British Journal of Medicine & Medical Research
4(34): 5324-5334, 2014

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Effect of Admission Hyperglycaemia on Infarct Size and Clinical Outcome in Black Patients with Acute ISCHAEMIC Stroke, Northeast Nigeria

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Authors' contributions

The author MMW designed the study, wrote the protocol, and wrote the first draft of the manuscript. The author YWN was involved in the analysis of the data. The author AA was involved in the analysis of the data and neuroimaging interpretation. The authors SABalarabe and AI were involved in data collection. The authors BB, IDG and MG managed the literature search. All authors read and approved the final manuscript.

Original Research Article

Received 18th June 2014
Accepted 2nd July 2014
Published 25th July 2014

ABSTRACT

Aims: To determine the relationship between admission blood glucose level, infarct size and stroke outcome in black African patients with acute ischaemic stroke.
Study Design: The study was cross-sectional.
Place and Duration of Study: University of Maiduguri Teaching Hospital, Northeast Nigeria, from January 2006 to January 2009.
Methodology: Sixty-two patients were recruited and clinical characteristics recorded. Stroke severity was assessed using the National Institutes of Health Stroke Score

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(NIHSS); disability assessed using Modified Rankin score (mRS) and Barthel Activity of Daily Living (ADL) index (BI). Infarct volume was calculated from CT scan using the '*method of measurements of the largest diameters'.* Random blood glucose (RBG) was measured on admission, and dichotomised into those with hyperglycaemia ≥ 7mmol/L those without < 7 mmol/L. Bivariate statistics were used to compare characteristics and outcome. Kaplan-Meier Statistic was used to compare mortality rates. The influence of hyperglycaemia on infarct volume and outcome was determined using logistic regression.
Results: Fourteen (22.6%) patients had hyperglycaemia on admission. Those with hyperglycaemia had a larger infarct volume (*P* < .0001) and higher NIHSS (*P* = .003) on presentation. They had worse stroke outcome (Discharge BI: P = .001; NIHSS: *P* < 0.0001; mRS: *P* = .001) and higher 30-day mortality (*P* = .005). Admission RBG positively correlated with infarct size (*P* < .001), NIHSS (*P* = .01), mRS (*P* = .02) and negatively with BI (*P* = .02). Survival time is significant with Log Rank (P = .009) and Wilcoxon test statistics (*P* = .006). Hyperglycaemia predicted a larger infarct (OR = 4.46, *P* = < .0001), poorer NIHSS on discharge (OR = 3.44, *P* = .001), poorer mRS (OR = 2.53, *P* = .02) and 30 – day mortality (OR = 2.04, *P* = .046).
Conclusion: Hyperglycaemia is associated with a larger infarct size, severe stroke at presentation and a worse stroke outcome.

Keywords: Stroke; glucose; hyperglycaemia; infarct volume; blacks; Nigeria.

1. INTRODUCTION

Hyperglycaemia may be present in up to 50% of stroke patients with or without pre-existing diabetes mellitus [1,2]. The mechanism of hyperglycaemia in acute ischaemic stroke is mainly a result of stress responses [3], due to increases in the level of catecholamine and corticosteroids [4]. A study reported a contrary view and observed that hyperglycaemia is not due to stress, as catecholamine levels were not associated with increased glucose levels [5].

Hyperglycaemia is associated with poorer outcome in both acute ischaemic and heamorrhagic stroke [6,7,8,9]; with these patients having a higher risk of in-hospital mortality, poor functional recovery, and a significantly higher cost of treatment [1,6,7]. Studies have found a positive relationship between admission hyperglycaemia and infarct size, and this may explain its association with increased morbidity and mortality [4,10,11]. Hyperglycaemia accelerates brain damage and expands infarct size by stimulating vasoconstrictive factors, reducing penumbral tissue salvage from high lactate level, and by inducing pro-inflammatory and pro-oxidative states that causes direct neurotoxicity [1,12,13,14]. Studies have shown that treatment with intravenous insulin reduces the harmful effects of hyperglycaemia; it also exerts an antioxidant and anti-inflammatory effect, substantially reducing morbidity and mortality [12,15,16]. Several clinical studies among Caucasians have shown the deleterious role of hyperglycaemia in stroke [1,6,7,9,10,16,17]. There is paucity of studies on the relationship between hyperglycaemia and stroke in Nigeria [18,19]. However, there is no available study on the effect of hyperglycaemia on infarct size, and thus this study sought to address this deficiency.

