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Clinical Outcome in Ischemic Stroke Patients with Hyperglycemia

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Abstract:

Introduction

Stroke is one of the leading causes of death and long term disability in India. Stroke is an important cause of premature death and disability in low-income and middle-income countries like India, largely driven by demographic changes and enhanced by the increasing prevalence of the key modifiable risk factors.

Among all the neurological diseases of adult life, cerebrovascular accidents clearly rank first in frequency of importance. Almost fifty percent of neurological diseases in general hospital are due to stroke.

Cerebrovascular accident includes ischemic stroke, hemorrhagic stroke and cerebrovascular anomalies such as intracranial aneurysm, AV malformation and cortical venous thrombosis. Stroke after heart disease, is the second most common cause of death among non-communicable diseases. With the introduction of effective treatment for hypertension, there has been a marked reduction in the frequency of stroke.

Diabetes mellitus by virtue of its association with micro vascular and macro vascular disease is an important risk factor in the genesis of stroke. Most of the diabetic patients with stroke have raised glycosylated hemoglobin indicating that most of them have uncontrolled diabetes. Diabetics and Stress Hyperglycemics have severe strokes resulting in poor outcome. Stroke is twice more common in diabetics than in non diabetics.

Hypertension is common in diabetes and accelerates atherosclerosis which promotes intracranial small vessel disease and heart disease leading to lacunar and embolic infarction respectively. There are several risk factors that determine the outcome of stroke. Hyperglycemia, fever, neuroprotective agents are those which are widely studied.

Aim of the study

To measure the random blood glucose level in the early phase of ischemic stroke (within 24 hours of onset) in both diabetics and in non diabetics and to evaluate the severity and prognosis in both diabetics and non diabetics in relation to hyperglycemia.

Materials and methods

A total of sixty of acute ischemic stroke patients admitted between April 2018 to November 2018 in the Department of General Medicine, Government Thiruvannamalai Medical College and Hospital, Thiruvannamalai were studied.

Out of the sixty patients, ten were dropped as follow up could not be done. Complete history was taken, clinical examination was done and clinical diagnosis for each patient was arrived. Blood pressure measurement, blood sugar, urea, creatinine, electrolytes, hemoglobin, total count, differential count; urine sugar, albumin, deposits; electrocardiogram and chest X ray was done for all patients

The severity of stroke for each patient was calculated based on NIH stroke scale

Conclusion

There is a linear correlation between admission day hyperglycemia and ischemic stroke in its severity, size and outcome. The combined diabetics and stress hyperglycemics were found to have larger sized severe stroke and poor functional outcome in the form of increased mortality. There is a good correlation between admission day glucose level and the outcome in ischemic stroke. Admission day elevated glucose level was a significant predictor of mortality and poor functional outcome after stroke. Hence restoration of normoglycemia as soon as possible should be encouraged. In the interim, we should farewell with adhering to good general stroke management, normalization of body temperature, fluid balance and hemodynamics or we may otherwise risk the favorable outcome even in the patients with normoglycemia.

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I. Introduction

Stroke is one of the leading causes of death and long term disability in India. Stroke is an important cause of premature death and disability in low-income and middle-income countries like India, largely driven by demographic changes and enhanced by the increasing prevalence of the key modifiable risk factors.

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Diabetes mellitus by virtue of its association with micro vascular and macro vascular disease is an important risk factor in the genesis of stroke. Most of the diabetic patients with stroke have raised glycosylated hemoglobin indicating that most of them have uncontrolled diabetes. Diabetics and Stress Hyperglycemics have severe strokes resulting in poor outcome. Stroke is twice more common in diabetics than in non diabetics.

Hypertension is common in diabetes and accelerates atherosclerosis which promotes intracranial small vessel disease and heart disease leading to lacunar and embolic infarction respectively. There are several risk factors that determine the outcome of stroke. Hyperglycemia, fever, neuro protective agents are those which are widely studied.

II. Aim Of The Study

To measure the random blood glucose level in the early phase of ischemic stroke (within 24 hours of onset) in both diabetics and in non diabetics and to evaluate the severity and prognosis in both diabetics and non diabetics in relation to hyperglycemia.

