger age group and sever stroke at admission but not affected by admission hyperglycemia in contrary to other studies which demonstrated that admission hyperglycemia independently increased the risk of death at 30 days [25,30].This discrepancy could be explained by small number of participants and those patients with severer stoke were possibly died before arriving to our hospital.

Limitations of our study include a relatively small sample size and hospital based study may likely over represent the more sever stroke cases. This could have introduced selection bias. Therefore, we acknowledge the limited generalizability of our findings to the general population.

Conclusions

The high prevalence of hyperglycemia in the acute phase of stroke is a known factor and it significantly affects the short term outcomes. Establishing the negative impact of admission hyperglycemia on the functional neurological outcome bring us to the awareness that achieving a normal blood glucose in the early stages of stroke has a significant role in improving the neurological outcome and also the quality of life of our stroke survivor patients. Further studies with larger sample size are required to determine its independent role in neurological outcomes.

Abbreviations

CT: Computerized Tomography, DALY's: Disability-adjusted life years lost, FBG: Fasting blood glucose, GBD: Global Burden of Diseases, IDF: International Diabetes Federation, mRS: modified Rankin Scale, RBG: random blood glucose, TIA: Transient Ischemic Attack, SSA: Sub-Saharan Africa

NIHSS: National Institute of Health Stroke Scale

Declarations

Ethics approval and consent to participate: The study protocol was approved by the institutional Review board of College of Health Science, Addis Ababa University and all participants were provided with a written informed consent.

Consent for publication: Not Applicable

Availability of data and materials: All are available in the manuscript

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Authors' contribution: YZ, AT and YF participated in data collection, data analysis, data interpretation and manuscript editing and preparation. In addition HN gave professional advice and all authors read and approved the final manuscript.

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Tables

Table 1 **Demographic characteristics and clinical profile of acute stroke patients at Tikur Anbessa Specialized Hospital**

Variables		Frequency, N (%)
Gender	Male	66 (64.1)
	Female	37 (35.9)
Age groups	< 65 years	67 (65.0)
	≥ 65 years	36 (35.0)
	Mean/ SD, yrs	55.53/15.34
Marital status	Married	82 (79.6)
	Widowed	13 (12.6)
	Single	8 (7.8)
Level of education	Can't read and write	40 (38.8)
	Can read and write only	26 (25.2)
	Primary school	14 913.6)
	Secondary school and above	23 (22.4)
Occupational status	Farmer	32 (31.1)
	Merchant	26 (25.2)
	Office work	13 (12.6)
	Housewife	21 (20.4)
	Retired/Pension	5 (4.9)
	Student	6 (5.8)
Stroke subtype	Ischemic stroke	52 (50.5)
	Hemorrhagic stroke	51 (49.5)
Diabetes mellitus	Previously diagnosed	8 (7.8)
	Newly diagnosed	3 (2.9)

Table 2: Clinical and laboratory parameters associated with admission hyperglycemia and normoglycemia among acute stroke patients

Variable	Hyperglycemia (N=51), (%)	Normoglycemia (N=52) (%)	COR	95% CI	*p* value
Gender					
Male	33 (50.0)	33 (50.0)	1.00		
Female	18 (48.6)	19 (51.4)	0.95		0.947
Age group (years)					
<65 years	32 (47.7)	35 (52.3)	1.00		
≥65 years	19 (52.7)	17 (47.3)	0.82		0.63
History of diabetes					
Present	7 (13.7)	1 (1.9)	0.12	1.58-2.17	0.025*
Absent	44(86.3)	51(98.1)			
Mean RBG±SD(mg/dl)	183.2±34.5	119.9±13.0			
Stroke subtype					
Ischemic	18 (35.3)	34 (65.4)	1.11		
Hemorrhagic	33 (64.7)	18 (34.6)	0.29	0.13-0.65	0.003*
Stroke severity (NIHSS)					
NIHSS ≤14	26 (51.0)	36 (69.2)			
NIHSS >14	25 (49.0)	16 (30.8)	0.46	0.21-0.83	0.04*
Median admission NIHSS	14	11			
mRS					
mRS 0-2	9(17.6)	18(34.6)			
mRS 3-6	42(82.4)	34(65.4)			

*statistically significant

Table 3 Factors associated with 30 day functional outcome among stroke survivors on multivariate analysis

Variables	30th day functional outcome among survivors N=91		AOR	95% CI	*p* value
	mRS 0-2	mRS 3-5			
Sex					
Male	17 (29.3)	41(70.7)			
Female	10 (30.3)	23 (69.7)	0.94		0.88
Age (years)					
<65 years	22 (39.3)	34 (60.7)			
≥65 years	5 (14.3)	30 (85.7)	3.03	0.08-0.88	0.031*
History of diabetes					
Present	1(12.5)	7 (87.5)			
Absent	26 (31.3)	57(68.7)	0.84		0.37
Admission BG					
<140 mg/dl	18 (37.5)	30 (62.5)			
≥140 mg/dl	9 (20.9)	34 (79.1)	3.83	1.99-6.19	0.041*
Stroke subtype					
Ischemic	18 (36.0)	32 (64.0)			
Hemorrhagic	9 (21.9)	32(78.1)	2.47		0.05
Admission NIHSS score					
≤ 14	24 (40.0)	36 (60.0)			
>14	3 (9.7)	28 (90.3)	8.0	0.04 -0.56	0.005*

*statistically significant

Table 4: Factors associated with case fatality at day 30 on multivariate analysis

Variables	Thirty day outcome Alive (mRS<6), n=91 (%)	Thirty day outcome Dead (mRS=6), n=12 (%)	AOR	95% CI	*p* value
Sex					
Male	58 (63.7)	8 (66.7)			
Female	33 (36.3)	4 (33.3)	0.04		0.84
Age group, years					
<65	56 (61.5)	11 (91.7)			
≥65	35 (38.5)	1 (8.3)	4.23	0.02-0.88	0.04*
History of diabetes					
Present	8(8.8)	0(0.0)			
Absent	83(91.2)	12 (100.0)	1.14	1.06-1.24	0.28
Admission RBS					
<140	48(52.7)	4 (33.3)			
≥140	43(47.3)	8 (66.7)	2.23		0.21
Stroke subtype					
Ischemic	50 (54.9)	2 (16.7)			
Hemorrhagic	41 (45.1)	10 (83.3)	6.21	1.26-29.41	0.013*
Admission NIHSS					
≤ 14	60(65.9)	2 (16.7)			
>14	31(34.1)	10 (83.3)	9.68	1.99-46.93	0.001*

*statistically significant

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