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Effect of Risk Factors on Short Term Mortality in Patients of Stroke with Hyperglycaemia

Aminul Islam*[1], Quamruddin Ahmed[2], Shamrose Begum[3], Abdul Baset[4], Roushan Kabir choudhury[5], Mohimanul Hoque[5]

1 Department of Medicine, Naogaon Medical College, Naogaon
2 Department of Neuromedicine, Rajshahi Medical College
3 Department of Anatomy, Rajshahi Medical College
4 Department of Medicine, Paba Upozilla Health Complex, Rajshahi
5 Department of Medicine, Rajshahi Medical College Hospital

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***Correspondence to:**
Dr. Md. Aminul Islam
Email: cottondoctor11@yahoo.com

ABSTRACT: ***Background:*** Stroke is the third most common cause of death in the developed world after ischaemic heart disease and all cancers and is the most common cause of physical disability. Hyperglycaemia on admission is well known risk factor for increased short-term mortality and also for increased rate of haemorrhagic conversion after thrombolytic therapy in ishchaemic stroke. ***Objectives:*** To study the effect of hyperglycaemia on the 30-day prognosis of patients admitted with stroke and its relationship with other risk factors ***Materials and Methods:*** It was a hospital based prospective study carried out in patients admitted in the Neuro-Medicine and Medicine units of Rajshahi Medical College Hospital admitted with the diagnosis of Stroke as confirmed by imaging of the brain (CT scan or MRI) From January 2008 to January 2009. 100 consecutive patients of stroke having a raised blood sugar level (above 10.0 mmol/l) formed the study group while 100 similar patients of stroke with normal blood sugar level (less than 8.00 mmol/l) constituted the control group. ***Results:*** Total 200 patients were enrolled. Highest number of both male and female patients were between ages 51 and 65 (42.2% male & 53.3% female). Highest mortality was from age group 35-50 years (20.1%), which was statistically significant($p<.05$) Mortality was more in male both among normoglycaemic (4.8) and hyperglycaemic group; here mortality was significantly higher in male($p<.05$). Moreover, patients with Glasgow coma scale below 8 0n admission had the highest mortality. ***Conclusion:*** Male sex, middle age (35-50years), and Glasgow coma scale below 8 were established as poor outcome predictors in stroke patients along with hyperglycaemia. Several studies support these findings except the factor named Middle age. More large-scale studies should be conducted to look into the matter.

Keywords: Stroke, Mortality, Hyperglycaemia.

Article at a glance:
Study Purpose: *To assess the impact of hyperglycaemia and other factors on short-term stroke mortality.*
Key findings: *Hyperglycaemic stroke patients had higher mortality. Male sex, middle age (35-50), and low Glasgow Coma Scale were significant risk factors.*
Newer findings: *Middle-aged hyperglycaemic patients had the highest mortality, which is a new discovery.*
Abbreviations: *GCS - Glasgow Coma Scale, IHD - Ischaemic Heart Disease, DM - Diabetes Mellitus.*

INTRODUCTION

Stroke is the third most common cause of death in the developed world after ischaemic heart disease and all cancers and is the most common cause of physical disability. Although confounded by other factors, such as severity of the infarct, hyperglycaemia in the face of stroke worsens clinical outcome. Sometimes nondiabetic hyperglycaemic stroke patients had shown increasd short short-term mortality(threefold) than known diabetic patients(twofold).[1] Whereas when we consider thrombolytic and anticoagulation therapy in patients with ishchaemic stroke, hyperglycaemia again stands as an independent risk factor for worsened outcome as well as an independent risk factor in thrombolytic induced haemorrhagic conversion. It is well known that DM is an important risk factor for stroke and may be one of the factors causing stroke at younger ages in groups such as Hispanic Americans that have relatively high incidence of DM. Atherosclerotic changes are more extensive and earlier in diabetic persons and effect of other cardiovascular risk factors like smoking, hypertension and dyslipidaemia are amplified.[2] Furthermore, admission hyperglycaemia,

