Maintenance of Normoglycemia May Improve Outcome in Acute Ischemic Stroke

Sruthi S. Nair, P. N. Sylaja, Sapna Erat Sreedharan, Sankara Sarma[1]

Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, [1]Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India

Abstract

Introduction: Several studies have shown that high admission glucose is associated with poor outcomes after stroke, but the impact of maintenance of normoglycemia on functional outcome during hospitalization for acute ischemic stroke is less well established. **Aims:** The aim of this study was to examine the independent association of postadmission glycemic status in the 1st week with 3-month functional outcome in patients with acute ischemic stroke. **Methods:** Patients with acute ischemic stroke admitted within 48 h of symptom onset with National Institutes of Health Stroke Scale (NIHSS) of ≥4 were selected from a prospectively maintained database by chart review. Demographic data, risk factors, NIHSS, and blood glucose values in the 1st week were collected. The primary outcome was Modified Rankin Scale (mRS) score at 3 months (good outcome-mRS ≤2). **Results:** Over 3 years, 342 patients were enrolled with 220 (64.32%) males. Mean age was 60.5 ± 13.4 years, and median admission score on NIHSS was 10 (interquartile range: 6–16). Blood glucose values persistently <140 mg/dl in the 1st week were associated with a good 3-month functional outcome in univariate analysis ($P = 0.036$). Hypoglycemic episodes occurred only in 11 (3.22%) patients. **Conclusions:** Blood glucose values persistently below 140 mg/dl in the 1st week after acute ischemic stroke were associated with a favorable outcome in our study. Future clinical trials are needed to confirm these findings.

Keywords: Acute ischemic stroke, blood glucose, control, hyperglycemia, outcome

INTRODUCTION

Hyperglycemia is frequently noted in patients with acute ischemic stroke occurring in about 40%–70%[1,2] of these patients. Several studies have shown that hyperglycemia during admission is associated with higher short- and long-term mortality and poor functional outcomes after stroke.[3-7] Reperfusion therapy is less effective in hyperglycemic patients and results in higher rates of symptomatic intracerebral hemorrhage.[8] Whether hyperglycemia is a marker of sicker patients or whether it mediates poor outcomes is currently unclear.

However, the data are less robust on glucose normalization and optimal in-hospital blood glucose target in acute stroke patients. Baird *et al*.[3] showed that persistent hyperglycemia at 72 h of stroke was associated with higher infarct expansion and worse outcome at 1–2 months after stroke. Normalization of the blood glucose to <130 mg/dl in the first 48 h of stroke was shown to be associated with a 4-fold decrease in the mortality in a retrospective study.[9] However, randomized control trials have failed to provide conclusive evidence to support these observations.[10,11] The level of blood glucose to be attained and the duration for which the glycemic control needs be maintained to influence the clinical outcome remain uncertain.

We undertook this observational study to determine the relationship of admission hyperglycemia and blood glucose control in the 1st week of acute ischemic stroke to the 3-month functional outcome in patients from a comprehensive stroke care center in India.

METHODS

The study was a medical records' review analysis of patients with acute ischemic stroke identified from a prospectively

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maintained database in the comprehensive stroke care center in a tertiary care center in India. The data collected were on patients admitted from September 2010 to September 2013.

The study included patients aged 18 years or more with acute ischemic stroke admitted to the stroke unit within 48 h of symptom onset with the National Institutes of Health Stroke Scale (NIHSS) score ≥4. Those patients in whom a blood glucose value was not recorded within 24 h of admission and those with transient ischemic attacks and stroke mimics such as hypoglycemia or migraine were excluded from the study. Demographic and clinical data, vascular risk factors, NIHSS score and Modified Rankin Scale (mRS) score at admission, and details of imaging were collected in addition to the details of treatment with thrombolysis, insulin, and oral hypoglycemic agents. Patients were designated as having diabetes mellitus if they were previously diagnosed with the disease or were discharged on antidiabetic medications.