III. Materials And Methods

A total of sixty of acute ischemic stroke patients admitted between April 2018 to November 2018 in the Department of General Medicine, Government Thiruvannamalai Medical College and Hospital, Thiruvannamalai were studied. The Patients were selected on the following basis

Inclusion Criteria:

1. Patients above the age of forty
2. Patients admitted within twenty four hours of onset of symptoms
3. Patients with the first episode of cerebrovascular accident
4. Blood sugar recorded with in twenty four hours of the onset of stroke

Exclusion Criteria:

1. Patients admitted after twenty four hours of stroke
2. Those patients who received intravenous glucose before or during study period
3. Patients with reliable information about diabetes could not be obtained
4. Patients who died before it could be established whether or not they had diabetes
5. Illness presented with stroke like symptoms

Out of the sixty patients, ten were dropped as follow up could not be done. Complete history was taken, clinical examination was done and clinical diagnosis for each patient was arrived. Blood pressure measurement, blood sugar, urea, creatinine, electrolytes, hemoglobin, total count, differential count; urine sugar, albumin, deposits; electrocardiogram and chest X ray was done for all patients

The severity of stroke for each patient was calculated based on NIH stroke scale, NIHSS which takes the following clinical findings in to account and each criteria awarded specific points

1a Level of conscious	
Alert	0
Drowsy	1
Stuporous	2
Comatose	3
1b LOC questions	
Answers both correctly	0
Answers one correctly	1

Incorrect	2
1c LOC commands	
Obeys both correctly	0
Obeys one correctly	1
Incorrect	2
2 Best gaze	
Normal	0
Partial gaze palsy	1
Forced deviation	2
3 Visual	
No visual loss	0
Partial hemianopia	1
Complete hemianopia	2
Bilateral hemianopia	3
4 Facial palsy	
Normal symmetric	0
Minor paralysis	1
Partial paralysis	2
Complete paralysis	3
5 Best motor arm (right and left)	
No drift	0
Drift	1
Some antigravity effort	2
No antigravity effort	3
No movement	4
6 Best motor leg (right and left)	
No drift	0
Drift	1
Some antigravity effort	2
No antigravity effort	3
No movement	4
7 Limb ataxia	
Absent	0
Present in one limb	1
Present in both limbs	2
8 Sensory	
No sensory loss	0
Mild to moderate sensory loss	1
Total sensory loss	2
9 Best languages	
Normal, no aphasia	0
Mild to moderate aphasia	1
Severe aphasia	2
Mute, global aphasia	3
10 Dysarthria	
Normal	0
Mild to moderate	1
Severe	2
11 Extinction/ inattention	
No abnormality	0
Visual/ tactile/ spatial/ personal inattention	1
Profound hemi inattention	2

The points were added, with a maximum of forty two points.

NIHSS Score	Stroke severity
0	No stroke symptoms
1-4	Minor stroke
5-15	Moderate stroke
16-20	Moderate to severe stroke
21-42	Severe stroke

Once clinical diagnosis of acute stroke was made venous blood sample was taken, with in twenty four hours of onset of symptoms, and sent to laboratory for glucose estimation.

In patients with blood sugar value more than 6.1 mmol/l (110 mg/dl) and without a history of diabetes, Hemoglobin A_1c was performed. (Hemoglobin A_1c is structurally similar to hemoglobin A except for the addition of glucose group to the terminal amino acid of the beta chain of the hemoglobin molecule (glycosylation). Therefore Hemoglobin A_1c is a function of the exposure of the red blood cells to glucose. Since the glucose linkage to hemoglobin is relatively stable, Hemoglobin A_1c accumulates through out of the life span of erythrocyte and its concentration reflects the integrated blood glucose concentration over a period approximating to the half life of erythrocytes i.e. six to eight weeks. Therefore measurement of hemoglobin A_1c helps to monitor the overall degree of diabetic control achieved. The normal range of Hemoglobin A_1c is 3.8% to 6.4%. Hence the patients can be classified into four groups

1) Blood sugar less than 6.1 mmol/l: **Non diabetics (Euglycemics)**
2) History of diabetes: **Known diabetics**
3) Blood sugar more than 6.1 mmol/l, no history of diabetes, and hemoglobin A_1c more than 6.4%: **Newly detected diabetics**
4) Blood sugar more than 6.1 mmol/l, no history of diabetes, and hemoglobin A_1c less than 6.4%: **Stress hyperglycemics**

Then computerized tomography CT of the brain was performed in all patients to:

- Confirm the diagnosis
- Detect the type of stroke
- Detect the size of lesion
- (small < 5mm; Medium 5 – 10 mm; Large > 10 mm or involving more than one vascular territory)
- Locate the site of lesion
- Identify the presence of cerebral edema or midline shift

The patients were followed up for thirty days and outcome in the form of death; poor, moderate and good improvement was recorded. Patients who were unable to return to any form of work, persistent disability, need for residential placement, dependant in activities of daily living and stable deficit with no recovery were classified as those with poor outcome. Patients whose symptoms improved, who were independent in attending day to day activities, improvement in motor function and aphasia and no persistent disability were grouped as patients with good outcome. Patients who fared in between these two groups were grouped as those with moderate outcome.