Our study aimed at determining the relationship between admission blood glucose level with size of lesion and stroke outcome in black Africans with acute ischaemic stroke. The

findings from this study may further support the importance of managing hyperglycaemia in black patients with ischaemic stroke.

2. METHODOLOGY

The study was a prospective, cross-sectional and hospital-based study, conducted at the University of Maiduguri Teaching Hospital, Northeast Nigeria, from January 2006 to January 2009. The study population consisted of newly diagnosed first-ever acute ischaemic stroke patients aged 18 years and above, presenting to the emergency department and the neurology clinic of the hospital. Stroke was defined based on the WHO criteria [20]. Exclusion criteria included: recurrent stroke, late presentation to the hospital (> 48 hours), those with no lesion or infarct detected, haemorrhagic stroke, history of diabetes mellitus and patients who received glucose infusion before blood sampling. Clinical history was taken on admission. The age, sex, alcohol intake, cigarette consumption, hypertension, transient ischaemic attack were recorded using a structured stroke proforma. Complete neurological and cardiovascular examinations were carried out and recorded.

Stroke severity was assessed using the National Institutes of Health Stroke Score (NIHSS) on admission and discharge. Stroke disability was assessed using Modified Rankin Score (mRS) and the Barthel ADL index (BI). All subjects recruited were assessed on or within 24 hours of admission and on discharge by a member. The assessment was cross-checked by another team member in order to improve the reliability of the stroke severity grading. The mRS and NIHSS was dichotomized into those with severe stroke on admission (NIHSS >8 and mRS 3 to 6; death was graded 6) and less severe stroke (NIHSS $\leq$ 8 and mRS 0, 1, or 2). Patients were followed up for 30 days or to discharge. Those who were discharged before 30 days were followed-up at the neurology out-patient clinics. Thirty-day mortality was assessed as one of the outcome measures. Complications were looked out for and recorded.

Random blood glucose was determined immediately on admission (< 3hours). Capillary blood was obtained from a finger-prick and the measurement was done using a standardized 'One Touch™ Glucometer', detected by the enzymatic glucose oxidase method. Admission blood glucose was categorised into 2 groups: random blood glucose (RBG) < 7mmol/L and blood glucose $\geq$ 7mmol/L; hyperglycaemia was considered as random blood glucose of 7mmol/L and above, in accordance with other studies [3,21].

2.1 Infarct Size Assessment

Computerized Tomography (CT) scan of the brain was done for all patients, using the Siemens Somatom AR.T Computerised tomography (Siemens Germany) with 3-mm continous axial slices, from the skull base to the vertex. A noncontrast CT examination was performed after 48hrs of presentation; image analysis was done by a qualified radiologist. The infarct was defined as a hypodense area on CT. The anatomical location of the infarct is also recorded, appropriate to the clinical deficit.

The infarct volume was calculated using the 'method of measurements of the largest diameters' [22,23].

Using the formula: $0.5 \times A \times B \times C$.

Where; A is the largest diameter of the infarct, B is the largest perpendicular distance, C is vertical diameter determined by summing the thickness of slices in which lesion is visible. The slice thickness of our brain imaging studies is usually set at 5mm.

The infarct size was dichotomized into those with larger infarcts (>100mm^3) and smaller infarcts ($\leq$ 100mm^3).

2.2 Statistical Analysis

A univariate analysis was carried out using the Chi-square test for categorical variables and a Student's t-test for continuous variables to compare stroke characteristics between those with and without hyperglycaemia. A univariate analysis was also done to compare outcome measures. A bivariate analysis using the Spearman's correlation was used to assess the relationship between RBG and infarct volume, and RBG and indices of stroke severity. Kaplan Meier statistic was used to compare mortality rates between the two groups of patient based on stratification (<7mmol and ≥7mmols), and the survival curve comparison between treatment groups was performed with the Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon) & Tarone-Ware statistics. A multiple logistic regression was carried out to determine the influence of hyperglycaemia on infarct volume and on worse clinical outcome, after adjustment for confounding factors such as age, sex and diastolic BP.