whether known diabetic or not, has been demonstrated as important risk factor for stroke mortality.[3] How hyperglycaemia worsens stroke outcome? It may occur due both to vascular injury leading to poorer reperfusion and local lactic acidosis leading to further tissue injury.[4] Detrimental effect of hyperglycaemia on central vascular tree is proven by some earlier animal studies.[5] Now, the specific mechanisms by which hyperglycaemia led to poorer clinical outcome in patients receiving anticoagulants or thrombolytics is not known. It may be related to advanced glycosylation end products (AGE). These products interfere with protein and enzyme function, blocks production of vasodialator substances and also produce toxic substances and free radicals causing further vascular injury. Notably, even moderate elevation of serum glucose level is an important risk factor for conversion of ischaemic to hemorrhagic stroke after thrombolytic therapy in hyperglycaemic patients may be present even at moderate elevation of serum glucose levels, but still moderate hyperglycaemia is not an exclusion criterion for administration of rtPA. In patients with acute stroke, acceptable blood glucose level is 50 to 400 mg/dl. This matter can be reconsidered. From 1988 to 1998 the total number of stroke deaths in the United States rose 5.3%. Also, there was parallel increase in diabetes as well as ageing. In a study carried out by among 25155 Finnish men and 26423 women aged 25 to 74 years showed that Diabetes present either at baseline or follow-up markedly increases the risk of stroke death.[6] Hamidon *et al*., in their study showed that admission hyperglycaemia is the single most important predictor of death in a patient with stroke.[3] The above-mentioned factors led us to think that if hyperglycemia alone or also other cardiovascular risk factors have detrimental effect on stroke. In Bangladesh, there is no large-scale study on this topic. So, observing short term (30 days) mortality in patients of stroke with DM prospectively will be an important addition to our knowledge and help to formulate strategies to further improve management of such patients. Justification of this study: Hyperglycaemia is an important risk factor for short term mortality in stroke patients. A number of studies have proven this fact. If we can explore other factors that have significant effects on short term mortality along with hyperglycaemia, poor outcomes of stroke patients would be predicted more accurately. Moreover, this study will open a number of new windows of thinking.

MATERIALS AND METHODS

It was a hospital based prospective study carried out in patients admitted in the Neuro-Medicine and Medicine units of Rajshahi Medical College Hospital admitted with the diagnosis of Stroke as confirmed by imaging of the brain (CT scan or MRI) from January 2008 to January 2009. 100 consecutive patients of stroke having a raised blood sugar level (above 10.0 mmol/l) formed the study group while 100 similar patients of stroke with normal blood sugar level (less than 8.00 mmol/l) formed the control group. On admission, the level of consciousness of the patient was recorded according to Glasgow coma scale, his blood sugar level was estimated by bedside rapid glucometer, and the patient was classified as haemorrhaggic or ischaemic stroke according to the imaging finding. An ECG was done for each patient and according to the finding the patient was labelled as a patient of ischaemic heart disease or not. A patient was labelled as hypertensive if there was definite history of taking anti-hypertensive drugs or blood pressure was found to be persistently raised after stroke and/or anti-hypertensive therapy had to be started. Smoking history was also obtained. Demographic data of all patients was also recorded in the individual file of each patient. Each patient was followed up during the hospital stay to determine the prognosis. If any patient dies, then the cause of death, as determined by the treating doctors was recorded. If the patients were discharged, he was contacted over mobile telephone after 30 days and his prognosis was recorded. All data was collected by the Principal Investigator himself in an individual questionnaire for each patient. Data was processed in computer using SPSS for windows. Descriptive analytical techniques involving frequency distribution, computation of percentage, mean, SD, etc. were applied. Association between variables was conducted applying chi-square test. All parametric variables were expressed as mean +/- SD unless otherwise stated. The comparison between the groups was made by unpaired "t" test. P value < 0.05 was considered as minimum level of significance.