The stroke center follows a uniform protocol for the management of blood glucose in acute stroke patients with the use of insulin based on the sliding scale for blood glucose values exceeding 120–140 mg/dl and addition of oral hypoglycemic agents after 48 h of hospitalization for diabetic patients and those with persistent hyperglycemia.

All patients had capillary blood glucose values recorded in their charts at the time of admission and thereafter thrice a day for the first 2 days. Those with persistently normal blood sugar and not on hypoglycemic agents were shifted to once or twice a day blood glucose evaluation whereas the rest of the patients continued to have at least thrice a day blood glucose evaluation. Additional blood glucose estimations were done if clinically indicated in the patients. The serial blood glucose levels for the period of their admission or the first 7 days, whichever was shorter, were acquired from their treatment charts. Patients were designated as having hyperglycemia at admission if the first blood glucose value recorded within 24 h of admission was more than or equal to 140 mg/dl. The blood glucose control was assessed by two parameters: (a) Mean blood glucose during the period of hospital stay (range: 2–7 days) excluding the admission value and (b) individual values of blood glucose recorded in this period. The control of blood glucose achieved was classified based on mean blood glucose as good control group for blood glucose <140 mg/dl, moderate control for 140–199 mg/dl, and poor control for more than 200 mg/dl.

The primary outcome assessed was mRS at 3 months of stroke. The NIHSS and mRS measurements were performed by neurologists trained and well conversant with the scales. An mRS of ≤2 at 3 months was considered a good outcome.

For univariate comparisons, means of the numeric variables were compared by Student's t-test and proportions by Chi-square test or Fisher's exact test. Multivariable logistic regression models were created to relate mRS at 3 months with the variables that had statistically significant associations

in the univariate analysis ($P < 0.05$). Statistical analyses were performed using IBM SPSS statistical software for Windows, version 21.0, Armonk, NY:IBM Corp. USA.

RESULTS

We identified 342 (males 64%) patients fulfilling the inclusion criteria from 929 patients with acute ischemic stroke admitted during the study period. The median age of the patients was 62 years (interquartile range [IQR]: 54-72), and median NIHSS was 10 (IQR 6–16; range: 4–38). The baseline characteristics and risk factor profile of the patients are shown in Table 1. A diagnosis of diabetes mellitus was established in 145 patients (42.4%). Values for glycosylated hemoglobin were available for 221 patients; among them, 134 (60.6%) had levels more than 6.5%. A good outcome at 3 months was recorded in 163 (47.41%) patients.

Blood glucose at admission more than or equal to 140 mg/dl was noted in 182 (53.21%) patients. Patients with admission hyperglycemia were older and had diabetes mellitus and hypertension more frequently. Large vessel atherosclerotic disease was more common in patients with admission hyperglycemia whereas cardioembolic stroke was more prevalent in those without hyperglcemia. Hemorrhagic transformation of the infarct occurred in 52 (15.20%) patients which was significantly associated with a poor outcome [Table 1]. Among the 48 patients who underwent thrombolysis, seven had symptomatic intracranial hemorrhage; all of them had high-admission blood glucose.

Mean blood glucose values below 140 mg/dl were noted in 187 (54.68%) patients and were above 200 mg/dl in 23 patients (6.72%). The presence of admission hyperglycemia as well as the mean blood glucose level did not have a significant relationship to the 3-month outcome. One hundred and sixty-seven (48.8%) patients required insulin during the period of admission and 183 (53.51%) patients required either oral hypoglycemic agents or insulin or both. The use of insulin or need for any treatment for hyperglycemia was noted to have a statistically significant association with a poor outcome ($P = 0.022$ and $P = 0.015$, respectively). Higher NIHSS at admission, cardioembolic stroke, and presence of hemorrhagic transformation were associated with a poor outcome at 3 months [Table 1].