IV. Observation And Results

Sex distribution:

Sex	Frequency	Percent
Male	30	60.0 %
Female	20	40.0 %
Total	50	100.0 %

Age wise distribution:

Age	Frequency	Percent
40-50 Years	9	18.0 %
51-60 Years	15	30.0 %
61-70 Years	14	28.0 %
71-80 Years	12	24.0 %
Total	50	100.0 %

Risk factors:

Hypertension

	Frequency	Percent
No	18	36.0 %
Yes	32	64.0 %
Total	50	100.0 %

Diabetes Mellitus

	Frequency	Percent
No	16	32.0 %
Yes	34	68.0 %
Total	50	100.0 %

Dyslipidaemia

	Frequency	Percent
No	21	42.0 %

Yes	29	58.0 %
Total	50	100.0 %

Smoker

	Frequency	Percent
No	34	68.0 %
Yes	16	32.0 %
Total	50	100.0 %

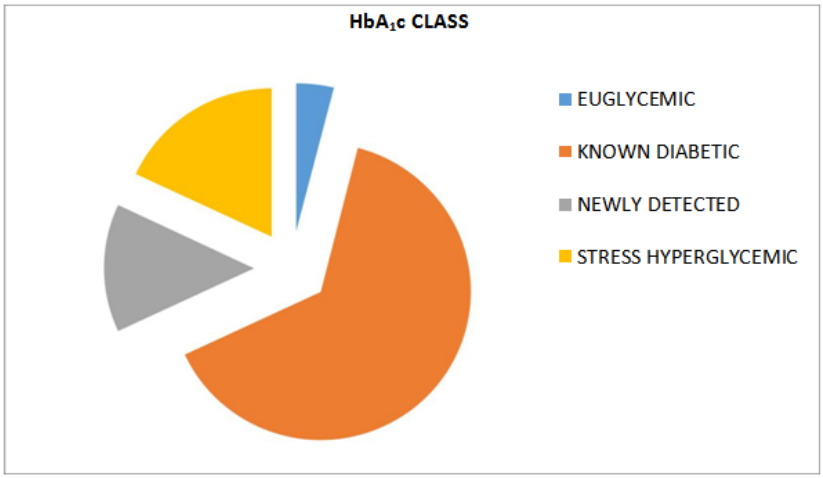
Alcoholic

	Frequency	Percent
No	36	72.0 %
Yes	14	28.0 %
Total	50	100.0 %

Glycemic status:

Based on HbA_1c

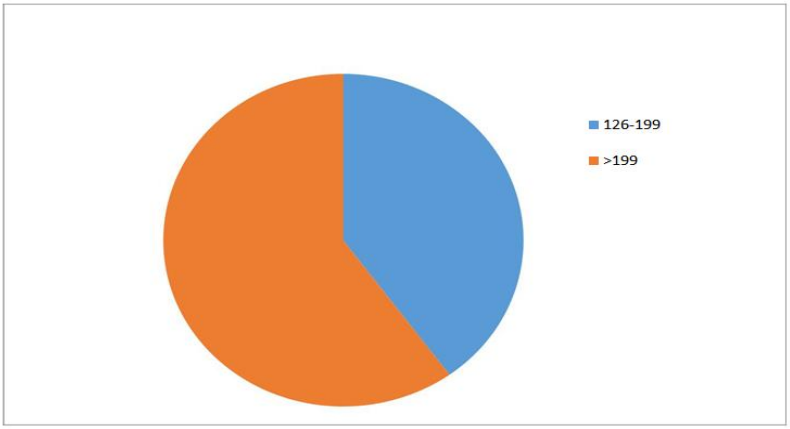
	Frequency	Percent
Euglycemic	2	4.0 %
Known diabetic	32	64.0 %
Newly detected	7	14.0 %
Stress Hyperglycemic	9	18.0 %
Total	50	100.0 %