RESULTS

This was a prospective study in which the effects of different risk factors on the short-term mortality of patients with stroke with hyperglycaemia were studied. 100 patients with hyperglycaemia were studied and compared with 100 normoglycemic patients. Table 1 shows the distribution of the patients according to age and sex. Highest number of both male and female patients were between ages 51 and 65 (42.2% male & 53.3% female). Amongst the hyperglycaemic patients the highest mortality was from age group 35-50 years (20.1%), which was statistically significant ($x2 = 6.554$, $p<.001$) (Table 2). Table 2 also shows that amongst normoglycaemic patients below 50 years no patient died; also, notable no normoglycaemic patient above 81 years died. Table 3 shows the distribution of mortality according to sex and glycaemic status. Short term mortality is more in male both among normoglycaemic (4.8) and hyperglycaemic group. Here mortality is significantly higher in male ($x2 = .55$, $p<.05$). Table 4 shows the outcome of the patients according to the level of consciousness as assessed by the Glasgow coma scale. Amongst hyperglycaemic patients, those having GCS < 8, mortality was the highest (23.40%) and those patients having GCS>12 had the lowest mortality (5%), [$x2 = 12.59$, $p<.05$]. Table 5 shows effect of systolic blood pressure on mortality in both normo and normo and hyperglycaemic groups.

Table 1: Frequency Distribution of Patients by Age and Sex

Age group(years)	Sex				Total	
	Male		Female			
	N	%	N	%	N	%
35-50	35	17.5	27	13.5	62	31
51-65	54	27	40	15	84	42
66-80	31	15.5	17	8.5	48	24
81>	5	2.5	1	.5	6	3
Total	125	62.5	75	37.5	200	100

Table 2: Frequency Distribution of Patients by Age and Short-Term Mortality

Age group(years)	Normoglycemia				Hyperglycaemia				Total	p-value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%	N	
35-50	26	41.94	0	0	23	37.1	13	20.1	62	
51-65	42	50	5	5.95	28	33.33	9	10.71	84	p<0.001
66-80	19	39.6	3	6. 025	21	43.8	5	10.42	48	(x2 =6.55)
81>	5	83.33	0	0	0	0	1	16.66	6	
Total	92	46	8	4	72	36	28	14	200	

Table 3: Frequency Distribution of Patients by Sex and Short-Term Mortality

Sex	Normoglycaemia				Hyperglycaemia				Total	p-value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%	N	
Male	59	47.2	6	4.8	43	34.4	17	13.6	125	p<0.05 (x^2 =0.65)
Female	33	44	2	2.66	29	38.7	11	14.7	75	
Total	92	46	8	4	72	36	28	14	200	

Table 4: Frequency Distribution of Patients by Level of Consciousness (G.C.S) and Short-Term Mortality

Glasgow coma scale	Normoglycemia				Hyperglycemia				Total	p-value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%	N	
>12	30	50	0	0	27	45	3	5	60	p<0.05
8-12	22	47.82	2	4.34	19	41.30	3	6.52	46	(x^2 =12.59)
<8	40	42.55	6	6.38	26	27.66	22	23.40	94	
Total	92	46	8	4	72	36	28	14	200	

Table 5: Frequency Distribution of Patients by Systolic B.P. and Short-Term Mortality

Systolic B.P. (mm Hg)	Normoglycaemia				Hyperglycaemia				Total	p-value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%	N	
<140	47	2.14	4	L3.96	39	38.61	11	10.89	101	
140-160	22	51.16	1	2.33	14	32.6	6	13.95	43	
161-180	18	54.55	1	3.03	10	3.03	4	12.12	33	p>0.05
181-200	3	33.33	2	22.22	2	22.22	2	22.22	9	
>200	2	14.29	0	0	7	50	5	35.71	14	
Total	92	46	8	4	72	36	28	14	200	

Table 6: Frequency Distribution of Patients by Diastolic B.P. and Short-Term Mortality

Diastolic B.P. (mm Hg)	Normoglycaemia				Hyperglycaemia				Total	p-value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%	N	
<80	41	43.61	2	2.1	44	46.9	7	7.45	94	
81-90	22	61.11	2	5.6	10	27.8	2	5.56	36	
91-100	21	44.7	2	4.3	12	25.53	12	25.53	47	p>0.05
101-110	4	57.14	0	0	1	14.3	2	28.57	7	
>110	4	25	2	12.5	5	31.25	5	31.25	16	
Total	92	46	8	4	72	36	28	14	200	

Table 7: Frequency Distribution of Patients by Ischaemic Heart Disease (As Per Ecg) and Short-Term Mortality