A P-value of $\leq$ 0.05 was considered statistically significant. All analyses were done using the Statistical Package for Social Sciences. SPSS Version 16.0 SPSS Inc; Chicago, Il, USA.

2.2.1 Hypothesis

We hypothesize that admission hyperglycaemia is not associated with larger infarct size, worse clinical outcome and survival.

2.3 Ethical Issues

All authors hereby declare that the study was approved by the research and ethics committee of the hospital. All patients or their legal representative had a written consent signed. The study was conducted in accordance with the declaration of Helsinki.

3. RESULTS AND DISCUSSION

3.1 Results

A total of 150 patients were seen during the recruitment period, 88 patients were excluded from the study due to: late presentation to the hospital, lack of neuroimaging, haemorrhagic stroke, and diagnoses of space occupying lesions. Those who had a preceding history of diabetes mellitus or received glucose infusion before blood sampling were also excluded from the study. A total of 62 patients were consecutively recruited for the study; there were 43 (69.4%) males and 19 (30.6%) females, with a mean age of 55.42±12.02 years. Fourteen (22.6%) patients had hyperglycaemia on admission.

The baseline characteristics of the patients are shown in Table 1. There was no age (Age; 56.14±12.75 years versus 55.21±11.93 years; *P* = .80) or sex (male versus females, *P* = .26) difference in these patients. There was no significant difference in risk factor, infarct

location and complication among those with or without hyperglycaemia. Those with hyperglycaemia had a higher mean RBG (9.90±3.30 versus 4.95±0.95; *P*<.0001), a larger infarct volume (114.5±90.7mm^3 versus 34.3±62.4mm^3; *P* < .0001) a higher NIHSS (19.69±8.16 versus 13.58±5.91; *P*=.003) and mRS (3.92±0.90 versus 3.40±0.86; *P* = .05 at presentation.

Table 1. Comparison of patient admission characteristics by random blood glucose

Characteristics	All N = 62	> 7mmol/L n = 14 (22.6%)	< 7mmol/L n = 48 (77.4%)	P value
Age	55.42±12.02	56.14±12.75	55.21±11.93	,80
Male	43 (69.4)	8 (57.1)	35 (72.9)	.26
Female	19 (30.6)	6 (42.9)	13 (27.1)	
Risk factors				
Hypertension	46 (74.2)	11 (78.6)	35 (72.9)	.67
Diabetes	4 (6.5)	2 (14.3)	2 (4.2)	.18
TIA	6 (9.7)	2 (14.3)	4 (8.3)	.51
Smoking	7 (11.3)	0 (0.0)	7 (14.6)	.13
Alcohol	11 (17.7)	1 (7.1)	10 (20.8)	.24
HIV	4 (6.5)	0 (0.0)	4 (8.3)	.27
Area of Infarct				
Hemisphere	42 (67.7)	11 (78.6)	31 (64.6)	.33
Basal ganglia	8 (12.9)	2 (14.3)	6 (12.5)	.86
Lacunar	6 (9.7)	0 (0.0)	6 (12.5)	.16
Internal capsule	2 (3.2)	0 (0.0)	2 (4.2)	.44
Thalamus	2 (3.2)	1 (7.1)	1 (2.1)	.35
Brainstem	1 (1.6)	0 (0.0)	1 (2.1)	.59
Hypothalamus	1 (1.6)	0 (0.0)	1 (2.1)	.59
Mean infarct size (mm^3)	52.4±76.8	114.5±90.7	34.3±62.4	< .0001
Mean RBG	6.071±2.71	9.90±3.30	4.95±0.95	< .0001
SBP	152.4±36.85	147.14±23.02	154.00±40.21	.55
DBP	95.4±21.35	94.71±13.94	95.61±23.23	.89
GCS	14.25±1.84	13.85±2.30	14.36±1.70	.37
Mean Barthel's index	28.53±26.82	18.85±24.08	31.33±27.17	.13
Mean NIHSS	15.00±6.93	19.69±8.16	13.58±5.91	.003
Mean mRS	3.51±0.89	3.92±0.90	3.40±0.86	.05
Complications	21 (33.87)	5 (35.71)	16 (33.33)	.87