Based on random blood glucose

	Frequency	Percent
126-199	20	40.0 %
>199	30	60.0 %
Total	50	100.0 %

RBS Group



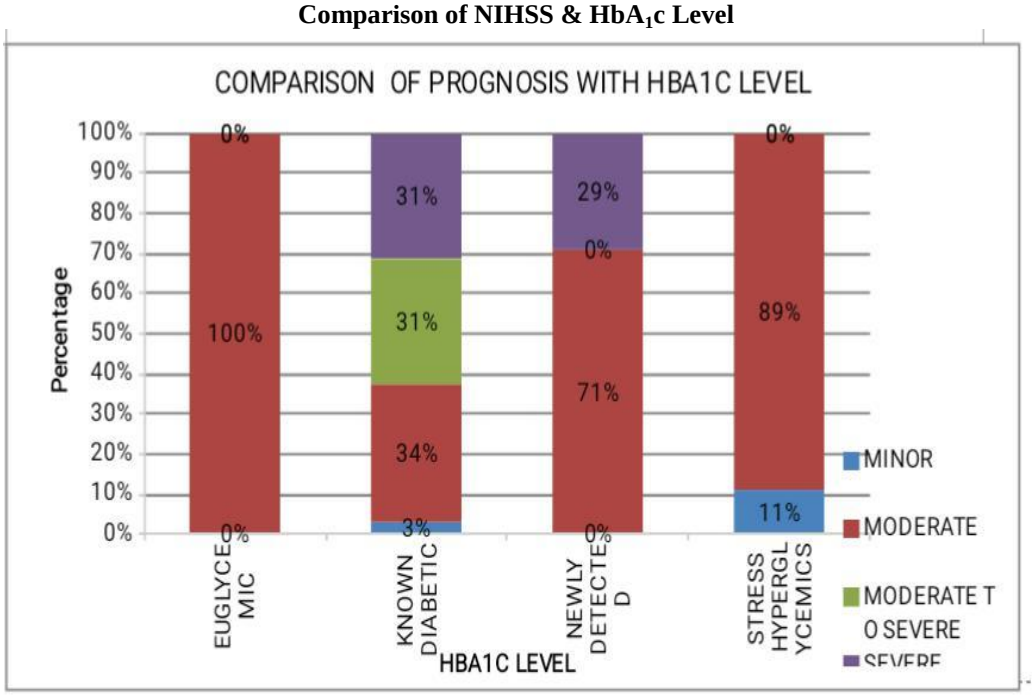
Statistical analysis:

NIHSS is equated to stroke severity and clinical outcome of patient after stroke onset assessed in varying intervals

NIHSS Vs HbA_1c							
Stroke severity			**Euglycemic**	**Known Diabetic**	**Newly Detected**	**Stress Hyperglycemic**	**Total**
NIHSS CLASS	**Minor**	**Count**	0	1	0	1	2
		% within HbA_1c Count	0.0 %	3.1 %	0.0 %	11.1 %	4.0 %
	Moderate	**Count**	2	11	5	8	26
		% within HbA_1c Count	100.0 %	34.4 %	71.4 %	88.9 %	52.0 %
	Moderate to Severe	**Count**	0	10	0	0	10
		% within HbA_1c Count	0.0 %	31.2 %	0. 0 %	0.0 %	20.0 %
	Severe	**Count**	0	10	2	0	12
		% within HbA_1c Count	0.0 %	31.2 %	28.6 %	0.0 %	24.0 %

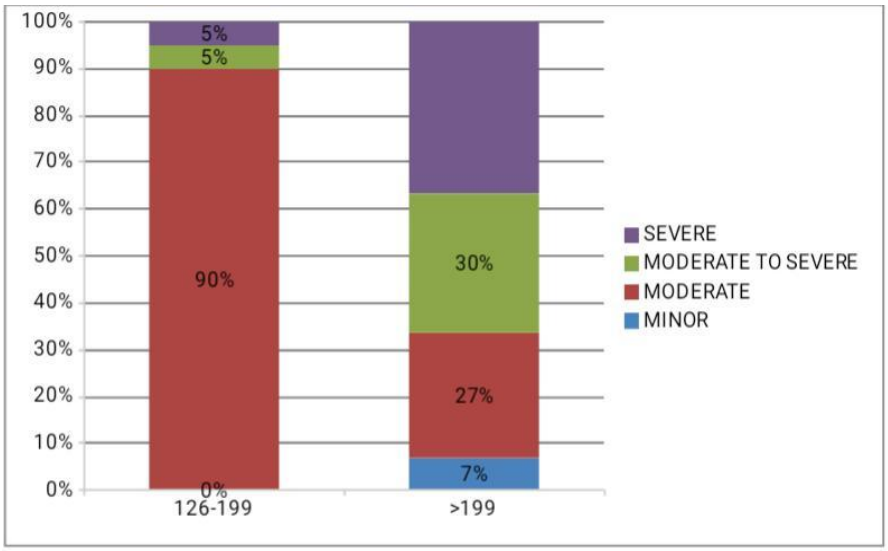
Pearson Chi-Square = 21.714* P = 0.010 significant

