

STRESS HYPERGLYCEMIA AND MORTALITY IN PATIENTS WITH ACUTE ISCHEMIC STROKE.

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ABSTRACT

Objectives: The objective of the study was to compare mortality and morbidity in patients of acute ischemic stroke presenting with and without stress hyperglycemia.

Background: A high proportion of patients suffering an acute stress such as stroke or myocardial infarction may develop hyperglycemia, even in the absence of a preexisting diagnosis of diabetes.

Place and Duration of Study: This study was carried out in neurology units of Military Hospital Rawalpindi, and in Combined Military Hospital Rawalpindi, both are tertiary referral hospitals. The duration of study was from 1st March to 25th August, 2004.

Results: In the hyperglycemic group, out of 50 patients, 22 (44%) died within 04 weeks of stroke. In the control group, 10 (20%) out of 50 patients expired. The study showed a statistically significant relative risk of 2.2 in case of hyperglycemics as compared to normoglycemics. In the study group, mortality rate was higher in males, 14 (63%) out of 22 as compared to females of 8 (36.36%). Even in survivors, functional outcome at 01 month was worse in the hyperglycemic group. Patients with stress hyperglycemia were 0.4 times less likely to improve as compared to normoglycemics.

Conclusion: In non-diabetic patients suffering from an ischemic stroke, moderately elevated glucose levels were associated with a more than 2-fold higher risk of short-term mortality compared with lower glucose levels. Even in survivors, stress hyperglycemia was associated with a poor functional outcome after acute ischemic strokes.

Keywords: Cerebrovascular accident, stress, hyperglycemia

INTRODUCTION

Stroke remains a leading cause of death world-wide [1]. Cerebrovascular diseases [2-4] predominates in the middle and late years of life. Most cerebrovascular diseases [5-7] present as the abrupt onset of a focal neurologic deficit.

A high proportion of patients suffering an acute stress such as stroke [8] or myocardial infarction [9] may develop hyperglycemia, even in the absence of a preexisting diagnosis of diabetes. Both human and animal studies suggest that this is not a

benign occurrence and that stress-induced hyperglycemia is associated with a high risk of mortality after both stroke and myocardial infarction [10].

Cerebral ischemia is caused by a reduction in blood flow that lasts for several seconds or a few minutes. If the cessation of flow lasts for more than a few minutes, infarction of brain tissue results. A generalized reduction in cerebral blood flow due to systemic hypotension (e.g., cardiac arrhythmia, myocardial infarction, or hemorrhagic shock) usually produces syncope, infarction in the border zones between the major cerebral artery distributions, or widespread brain necrosis,

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depending on the duration of hypotension. Focal ischemia or infarction, on the other hand, is usually caused by disease in the cerebral vessels themselves or by emboli from a proximal arterial source or the heart.

This study was carried out to compare the mortality and morbidity in patients of acute ischemic stroke presenting with and without stress hyperglycemia.

PATIENTS AND METHODS

It was a cohort comparative study.

The study comprised of 100 patients of acute ischemic stroke, 50 with stress hyperglycaemia and 50 with normoglycemia. Patients were selected by nonprobability purposive sampling. Patients presenting in the emergency department with clinical features of stroke were screened by detailed history, clinical examination and CT scan brain.

In stroke patients, stress hyperglycemia was defined (in the absence of known diabetes) as a random plasma glucose level of above 200 mg/dl (11.1 mmol/liter).

Patients were observed for 4 weeks since time of admission. Primary endpoint was the completion of study of 100 patients. The sequelae in the survivors were measured by the Glasgow coma scale.

RESULTS

In the hyperglycemic group, out of 50 patients, 22 (44%) died within 04 weeks of stroke. In the control group, 10 (20%) out of 50 patients expired.

Relative risk was 2.2.

Patients of acute ischemic stroke with stress hyperglycemia were 2.2 times more likely to die than normoglycemics (tab-1).

In patients of stroke who expired, among the males, the mean age of patients in the normoglycemic group was 54 ± 3 yrs; and in hyperglycemics, it was 51 ± 4 yrs. As regards to females, the mean age in normoglycemics was 50 ± 4 yrs; and in hyperglycemics, it was 49 ± 3 yrs.

In the study group, mortality rate was higher in males, 14 (63%) out of 22 as compared to females of 8 (36.36%).

Even in survivors, functional outcome at 01 month was worse in the hyperglycemic group. Patients with stress hyperglycemia were 0.41 times less likely to improve as compared to normoglycemics (tab-2).

DISCUSSION

This study demonstrated that in Nondiabetic-patients, who suffered from ischemic strokes, even a moderate elevation of blood glucose levels, was associated with a more than two fold higher risk of short-term mortality as compared to the normoglycemic group.

From the 1,259 patients in the TOAST trial of heparin treatment, admission hyperglycemia was associated with worse outcome in nonlacunar stroke but was not associated with hemorrhagic change [11].

Thus, normalization of glucose might be a reasonable component of acute stroke management if the risks of treatment induced hypoglycemia could be equivocate [12].

It is now generally agreed that anticoagulant drugs are of no value in the treatment of a completed stroke and some workers continue to use them in cases of "stroke-in-evolution" in an attempt to restrict extension of the thrombosis and thus of the infarct, in such cases, too, their use has been largely abandoned. [13-15].