Student's t-test for continuous variable and Pearson's χ^2 for categorical variable. TIA – transient ischaemic attack. HIV – human immunodeficiency virus infection. SBP – systolic blood pressure. DBP – diastolic blood pressure. GCS – Glasgow coma score

Table 2 represents the outcome measures in relation to blood glucose level. We demonstrated a worse stroke outcome among those with hyperglycaemia (Discharge BI: *P* = .001; NIHSS: *P* < .0001; mRS: *P* = .001). Thirty–day mortality was higher among those with hyperglycaemia (50% versus 14.6%, *P* = .005). We found a slightly higher (though non-significant) duration of stay in those with hyperglycaemia (36.00±30.87 versus 31.91±21.82 days; *P* = .58).

Using the Spearman's rho correlation, admission RBG positively correlated with infarct size (Spearman ρ = 0.530; *P* < .001). There was a positive correlation between RBG with

admission NIHSS (Spearman ρ = 0.333; *P* = .012) and mRS (Spearman ρ = 0.310; *P* = .02). RBG negatively correlated with admission BI (Spearman ρ = - 0.311; *P* = .02).

Table 2. Patient outcome measures by random blood glucose

Outcome	≥ 7mmol/L n = 14	< 7mmol/L n = 48	*P* Value
Discharge BI (Mean±SD)	32.73±35.38	66.32±29.03	.001
Discharge NIHSS (Mean±SD)	21.80±16.17	7.97±10.95	<.0001
Discharge mRS (Mean±SD)	4.20±1.81	2.47±1.56	.001
Duration of stay (Mean±SD)	36.00±30.87	31.91±21.82	.58
30-day fatality	7 (50.0)	7 (14.6)	0.005

Student's t-test for continuous variable and Pearson's χ^2 for categorical variable

Table 3 and 4 depicts the means and median survival time, it is observed that the mean RBG of patients <7mmol/l is higher than patients with RBG ≥ 7mmol/l and since there is no overlap in their confidence interval, it can be inferred that this difference in survival time is significant. Log Rank (Mantel-Cox: χ^2 = 6.785; P = 0.009), Breslow (Wilcoxon test statistics: χ^2 = 7.580; P = 0.006) and Tarone-Ware test statistics (χ^2 = 7.240; P = 0.007). This difference is depicted further by the survival plot shown (Fig. 1), in which patients with RBG ≥ 7mmol/l had a lower cumulative survival, with deaths occurring relatively early.

