COMPARISON OF SHORT TERM MORTALITY IN ISCHEMIC STROKE PATIENTS WITH OR WITHOUT STRESS HYPERGLYCEMIA

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ABSTRACT

Objective: To compare short term mortality in non-diabetic ischemic stroke patients with or without stress hyperglycemia.

Study Design: Cohort study.

Place and Duration of Study: This study was carried out at Neurology Department of Military Hospital, Rawalpindi from Jan 2010 to Jul 2012 for a total duration of six months.

Material and Methods: Non-diabetic ischemic stroke patients were included in the study and they were divided in two groups. Each group had 75 patients. Group 'I' (Normoglycemic or control group) had normal blood glucose level while group 'II' (Hyperglycaemic or cohort) had hyperglycaemia on presentation or over next 72 hours. Prognosis in terms of patient either being dead or alive was determined within or at 4 weeks of admission in both groups. Data were entered and analysed using Statistical Package for Social Sciences SPSS version 10. Descriptive statistics were calculated for both qualitative and quantitative variables. For comparison of short term mortality in hyperglycaemic and normoglycemic stroke patients, chi-square test was applied. *p*-value <0.05 was considered statistically significant.

Results: Short term mortality was higher in cohort (hyperglycemic) group as compared to control (normoglycemic) group (34.7% vs. 14.7%). Relative risk was 2.36. The groups had a statistically significant difference in the short term mortality within four weeks with a Chi-Square '*p*' value of 0.004 (*p*=0.004).

Conclusion: Short term mortality in non-diabetic ischemic stroke patients with stress hyperglycemia is higher than those patients who do not have stress hyperglycemia.

Keywords: Stress Hyperglycemia, Ischemic stroke, Non-diabetic, Mortality.

INTRODUCTION

Stroke is the third most common cause of death and the leading cause of disability in the developed and developing countries. According to World Health Organization, 5.5 million people died of stroke in 2002, and roughly 20% of these deaths occurred in South Asia[1]. A high proportion of patients suffering from an acute stress such as stroke or myocardial infarction may develop hyperglycemia, even in the absence of preexisting diabetes mellitus. The hyperglycemic reaction following acute stroke may be attributed to several underlying mechanisms. These include: a non-specific reaction to acute stress and tissue injury with the associated autonomic, hormonal and metabolic alterations; uncovering of underlying latent diabetes by the acute stroke; increased secretion of growth hormone; and irritation of the glucose regulatory centers in the hypothalamus and brain stem by blood-laden cerebrospinal fluid or local ischemia[2].

Hyperglycemia on presentation is associated with significantly poorer outcomes following acute ischemic stroke. Patients with hyperglycemia and no prior history of diabetes mellitus (DM) have a particularly poor prognosis, even worse than that for patients with known diabetes and hyperglycemia. A study, which was carried out in Pakistan by Saif et al. in 2004, had shown that non-diabetic ischemic stroke patients

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having stress hyperglycemia on admission (using 200 mg/dl as the threshold for labeling hyperglycemia) had a short term mortality of 44% while it was 20% in normoglycemic ischemic stroke patients[3]. A more recent international study carried out by Kes et al showed that hyperglycemic ischemic stroke patients, without a prior history of DM, had a short term mortality of 25% at 4 weeks after the stroke episode[2]. The detrimental effect of stress hyperglycemia on outcome in ischemic stroke patients has led to the idea that higher glucose level reduction by aggressive treatment with insulin may improve the outcome in these patients. The present study was performed to determine the effect of stress hyperglycemia on mortality in non-diabetic ischemic stroke patients.

MATERIAL AND METHODS

This cohort study was carried out at Neurology Department of Military Hospital, Rawalpindi from Jan 2012 to Jul 2012 for a total duration of six months. Stress hyperglycemia was defined as blood glucose level more than 155 mg/dl at the time of admission or after 24, 48 and 72 hours of admission[4]. Mortality within or at 4 weeks of admission was labeled as short term mortality. All the patients admitted in the medical wards or reporting to Emergency Reception (ER) within 24 hours of onset of stroke symptoms were considered for the study. A detailed history was taken from the patient or the family for any pre-existing DM or use of anti-diabetic drugs or insulin. Patients who had ischemic stroke as evident on computed tomography scan and also fulfilled the rest of the inclusion criteria were included in the study. Patients with hemorrhagic stroke, transient ischemic attack (TIA), having a history of prolonged use of steroids (as these patients may have steroids induced DM), Glasgow coma scale (GCS) <8 at the time of admission and the patients who had developed aspiration pneumonia were excluded from the study. The study sample consisted of 150 patients by using consecutive (Non-probability) sampling technique. They were divided in two groups. Group I (control/Unexposed group) consisted of patients who were normoglycemic on admission or over next 72 hours and Group II (cohort/exposed group) included patients with stress hyperglycemia. A written informed consent was taken from every patient who was included in the study. Demographic characteristics (name, age, sex, residence, contact number) were recorded for each patient. Capillary finger-prick glucose (mg/dl) was measured using a glucometer on admission and three more readings were taken after 24, 48 and 72 hours. A patient with any of these readings mo re than 155 mg/dl was considered having stress hyperglycemia and was taken in cohort/ exposed group. Those patients having blood sugar <155 mg/dl were taken in control group. Prognosis in terms of patient either being dead or alive was determined after 4 weeks of admission. Family of the patient was contacted by trainee researcher on telephone to determine the prognosis if the patient had been discharged within four weeks of admission. Data for each patient was entered on a patient's performa. Data was entered and analyzed using Statistical Package for Social Sciences SPSS version 10. Descriptive statistics were calculated for both qualitative and quantitative variables. Frequencies and percentages were calculated for qualitative variables like gender and short term mortality in both groups. Mean and standard deviation were calculated for quantitative variables like age and blood glucose levels in each group. Relative risk (RR) was calculated. For comparison of short term mortality in hyperglycemic and normoglycemic stroke patients, chi-square test was applied. *p*-value <0.05 was considered statistically significant. The mortality was also compared gender wise in both hyperglycemic and normoglycemic groups and chi-square test was applied.