A study by Pulsinelli and Levy [16] showed a worse neurologic outcome in patients with stress hyperglycemia as compared to the control group.

However, findings of a study carried out in Northern Ireland by Power and Fullerton [17] did not support our results. Similarly data from a study by Matchar and Divine did not support an association between level of glycemia and outcome from acute stroke [18].

A study by Capes and Osler [19] carried out in Canada, revealed that in patients

without diabetes, stress hyperglycemia was associated with a 3-fold increased risk of mortality after stroke (pooled relative risk, 3.07; 95% CI, 2.50 to 3.79). In our study, this risk was slightly more than 2-fold.

Our study also matched with the results of a study by Umpierrez and Isaacs [20].

Most human studies have shown that in acute stroke, admission hyperglycemia in patients without diabetes is associated with a worse clinical outcome than in patients without hyperglycemia. This was supported by a study carried out by Levy and Knobler [21].

In patients with no history of diabetes who have an ischemic stroke, even moderately elevated glucose levels are associated with both a 3-fold higher risk of short-term mortality and an increased risk of poor functional recovery compared with lower glucose levels. It is supported by multivariate analyses of data from 2 large studies, in which admission glucose level was a significant predictor of mortality [22] or poor functional recovery [23] after stroke independent of other prognostic factors.

Several explanations may account for the observed association between hyperglycemia and poor prognosis after ischemic stroke. First, hyperglycemia may be directly toxic to the ischemic brain. Although the mechanism is not fully understood, accumulation of lactate and intracellular acidosis in the ischemic brain may contribute. Intracellular acidosis may promote and accelerate ischemic injury by enhancing lipid per oxidation and free radical formation, allowing accumulation of intracellular calcium (a key component of the glutamate-dependent excitotoxicity seen in ischemic neurons), and impairing mitochondrial function. These neurotoxic effects may be particularly important in the ischemic penumbra (the region of brain tissue surrounding the core of infarcted tissue where neurons are injured but still viable). Indeed, in an animal model of stroke, hyperglycemia facilitated the development of

Table-1: Mortality in hyperglycemics & normoglycemics

Risk factor	Dead	Alive	Total
Hyperglycemics	22	28	50
Normoglycemics	10	40	50
Total	32	68	100

Risk of death in hyperglycemics = 44%
Risk of death in normoglycemics = 20%
Relative risk = 2.2
Patients of acute ischemic stroke with stress hyperglycemia were 2.2 times more likely to die than normoglycemics.

Table-2: Morbidity in Hyperglycemics and normoglycemics

Risk factor	Improvement	No improvement	Total
Hyperglycemics	10	40	50
Normoglycemics	24	26	50
Total	34	66	100

Relative risk = 0.41.
Patients of stroke with stress hyperglycemia were 0.41 times less likely to improve as compared to normoglycemics.

cellular acidosis in the ischemic penumbra and resulted in a greater infarct volume compared with insulin-treated hypoglycemic animals. Thus, hyperglycemia may promote the recruitment of potentially salvageable neurons into the infarction.

Second, patients without a diagnosis of diabetes who develop stress hyperglycemia are likely to have dysglycemia (i.e., blood glucose level above the normal range but below the threshold for diabetes) or undiagnosed diabetes when not stressed. Patients with dysglycemia or undiagnosed diabetes have a higher risk of vascular disease than patients with normal blood glucose level. These patients could sustain more ischemic damage at the time of infarction as a result of more extensive underlying cerebral vasculopathy compared with those who do not develop stress hyperglycemia. Although the extent of cerebral atherosclerosis in patients with and without stress hyperglycemia has not been studied, hyperglycemia may be an important determinant of the widespread changes in both small cerebral blood vessels and large

extra cranial vessels seen in diabetic patients. Furthermore, even Nondiabetic - range hyperglycemia is associated with endothelial dysfunction, another potential mechanism of cerebrovascular disease in these patients.

Third, hyperglycemia may disrupt the blood-brain barrier and promote hemorrhagic infarct conversion. Consistent with this possibility is the observation that in 138 diabetic and Nondiabetic patients with ischemic stroke treated with intravenous recombinant tissue plasminogen activator, higher admission serum glucose level was associated with a higher risk of hemorrhagic conversion of the infarct, with a substantial increase in risk with levels >8.4 mmol/L.

Fourth, stress hyperglycemia may be a marker of the extent of ischemic damage in patients with stroke. For example, patients with severe or fatal strokes might develop hyperglycemia because of greater release of "stress hormones" such as cortisol and nor epinephrine.

CONCLUSION

Stress hyperglycemia is a commonly encountered condition. It is important to distinguish between diabetes mellitus and stress hyperglycemia for proper management of the patient. Inability to do so may result in over enthusiastic diagnosis of diabetes mellitus and use of glucose lowering medication, which may be harmful to the patient. However, at the same time presence of stress hyperglycemia should not be overlooked because of its prognostic implications in many clinical settings. Thus, close monitoring by plasma glucose estimation and guarded management of hyperglycemia is recommended in such patients.

Stress hyperglycemia predicts increased risk of in-hospital mortality after ischemic stroke and increased risk of poor functional recovery in nondiabetic stroke survivors.

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