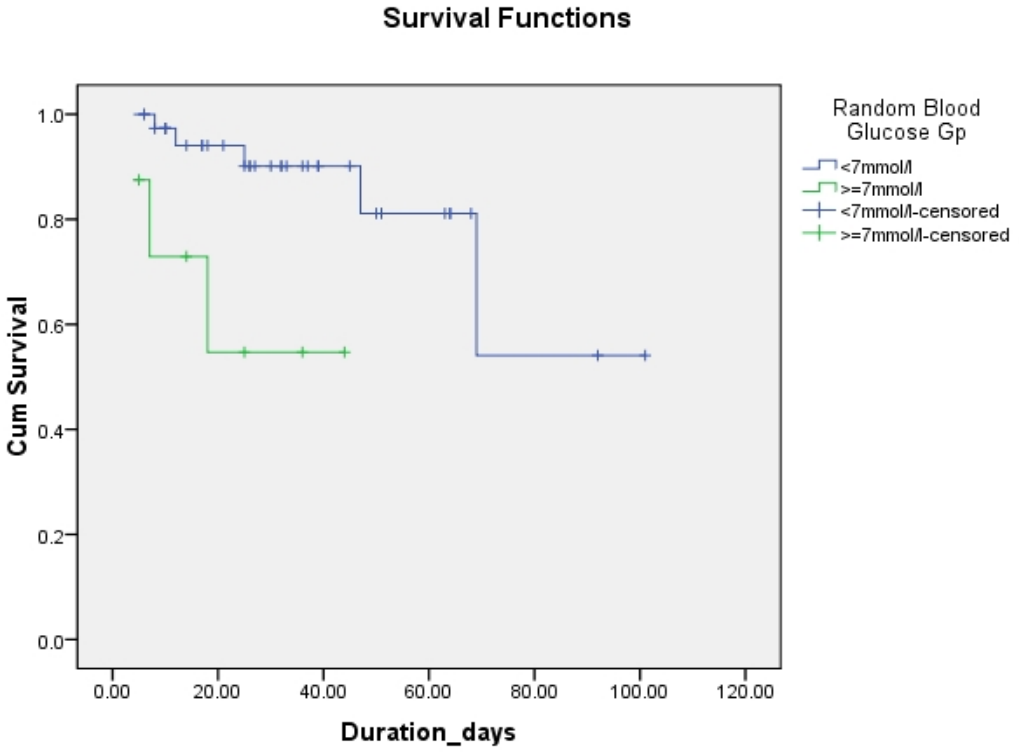

Fig. 1. Kaplan – Meier curve describing the survival between stroke subjects with admission RBG < 7mmol/L and blood glucose ≥ 7mmol/L

Table 3. Means and medians for survival time

Random blood glucose	Mean[a]			
	Estimate	Std. Error	95% confidence interval	
			Lower bound	Upper bound
<7mmol/l	79.101	8.838	61.779	96.424
≥7mmol/l	28.865	6.661	15.808	41.921
Overall	74.674	8.611	57.796	91.553

Estimation is limited to the largest survival time if it is censored

Table 4. Overall comparisons

	Chi-square	df	Sig.
Log Rank (Mantel-Cox)	6.785	1	.009
Breslow (Generalized Wilcoxon)	7.580	1	.006
Tarone-Ware	7.240	1	.007

Test of equality of survival distributions for the different levels of Random Blood Glucose

The result of the multiple logistic regression analyses is shown in Table 5. The result indicate that hyperglycaemia was associated with Larger infarct >100mm^3 (OR = 4.46, 95% CI = 0.230 – 0.606, P = < 0.0001), a higher NIHSS on discharge (OR = 3.44, 95% CI = 0.150 – 0.576, P = 0.001) and a higher mRS on discharge (OR = 2.53, 95% CI = 0.058 – 0.513, P = 0.015). The regression analysis also showed that hyperglycaemia was a predictor of 30 – day mortality (OR = 2.04, 95% CI = 0.005 – 0.551, P = 0.046).

Table 5. Logistic regression analysis of RBG in relation to outcome measures

Independent variable	OR	95% CI	*P* value
Larger infarct >100mm^3	4.46	0.230 – 0.606	< .0001
NIHSS $\geq$ 8	3.44	0.150 – 0.576	.001
MRS $\geq$ 3	2.53	0.058 – 0.513	.015
30-day fatality	2.04	0,005 – 0.551	.05

3.2 Discussions

This is the first prospective study in our centre on the effect of admission RBG on infarct size and clinical outcome. Our study demonstrates that those with hyperglycaemia ($\geq$ 7mmol/L) had a larger infarct size, a more severe stroke on presentation and a worse stroke outcome. Multiple logistic regression analyses revealed that hyperglycaemia was a predictor of larger infarct, severe stroke and 30-mortality. Patients with admission RBG $\leq$7mmol/l have better chances of survival.

The percentage of our patient with hyperglycaemia of 22.6% is similar to a study reported by Capes et al. [1], but lower than other studies [6,13,24]. The variation in percentages of hyperglycaemia may be due to differences in the definition and cut-off point for hyperglycaemia. The lower rate of hyperglycaemia in our study may be attributed to the small sample size and exclusion of diabetic patients from the study. The study by van Hooten et al. [5] reported a lower rate among patient with idiopathic hyperglycaemia but higher in patients with diabetes. The exclusion of diabetics in this study was to remove any bias that patients with diabetes may have on the study, since it is well known that diabetes

independently has an influence on a higher RBG, infarct size and worse stroke outcome than non-diabetics [1,2,16,25]. We chose 7mmol/L and above as a cut-off value for hyperglycaemia in accordance with an experimental study that found a U-shaped association between blood glucose and infarct volume, with a nadir of approximately 7 mmol/L [26].