Comparison of NIHSS & HbA_1c Level

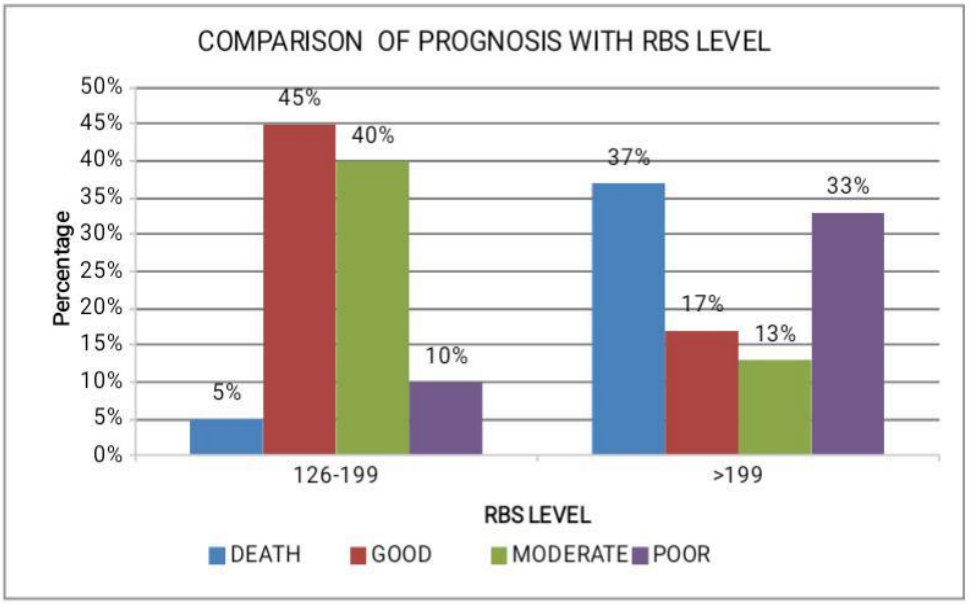


NIHSS Vs RANDOM BLOOD SUGAR LEVELS					
Stroke severity			**RBS Group**		**Total**
			126 – 199	**> 199**	
NIHSS CLASS	**Minor**	**Count**	0	2	2
		% within RBS Group	0.0 %	6.7 %	4.0 %
	Moderate	**Count**	18	8	26
		% within RBS Group	90.0 %	26.7 %	52.0 %
	Moderate to Severe	**Count**	1	9	10
		% within RBS Group	5.0 %	30.0 %	20.0 %
	Severe	**Count**	1	11	12
		% within RBS Group	5.0 %	36.7%	24.0 %
Total		**Count**	20	30	50
		% within RBS Group	100.0 %	100.0 %	100.0 %

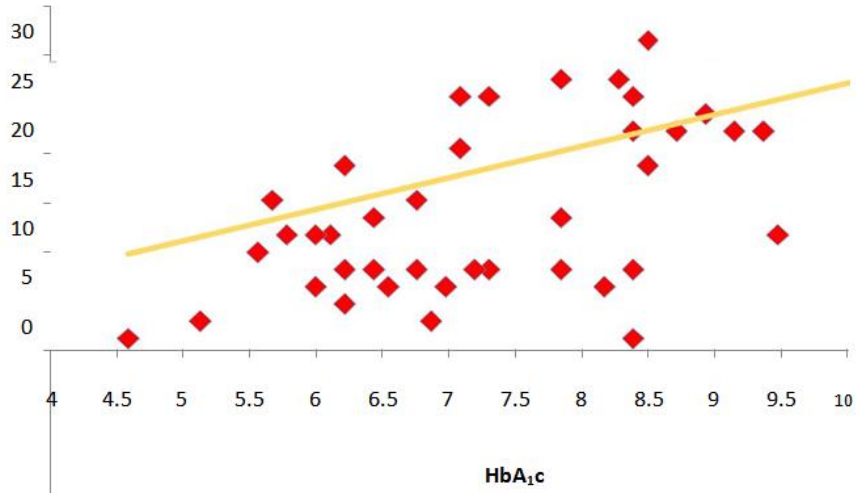
Pearson Chi-Square = 21.819** P < 0.0001significant