RESULT

A total of 150 patients with ischemic stroke fulfilling the eligibility criteria participated in the study. None of the subjects dropped out, or lost at any point during the study. The age ranged

from 37-95 years in the study population. Mean age of the study population was 65.40 (SD ± 11.402). Mean age in Group-1 was 65.79 (SD ± 11.93) and it was 65.01 (SD ± 10.917) in Group-2 (table-I).

Out of total 150 patients, 96.7% (n=145) patients were males and 3.3% (n=5) were females. Normoglycemic group (Group-1) had 94.67% (n=71) males and 5.33% (n=4) females. Table-II. Hyperglycemic group (Group-2) had 98.67% (n=74) males and 1.33% (n=1) females. The mean blood glucose level in the normoglycemic group was 122.26 (SD ± 11.33) with the minimum value of 96 mg/dl and maximum value of 147md/dl. The mean blood glucose level in the hyperglycemic group was 188.36 mg/dl (SD ± 49.23) with the minimum sugar level of 130 mg/dl and the maximum was 368 mg/dl. Out of 150 patients, 24.7% (n=37) died within four weeks of the stroke episode. In the normoglycemic group 14.7% (n=11) died while 85.3% (n=64) were alive. In hyperglycemic group, 34.7% (n=26) patients died within four weeks while 65.3% (n=49) were alive. In the normoglycemic group, out of 11 patients who died, 72.7% (n=8) were males while 27.3% (n=3) were females. In the hyperglycemic group, out of 26 patients who died, 100% (n=26) were males while 0% (n=0) were females (table-III).

Relative risk was 2.36. Patients of acute ischemic stroke having stress hyperglycemias were 2.36 times more likely to die within four weeks of the stroke episode than normoglycemic stroke patients. The groups had a statistically significant difference in the short term mortality within four weeks with a Chi-square *p*-value of 0.004 (p=0.004). Gender wise stratification of the results shows that mortality difference between hyperglycemic and normoglycemic groups is significant in males with a *p* value of 0.001 while

Table-I: Distribution of age in the study groups.

Study Group	N	Minimum	Maximum	Mean	SD
Normoglycemic Group	75	38	90	65.79	11.93
Hyperglycemic Group	75	37	95	65.01	10.917

Table-II: Gender wise distribution of the study results.

Sex	Group	Prognosis		Total	*p*-value
Male		Alive	Dead		
	Hyperglycemic	48	26	74	0.001
	Normoglycemic	63	8	71	
	Total	111	34	145	
Female	Hyperglycemic	1	0	1	0.4
	Normoglycemic	1	3	4	
	Total	2	3	5	

Table-III: Comparison of short term mortality in normoglycemic (Control or Group-1) and hyperglycemic (Cohort or Group-2) stroke patients (n=150).

			Prognosis		
			Alive	Dead	Total
Groups	Normoglycemic group	Count	64	11	75
		% within Group	85.3%	14.7%	100%
	Hyperglycemic group	Count	49	26	75
		% within Group	65.3%	34.7%	100.0%
Total		Count	113	37	150
		% within Group	75.3%	24.7%	100%

p=0.004

its statistically insignificant in females with a *p*-value of 0.4.

DISCUSSION

Stress hyperglycemia is a common finding after myocardial infarction[5] and stroke[6]. Several human studies have shown that stress hyperglycemia results in poor prognosis and increased mortality in both diabetic[7] and non-diabetic[8] ischemic stroke patients. Animal studies have also confirmed this finding[9]. But it has been shown that stress hyperglycemia specifically results in increased mortality in non-diabetic patients as compared to diabetic patients[8]. Not only short term mortality is increases with stress hyperglycemia but italso results in long term poor prognosis[10,11].