Our study indicated that those who are hyperglycaemic had more than 4-fold risk of having a larger infarct volume and RBG correlated positively with infarct size. This finding has been reported in other studies [27,28].

Our study may be criticized due to our inability to assess the role of increases in stress hormones, since there have been debates as to whether a larger infarct was the cause of hyperglycaemia or vice-versa. In a study by Berger and Hakim [27], they reported that increase in infarct size was a result of the hyperglycaemia rather than a larger infarct causing hyperglycaemia. This may further be explained by studies that have shown that regional blood flow decreases in patients with hyperglycaemia [29], apart from other procoagulant and proinflammatory effects [12,14].

There have been conflicting reports regarding the relationship between site of brain infarct and hyperglycaemia. Studies have reported that hyperglycaemia was more likely to occur in those with cortical infarct [4], insular cortical infarct [30], and brainstem infarcts [31], but our study found no relationship between blood glucose level and site of brain infarct. Although this study did not look at the relationship between stroke subtypes and glucose level; we however reported no significant difference in lacunar strokes in relation to glucose level. Studies have shown that patients with lacunar strokes are more likely to have a milder stroke, a higher likelihood of an excellent outcome and lower chance of having secondary hyperglycaemia [32,33].

This study is congruent with previous studies showing that hyperglycaemia on admission is associated with severe stroke and mortality [4,6,11,18,19,24]. The poorer outcome may be related to larger infarct in addition to the independent effect of hyperglycaemia on stroke outcome. Yong and Kaste [34], are of the opinion that persistent hyperglycaemia is more likely to predict functional outcome and mortality rather than a single point blood glucose measurement. This should be a point for further study in our centre, whereby we can assess the role of persistent hyperglycaemia on infarct size and stroke outcome rather than the single-point blood glucose used in this study.

We did not consider gender differences in relation to influence of hyperglycaemia on infarct size. It has been reported that in-hospital mortality in women was higher in diabetics, which may be a reflection of the metabolic derangement caused by the hyperglycemia [35].

Insulin therapy has been shown to reduce infarct size and improve outcome [12,16,36,37], but this is not universal; as Rosso et al. [38] reported that intensive insulin therapy was not associated with reduced infarct growth but observed that those who received this treatment had largest infarct growth. A study by Ntaios et al. [39] observed a J-shaped relation between serum glucose values and favourable outcome, and suggested that reductions of blood glucose are necessary to significantly improve outcome but lowering serum glucose < 3.7 mmol/L may be detrimental. Two recent studies reported that moderate rather than tight control of blood glucose in acute stroke patients relates better to an improved neurological outcome [15,40]. Although there is weak evidence; the European Stroke Organization recommends treatment of serum glucose levels > 10 mmol/l with slow insulin titration [41].

Our study has several limitations. Firstly, the small sample size may have influenced the statistical outcome, the inclusion criteria appear stringent and more than half of the screened patients were excluded. We believe that a future multicentre study may be pertinent. Secondly, Lack of HbA1c results to objectively rule out patients with diabetes or new onset diabetes. Thirdly, the lack of serial blood glucose monitoring, this would have been better than the single-point glucose estimation used in this study, this also has implication in interpreting stroke severity indices in relation to blood glucose, keeping in mind that some strokes may vary in the rapidity of clinical or radiological deterioration independently of a single RBG measurement. Fourthly, during our recruitment we may have missed some lacunar stroke patients because of the slice thickness of 5mm and also brainstem infarct since CT is not the preferred neuroimaging.

4. CONCLUSION

This study showed that hyperglycaemia was associated with larger infarct size in patients with ischaemic stroke. In addition, patients with hyperglycaemia at presentation tended to have worse stroke and are more likely to die or be disabled on discharge. Since hyperglycaemia in the setting of ischaemic stroke is treatable, prompt detection and treatment will go a long way in reducing morbidity and mortality among stroke patients in our setting. Further studies are needed to determine the effect of treating hyperglycaemia with insulin in patients presenting with ischaemic stroke in the acute phase.

ACKNOWLEDGEMENTS

We acknowledge the members of staff of the radiology and chemical pathology department for their contributions. We also thank Dr. Omeiza for his contributions in the statistical analysis.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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