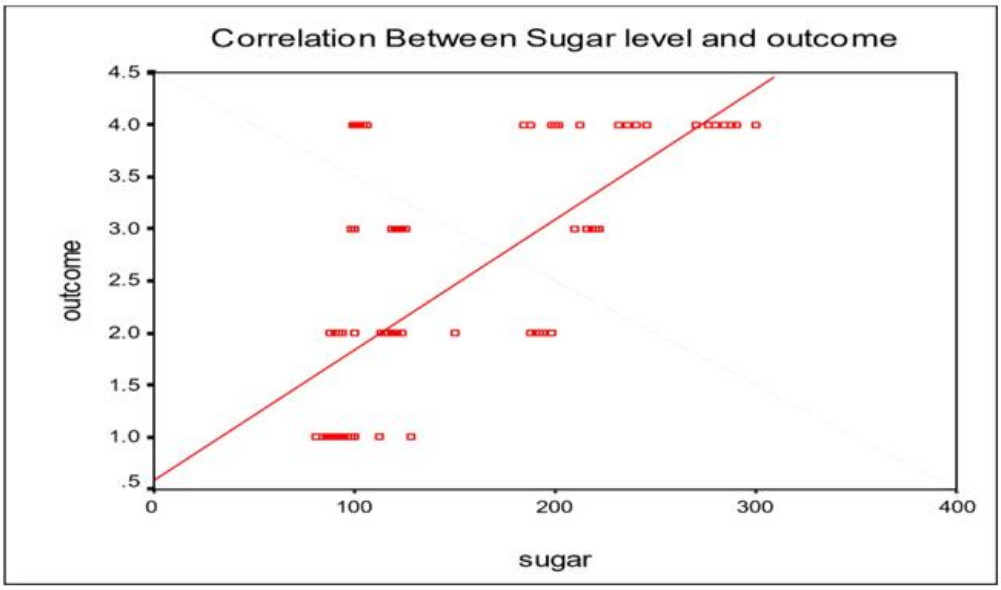


Comparison of Clinical Outcome & RBS



CORRELATION BETWEEN NIHSS Vs HbA_1c





V. Discussion

Age, Sex and Risk Factors:

In our study of fifty patients majority of them belonged to male sex showing a male preponderance which is commonly seen in most studies. Majority of the patients (Fifteen) were between the age group of 51 to 60. Among the fifty patients 32 had hypertension, 34 had diabetes, 29 had hypercholesterolemia, 3 had previous history of myocardial infarction, and one female patient had atrial fibrillation. More than two third of the male patients were smokers and one half had history of alcohol intake. 36 patients had right sided weakness and 24 patients had left sided weakness.

Glycemic status:

Among the fifty patients in our study group, 30 patients had elevated admission day blood glucose level and 20 patients had normal blood glucose values. Diabetes was noticed in 32 patients and stress hyperglycemia in another 9 patients. Stress hyperglycemia amounted to more than one third of the patients.

Severity of stroke:

Severity of stroke was assessed with NIH Stroke scaling system. Admission day hyperglycemic patients had a higher score when compared to Euglycemic patients, which was statistically significant with $p = 0.0001$. Among the admission day hyperglycemic patients uncontrolled diabetes patients had the highest mean NIHSS. Hence an elevated blood sugar at the time of stroke resulted in severe stroke.

Size of stroke:

The size of the lesion was analyzed with the help of CT scan brain. Most of the euglycemic patients had small sized infarcts whereas majority of the admission day hyperglycemic patients had large sized lesion with edema and midline shift. These data's were statistically significant with $p = 0.001$. Hyperglycemia by virtue of increased anaerobic metabolism, increased brain lactate, impaired mitochondrial function, vascular disease, increased free radical production, increased expression of c-fos and cox-2 causes severe brain injury and large sized infarcts. Hyperglycemia can disrupt the blood brain barrier resulting in large hemorrhage and hemorrhagic transformation of infarcts.