It was argued initially that whether stress hyperglycemia directly results in poor outcomes or is simply a marker of acute illness severity. But Baird et al carried out first clinical study to examine continuous physiologicalglucose monitoring early after stroke onset and demonstrated that persisting hyperglycemia after ischemic stroke is an independentc determinant of infarct expansion on Magnetic Resonance Imaging (MRI) and results in worseclinical outcome[12]. Stress hyperglycemia after ischemic stroke is a continuous process and it persists for 88 hours post stroke[13]. Different cut off values to label hyperglycemia have been used in studies. According to Fuentes et al. blood glucose level >155 mg/dl causes worst prognosis[4]. It is not clear why hyperglycemia particularly affects stroke prognosis in patients without diabetes. Few explanations have been presented to answer this. Firstly, diabetes results in micro-circulatory abnormalities in the brain, including arteriovenous shunting and it also causes a reduction in glucose transport across the blood-brain barrier[14]. Because of these processes, glucose delivery from blood to brain is reduced thus possibly resulting in protection from high glucose level after stroke. Secondly, although a single definition of stress hyperglycemia has yet not been agreed upon in non-diabetic patients, but it is even more difficult in diabetic patients as unstressed baseline level of glucose is not known and it may be different in different patients[15]. and decreased plasminogen activator inhibitor-1 activity[16]. These properties are said to reduce infarct size and its expansion.

The results found in most of the local as well as international studies are consistent with, or at least in the same direction, as are our study results. A comprehensive systematic review of 32 cohort studies was performed by Capes et al, showed 30-day mortality associated with admission glucose level >108 to 144 mg/dL was 3.07 (95% CI, 2.50 to 3.79) in non-diabetic patients and 1.30 (95% CI, 0.49 to 3.43) in diabetic patients. There are few studies with opposing results. Ntaios et al[17] showed that persistent hyperglycemia (>7.3 mmol/l) at 24-48 h after stroke onset was not associated with a worse functional outcome at 3 months whether the patient was previously diabetic or not. Uyttenboogaart et al[18] performed a study in which the relation between serum glucose measured within 6 h after stroke onset and functional outcome was analyzed in 1375 ischemic stroke patients and it showed that hyperglycemia has a detrimental effect in non-lacunar stroke, but moderate hyperglycemia may be beneficial in lacunar stroke But majority of the recent studies performed to determine the effect of admission hyperglycaemia on stroke prognosis have shown a detrimental effect. There is a variation in the relative risk of increased mortality with stress hyperglycaemia in ischemic stroke patients in different studies but it ranges from 0.56[19] to 12.86[6].

There are few limitations of our study. Relative risk was not adjusted for other risk factors like age, sex and the stroke severity and comorbid clinical conditions. There is still no consensus that what blood glucose level should be used to label as stress hyperglycemia. We have used a cutoff of 155mg/dl because one study found that blood glucose level more than this resulted in poor prognosis. But it is possible that even glucose level lower than this may have poor

prognostic impact. We included non-diabetic patients in our study group and it was based on the history provided by the patients so all the patients who were known non-diabetics had been included but there is a possibility that some patients, who were unaware of their diabetic status, stress hyperglycemia actually had revealed their pre-existing DM or stroke had provoked latent diabetes mellitus. This limitation can be overcome partially by utilizing HbA1C level of all the stroke patients to label them diabetic or non-diabetic, yet not completely as HbA1C level can only be used to detect DM accurately in non-stressed conditions and it might not be accurate in severe illnesses like stroke according to World Health Organization diagnostic criteria for DM. We treated our hyperglycemic patients with subcutaneous regular insulin regimen as and when required and the target was to keep blood glucose level less than 150 mg/dl. On the other hand, higher glucose levels reduction by aggressive treatment with continuous intravenous insulin in 46 patients with baseline glucose values ≥150 mg/dL was associated with better outcomes in a recently published pilot trial (Treatment of hyperglycemia in ischemic stroke[20].

Implications of our study results, that have showed increased mortality with stress hyperglycemia, is that blood glucose level should be measured in every stroke patient for at least 72 hours even if there is no preceding history of diabetes. Every possible measure should be taken to keep a tight glycemic control after stroke with the help of either subcutaneous or intravenous insulin. As until now it is not defined how and to what level stress hyperglycemia should be managed[21,22] so further randomized controlled trials are required to determine what is the ideal insulin regimen and route of administration and what blood glucose level should be aimed for in hyperglycemic ischemic stroke patients.Future research should focus to determine that what blood glucose level in ischemic stroke patients results in increased cerebral ischemic and worse prognosis.

CONCLUSION

Stress hyperglycaemia should be looked for in all stroke patients, whether they are diabetic or not. It is associated with poor prognosis and increased mortality specifically in non-diabetic patients.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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