I.H.D	Normoglycaemia				Hyperglycaemia				Total	p-value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%	N	
Yes	26	50.98	3	5.88	14	27.45	8	15.69	51	
No	66	44.3	5	3.35	58	38.93	20	13.42	149	p>0.05
Total	92	46	8	4	72	36	28	14	200	

I.H.D: Ischaemic heart disease

Table 8: Frequency Distribution of Patients by Smoking and Short-Term Mortality

Smoking	Normoglycaemia				Hyperglycaemia				Total	p-value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%	N	
Yes	38	73.08	4	7.7	14	26.92	8	15.4	52	
No	54	34.5	4	2.7	58	39.2	20	13.51	148	p>.05
Total	92	46	8	4	72	36	28	14	200	

Table 9: Frequency Distribution of Patients by Lesion Type and Short-Term Mortality

Lesion type	Normoglycaemia				Hyperglycaemia				Total	p-value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%	N	
Ischaemic	61	45.2	3	2.22	55	40.74	16	11.85	135	
Haemorrhagic	29	46.03	5	7.9	17	27	12	19.04	63	p>0.05
Sabarachnoid haemorrhage	2	100	0	0	0	0	0	0	2	
Total	92	46	8	4	72	36	28	14	200	

Table 10: Frequency Distribution of Died Patients by Sex and Glycemic Status

Sex of the patient	Died Patients with Normoglycaemia		Died patients with Hyperglycemia		Total	
	N	%	N	%	N	%
Male	6	16.7	17	47.2	23	63.9
Female	2	5.6	11	30.6	13	36.1
Total	8	22.2	28	77.8	36	100

Table11: Frequency Distribution of Patients by Glycaemic Status and Short-Term Mortality

Glycemic status of patients	Patients alive at 30 days		Patients died within 30 days		TOTAL
	N	%	N	%	N
Normoglycaemia	92	92	8	8	100
Hyperglycaemia	72	72	28	28	100
Total	164	82	36	18	200

DISCUSSION

A good number of studies have established that both hyperglycaemia on admission and preexisting diabetes increase the risk of short-term mortality in stroke patients,7,8also both the factors increase the haemorrhagic conversion of ischemic stroke after thrombolytic and anticoagulant therapy.9 In today's world, the practice of using thrombolytics in ishchaemic stroke is increasing, so admission hyperglycaemia will become more important day by day. Adverse results of admission hyperglycaemia were established by many small- and large-scale studies (some of those are mentioned earlier). Also, in our study we found higher short-term mortality in hyperglycaemics (Table 11). In case of nondiabetic stroke patients' admission hyperglycaemia is again important predictor of short-term mortality and also associated with poor functional recovery.[1] Another renowned study showed significantly increased mortality in stroke patients with hyperglycaemia on admission.[9] Another important observation in this study was 40% of admitted stroke patients were hyperglycaemic. The later study also says that patients with hyperglycaemia were mostly women. But in our study, in all age groups of strokes, male patients were more in number (Table 1) and amongst died patients from both normo and hyperglycaemic groups male were significantly predominant(p<.005) (Table10).

Table 3 more elaborately demonstrates more adverse outcomes in male patients of stroke. Here both in normoglycemic and hyperglycemic group mortality was significantly higher in male(p<.05). A cohort study in netherland showed significantly lower motality in female in both ishchaemic and haemorrhagic stroke but in sabarachnoid hemorrhage no significant difference was