Outcome of stroke:

In this study of fifty acute stroke patients, euglycemic patients had a better outcome when compared to admission day hyperglycemic patients. Euglycemic patients had a better recovery after acute stroke. Seventy two percent of euglycemic (patients including treated) had a good functional recovery. On the contrary only three percent of admission day hyperglycemic patients had good functional recovery at the end of thirty day follow up.

Early inpatient mortality was high in admission day hyperglycemic patients. Fifty percent of the admission day hyperglycemic patients died within the first thirty days. In the euglycemic patients the early case fatality rate was only fifteen percent. Hence there was a threefold increased risk of early mortality in admission

day hyperglycemic patients when compared to euglycemics. Poor outcome was noticed in thirty eight percent of admission day hyperglycemic patients and in three percent of euglycemic patients.

This study of fifty acute stroke patients shows that admission day elevated blood glucose level was associated with a high early mortality rate and an increased risk of poor functional recovery.
These data's were statistically significant with $\chi 2 = 21.819$ and $p = 0.0001$.

In the ischemic stroke group early mortality rate was 2.07% in euglycemic patients and 14.8 % in hyperglycemic patients. Poor outcome was noticed in 3.18 % in euglycemics and 38.3 % in hyperglycemics. Hence hyperglycemia was associated with an increased early mortality rate and poor functional outcome in ischemic stroke group which was also statistically significant.

Our study clearly shows a positive correlation ($r = 0.71$, $p = 0.01$) between admission day sugar value and the outcome of stroke. Higher admission day elevated blood glucose level had increased mortality and high risk of poor functional recovery.

Comparison with other studies:

According to Perttu J. Lindsberg and Risto o Roine hyperglycemia was noted in two third (66%) of all ischemic stroke patients. In our study hyperglycemia was noticed in 60% of patients with ischemic stroke. In their study known diabetes and newly diagnosed diabetes contributed one third of cases (33%). In our study the same group contributed to 62 %.

A study published in European Journal of Neurology, 2002 concluded that elevated glucose level after acute stroke is associated with higher stroke severity than those with normal level. The mean NIHSS was 5.6 in euglycemics and 14.5 in hyperglycemic patients in our study.

In the journal of clinical endocrinology and metabolism, 2002 a study confirmed that patients with newly detected hyperglycemia had a significant higher early mortality and a lower functional outcome than patients with a history of diabetes or normoglycemia. Our study in fifty acute stroke patients had the same results.

Sarah E capes et al analyzed thirty two similar studies and concluded that hyperglycemic patients had three fold increased early mortality than euglycemic patients. After ischemic stroke admission hyperglycemia was associated with three fold increased 30 day mortality than euglycemics.

In our study, ischemic patients, who had elevated admission day glucose level experienced a three and a half fold increased early mortality than euglycemics. Similar results were noticed in non diabetic patients. Non diabetic stress hyperglycemic patients with ischemic stroke had three and a half fold increased early mortality when compared to euglycemics. In the diabetic group since the sugar value before the onset of stroke was not known, the effect of stress in diabetic group could not be studied.

The study clearly shows an increased early mortality rate and poor functional recovery in patients with diabetes and stress hyperglycemia when compared to euglycemics. Hence there is an urgent need to confirm the improvement in these patients by normalizing blood sugar. Several trails are now under way to improve the outcome of Stroke by normalizing the blood glucose with human recombinant insulin. Stephan M. Vinychuk et al showed that administration of insulin to patients with hyperglycemia improves functional recovery and vital activity of mild to moderate ischemic stroke patients. However, other clinical benefits of the insulin therapy remain to be determined.

VI. Conclusion

There is a linear correlation between admission day hyperglycemia and ischemic stroke in its severity, size and outcome. The combined diabetics and stress hyperglycemics were found to have larger sized severe stroke and poor functional outcome in the form of increased mortality. There is a good correlation between admission day glucose level and the outcome in ischemic stroke. Admission day elevated glucose level was a significant predictor of mortality and poor functional outcome after stroke. Hence restoration of normoglycemia as soon as possible should be encouraged. In the interim, we should farewell with adhering to good general stroke management, normalization of body temperature, fluid balance and hemodynamics or we may otherwise risk the favorable outcome even in the patients with normoglycemia.

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