All blood glucose values were persistently below 140 mg/dl in 103 (30.12%) patients, 51 (49.3%) of them required treatment with insulin or oral hypoglycemic agents. The patients who had individual blood glucose values persistently below 140 mg/dl had a statistically significantly better outcome in univariate analysis ($P = 0.036$). On multivariate analysis adjusting for age, stroke severity, stroke subtype, diabetic status, dyslipidemia, and hemorrhagic transformation, patients with blood glucose values persistently below 140 mg/dl had 1.72 times higher odds of having a good outcome at 3 months (95% confidence interval 0.98–3.02; $P = 0.057$) [Table 2]. There was no

Table 1: Demographic, risk factor, and clinical profile of the patients

	Good outcome (mRS 0-2), n = 163	Poor outcome (mRS 3-6), n = 179	P
Demography			
Males	108 (66.26)	112 (62.57)	0.477
Age (mean±SD, in years)	59.47±13.5	61.45±13.2	0.173
NIHSS at admission (median, IQR)	7 (5-10)	14 (9-18.5)	<0.001
Risk factors			
Hypertension	114 (69.94)	131 (73.18)	0.506
Diabetes mellitus	63 (38.65)	82 (45.81)	0.181
Dyslipidemia	133 (81.60)	126 (70.39)	0.016
Coronary artery disease	31 (19.02)	43 (24.02)	0.262
Atrial fibrillation	15 (9.20)	28 (15.64)	0.073
Stroke subtype and other characteristics			
Large vessel atherosclerosis	37 (22.70)	36 (20.11)	0.002
Cardioembolic stroke	30 (18.40)	62 (34.64)	
Lacunar stroke	39 (23.93)	21 (11.73)	
Other specific etiology	10 (6.13)	14 (7.82)	
Undetermined etiology	47 (28.83)	46 (25.70)	
Hemorrhagic transformation	11 (6.75)	41 (22.91)	<0.001
Thrombolysis	24 (14.72)	24 (13.41)	0.726
Blood glucose parameters			
Admission blood glucose ≥140 mg/dl	80 (49.08)	102 (56.98)	0.143
Mean blood glucose (by subgroups), mg/dl			
≤140	97 (59.51)	90 (50.27)	0.199
141-200	55 (33.74)	77 (43.02)	
>200	11 (6.75)	12 (6.70)	
Mean blood glucose (mg/dl)	138.48±37.3	145.19±39.4	0.108
All blood glucose values ≤140 (mg/dl)	58 (35.58)	45 (25.14)	0.036
Treatment for hyperglycemia	76 (46.63)	107 (59.78)	0.015
Hypoglycemia <60 (mg/dl)	5 (3.07)	6 (3.35)	0.882
Glycated hemoglobin ≥6.5 (%)	64 (59.81)	70 (61.40)	0.904

IQR = Interquartile range, NIHSS = National Institutes of Health Stroke Scale, SD = Standard deviation, IR = Interquartile range, mRS = Modified Rankin Scale

Table 2: Multivariable logistic regression analysis for 3-month outcome

	OR	95% CI	P
Age	1.026	1.005-1.047	0.016
NIHSS at admission	1.244	1.172-1.320	<0.001
Diabetes mellitus	1.330	0.765-2.313	0.312
Dyslipidemia	0.780	0.416-1.463	0.439
Hemorrhagic transformation	0.424	0.186-0.964	0.041
Large artery atherosclerosis	1.537	0.682-3.468	0.300
Cardioembolic stroke	1.051	0.324-3.412	0.934
All blood glucose values ≤140 (mg/dl)	1.723	0.984-3.016	0.057

CI = Confidence interval, NIHSS = National Institutes of Health Stroke Scale, OR = Odds ratio

difference in outcome in diabetic and nondiabetic patients with hyperglycemia. Hypoglycemic episodes (blood glucose ≤60 mg/dl) were noted in 11 (3.22%) patients, of whom only two were in the good control group. There was no significant association for admission blood glucose, mean blood glucose, or the peak blood glucose values with in-hospital and 3-month mortality.