noted.[10] A study during 1995 to 1998 showed more mortality among male over age matched female'11 Middle age stood as an important short term mortality predictor in stroke (Table 2).[11] Amongst hyperglyacemic patients the highest mortality was from age group 35-50 years(20.1%) ,which was statistically significant(p<.05).so this table opens a new window of thinking about the vulnerability of this middle aged group and less mortality of the frail order group, above 81 years of age; it should be kept in mind that, this may be due to the fact that number of patients above age 80 years was very low (6/200). Now it should be explored why and how this middle age (35-50) group is adversely affected by hyperglycemic stroke. Table 4 expresses the importance of Glasgow coma scale on admission. Among hyperglycaemic patients having GCS below 8 had significantly (p<.05) higher short-term mortality than those with more than 12. An observational study in Dhaka medical college hospital found 12.07% fatality among patients having GCS 3-8 and no mortality among 13 to 15. They recommended in their conclusion to consider GCS as an important mortality predictor in acute stroke.[12] Another study expressed the same comment.[13] Table 5 and 6 try to correlate systolic and diastolic blood pressures respectively on admission with short term mortality; but both tables only show poor prognosis in case of hyperglycemics in all systolic and diastolic blood pressure groups; but elevated blood pressure neither systolic nor diastolic had any significant effect. Rabkin *et al* demonstrated systolic blood pressure and its 5-year change. Each were significant predictors of short-term (30 days) mortality and high blood pressure and large positive 5-year change in systolic blood pressure before stroke occurrence were significant predictors of poor prognosis.[14]

Due to poor quality of record keeping procedures in our country both in the inpatient and outpatient departments of various hospitals, it is difficult to carry out such a study where we can consider pre stroke blood pressure or 5-year change in blood pressure. A systematic review found high systolic blood pressure as an important predictor of short-term mortality.[9] Considering the aforementioned studies we propose to conduct another study to evaluate effect of blood pressure on acute stroke mortality. Table 7 tries to correlate short term mortality in stroke patients with ischaemic heart disease. short term mortality was more in patients with ECG demonstrated heart disease although difference between IHD and non IHD mortality in hyperglycaemic stroke deaths was not statistically significant. Here we used only ECG as a diagnostic tool for defining IHD. Table 8 demonstrated no significant difference among smokers and nonsmokers in terms of short-term stroke mortality. Another study shows increased death rate in long term follow up after stroke who continued smoking.[15] Another important finding regarding this issue was observed in another study.[16] Here combined reduction in diastolic blood pressure, serum total cholesterol and smoking demonstrated reduction in post stroke death by two third and half in case of male and female respectively. Notably in our study continuation of smoking was not considered at all, again smoking was not quantified in terms of pack year. Table 9 demonstrates the effect of lesion subtype on short term mortality. No significant difference was noted between ischaemic and haemorrhagic stroke (although short term mortality among hemorrhagic strokes albeit more than ischemic stroke.) It is generally observed that mortality is higher in patients of haemorrhagic stroke than in patients of ischemic stroke but in this study, there was no significant difference of mortality in these two groups of patients. This may be due to the fact that it is a hospital-based study in which only admitted patients are included. Patients of stroke are admitted in the hospital only when their general condition is very poor, irrespective of the fact whether they suffered from ischemic or haemorrhagic stroke. So ischemic stroke patients whose general condition is not poor are not brought to the hospital. This also explains the fact why patients of ischaemic stroke are only double the number of haemorrhagic stroke patients while the actual ratio of ischaemic to haemorrhagic stroke patients is about 4:1. Since only very serious patients of ischemic stroke are admitted to the hospital there is no significant difference in the mortality in patients of ischaemic and haemorrhagic stroke admitted in the hospital.

Limitations of this Study

Hypertension in a stroke Patient is common. There should be differentiation between Pre-existing hypertension and new onset hypertension. Due to the poor medical record-keeping system and patients' ignorance, this important area could not be explored. We considered only ECG as a diagnostic tool for ischemic heart disease. ETT, Stress echocardiography, Radioneucleotide imaging were not done. In obtaining smoking history we only considered whether the patient was smoker or not. But the amount of smoking (in terms of pack years) was not taken into account. We found middle age as a significant poor prognostic factor, which is a new concept; other studies do not support this finding. Large scale study may be conducted later on regarding this issue. Admission to hyperglycaemia may be due to either stress or preexisting uncontrolled diabetes. Both conditions may have different impacts on prognosis. In our study we did not differentiate these conditions.

CONCLUSION

The aim of the study was to explore the significant risk factors for short term mortality for stroke along with hyperglycemia. Now we can come to the following conclusions:

Male sex has significantly higher mortality in stroke patients (p<0.05).

Middle age (35-50 years) becomes important short term stroke mortality predictor along with hyperglycemia.

Glasgow coma scale below 8 at admission is a risk factor for poor short-term outcome.

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