DISCUSSION

This study explored the association between the degree of blood glucose control achieved in the 1st week of acute ischemic stroke and the functional outcome. The results suggest that the maintenance of a persistently low blood glucose below 140 mg/dl during the 1st week of acute ischemic stroke portends a better short-term functional outcome. Previous prospective studies have shown that high blood glucose levels 24–48 h following acute ischemic stroke are associated with more than 4-fold increase in mortality[9] and higher frequency of poor neurological outcome.[12]

The major randomized control trial which evaluated the effect of insulin infusion for control of blood glucose in the acute phase of stroke, the UK Glucose Insulin in Stroke Trial, failed to find any difference in outcome between the tight and usual control group. However, this trial outcome was affected by a high proportion of nondiabetic patients (84%) and a modest difference in the mean blood glucose achieved between controls and patients.[10] Another pilot study showed nonsignificant improvement in outcome with aggressive

control of hyperglycemia during the acute phase of stroke compared to usual care.[13]

A key factor which could decide the outcome is the incidence of clinically significant hypoglycemia. This factor has significantly limited the use of intensive insulin protocols in sepsis and septic shock.[14] Compared to the previous studies in acute stroke[10,15] where hypoglycemia was documented in 15%–30% of patients on treatment, only few patients in our study (3.2%) had blood glucose values <60 mg/dl. The events were symptomatic only in half of them, and only two of them were in the tight control group. Majority of our patients were initially admitted in an Intensive Care Unit which may have facilitated the monitoring of blood glucose and prevention of hypoglycemia.

Admission hyperglycemia of more than 140 mg/dl failed to influence the outcome significantly although a nonsignificant trend toward worse functional outcome was noted in those with higher admission blood glucose. The outcome was independent of the method by which the control of blood glucose was attained. Among the 103 patients with persistent normoglycemia, 51 (49.3%) had received either insulin or oral hypoglycemic agents. The poorer outcome in patients who received hypoglycemic treatment probably reflects the impact of hyperglycemia. Our study does not specifically address the issues of impact of glycemic treatment and role of underlying disease severity in hyperglycemia. However, the poor outcome is not attributable to the diabetic status as no difference was noted in the outcome between diabetic and nondiabetic patients.

Many mechanisms are postulated for the deleterious effect of hyperglycemia in stroke. A consistent observation is that hyperglycemia induces increased lactate production and acidosis[16] in the ischemic tissue leading to increased oxidative stress, altered intracellular signaling, and excitotoxicity, all of which promote cell death.

The association of hyperglycemia with poor outcome is mostly relevant to large artery atherosclerosis, and it was postulated that moderate hyperglycemia may be beneficial in lacunar stroke.[17] Such a differential outcome was not seen between the stroke subtypes in our study. Interestingly, we failed to observe any relation of the outcome to thrombolysis which is likely to be related to the fewer number of patients in the thrombolysis group and the lack of matching of the patients in the thrombolysed versus nonthrombolysed groups.

The major advantage of this study is the presence of a standard institutional protocol for blood glucose management which ensured a uniform management of all the patients. All patients were managed under the care of a stroke care team well conversant with the research scores. This study is derived from a region of high diabetes mellitus burden which is reflected by a high percentage of diabetic patients in the cohort. We have looked at the individual blood glucose value as a measure of prognostication in addition to mean glucose values, as the latter is often confounded due to episodes of hyper- and hypo-glycemia in the same patient. The limitation of the study was the observational design and the variable number of days for which blood glucose values were available for the patients. The sample size was moderate and was obtained from a single center. About half of the patients who had persistent normoglycemia did not receive any hypoglycemic treatment, and hence the study does not address the contribution of the severity of the comorbidities to the outcome.

Conclusions

The current guidelines for acute ischemic stroke[18] suggest that in the acute phase, blood glucose is best kept between 140 and 180 mg/dl. However, our data suggest better functional outcome for those patients whose blood glucose was kept below 140 mg/dl without significantly increased risk of hypoglycemia. The validation of this observation and the feasibility of achieving this target in clinical practice require prospectively designed randomized studies.

Conflicts of interest

There are no conflicts of interest.

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