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Original Article

Glycated Hemoglobin Level is Associated with Neurological and Functional Outcome in Acute Ischemic Stroke

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Abstract

Introduction: Among all the neurologic diseases of adult life, stroke ranks first in frequency and importance. Stroke is one of the leading causes of mortality and morbidity worldwide. Approximately 20 million people each year will suffer from stroke and of these 5 million will not survive.

Materials and Methods: An observational study of 90 acute ischemic stroke (AIS) patients, presenting within 24 h of onset, was under taken. Patients were divided into three groups, non-diabetic (glycated hemoglobin [HbA_{1c}] <5.7%), pre-diabetic (HbA_{1c} 5.7-6.4%), and diabetic (HbA_{1c} ≥6.5%) on the basis of HbA_{1c} levels. Neurological status was assessed by NIHSS (National Institutes of Health Stroke Scale) score on admission and on day 7/discharge which ever was earlier. Post-stroke functional impairment was assessed by Modified Rankin Scale (MRS) on day 7/discharge whichever was earlier. Neurological outcomes were neurological improvement defined as four-point decrease in NIHSS during hospitalization or a 0 point status on NIHSS on day 7 or at discharge and neurological deterioration defined as ≥1 point increase in NIHSS during hospitalization. A poor functional outcome was defined as death (MRS 6) or dependency (MRS 2-5).

Results: The average age of the patients was 55.88 ± 11.67 years. The average HbA_{1c} level of AIS patients on admission was 6.61% ± 2.06%. Neurological improvement was noted in non-diabetic group as there was decrease in mean NIHSS score from admission to day 7. Neurological deterioration was noted in pre-diabetic and diabetic groups as there was increase in mean NIHSS score from admission to day 7. Poor functional outcomes as defined by higher MRS score on discharge, were noted in prediabetic and diabetic patients.

Conclusion: HbA_{1c} level is an important tool to know the prognosis in AIS. Both diabetes and pre-diabetes are associated with poor neurological and functional outcome as compare to non-diabetes in AIS.

Key words: Acute ischemic stroke, Glycated hemoglobin level, MRS, NIHSS

INTRODUCTION

Among all the neurologic diseases of adult life, stroke ranks first in frequency and importance. The common mode of expression of stroke is a relatively sudden occurrence of a focal neurologic deficit. Strokes are broadly categorized as ischemic or hemorrhagic. Ischemic stroke is due to the occlusion of a cerebral blood vessel and causes cerebral infarction.[1] Stroke is one of the leading causes of mortality and morbidity worldwide. Approximately 20 million people each year will suffer from stroke and of these 5 million will not survive.[2] Developing countries account for 85% of global deaths from stroke.[3] Stroke is also a leading cause of functional impairments, with 20% of survivors requiring institutional care after 3 months and 15%-30% being permanently disabled.[4]

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Diabetes is an established risk factor for the development of cardiovascular diseases, including stroke. The risk of stroke in diabetic patients is twice as high as in non-diabetic

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people in a general population.[5] Furthermore, if stroke occurs in diabetic patients, their outcomes are less favorable than in non-diabetic patients. A large number of studies have demonstrated residual neurological deficits and functional outcome to be worse compared with non-diabetics; consequently, hospital and long-term mortality were worse in diabetic patients compared with non-diabetics.[6]

Pre-diabetes is an intermediate metabolic state between normal glucose metabolism and type 2 diabetes, representing a high risk of developing type 2 diabetes in the future. Up to 70% of the patients with pre-diabetes may develop type 2 diabetes. Pre-diabetes comprises impaired fasting glucose and/or impaired glucose tolerance and/or impaired glycated hemoglobin (HbA_{1c}). The risk of developing type 2 diabetes is approximately 0.7% per year in normoglycemic individuals, whereas patients with impaired fasting glucose or impaired glucose tolerance have a yearly risk of 5-10%. The transition from pre-diabetes to type 2 diabetes usually takes several years but may also be more rapid. Patients with pre-diabetes do not only have an increased risk of type 2 diabetes but also of cardiovascular diseases, including stroke and recurrent stroke. There is a growing recognition that patients with pre-diabetes should be treated more aggressively.[7]

HbA_{1c} level reflects the mean glucose control range for the previous 2-3 months in patients with or without diabetes mellitus. HbA_{1c} level is widely recommended as the therapeutic guideline for the prevention of cardiovascular complications in patients with diabetes. Recently, published clinical practice recommendations from the American Diabetes Association advocate the use of a HbA_{1c} level greater than 6.5% for the diagnosis of diabetes, largely on the basis of the established association between HbA_{1c} level and microvascular complications. Compared with fasting glucose, HbA_{1c} has higher repeatability, can be tested in a non-fasting status, and is a relatively stable marker for glucose level.[8] The following levels of HbA_{1c} were used to diagnose diabetes;[9] normal: <5.7%, pre-diabetes: 5.7-6.4%, diabetes: 6.5% or higher.

The role of HbA_{1c} in the prediction of ischemic stroke in non-diabetic subjects is not clear. Different HbA_{1c} levels in patients with acute stroke has different neurological impairment on admission and on discharge, prognosis are also different, showing that a higher blood HbA_{1c} levels have a more serious neurological impairment and the prognosis is worse. The aim of the present study was to investigate the association between HbA_{1c} on admission, and neurological and functional outcomes after acute ischemic stroke (AIS).

MATERIALS AND METHODS

This was an observational study done in the Department of Medicine, Dr. B.R.A.M. Hospital Raipur on 90 patients of AIS admitted in Wards, MICU and ICCU between August 2014 and September 2015. Patients were selected based on the inclusion criteria which included, all AIS patients irrespective of diabetic status, presented within 24 h from onset, confirmed by non-contrast computed tomography (NCCT) head, not confirmed by NCCT but having neurological symptoms. All AIS patients, presented after 24 h from onset, with hemorrhagic stroke, previous history of stroke, cerebellar/brain stem infarction, with cardioembolic ischemic stroke, transient ischemic attack defined as, focal neurologic deficit that lasts for <24 h, is presumed to be of vascular origin and is confined to an area of the brain or eye perfused by a specific artery, were excluded from study. Patients in whom stroke was clinically diagnosed, repeat CT was performed after 3 days to confirm ischemic stroke, if scan was negative for ischemic stroke, then the patient was excluded from the study group. The study was approved by the Ethical Committee of Institute. Written informed consent was taken from all patients. A complete history, physical examination, and systemic examination were done in all patients. Five milliliters venous blood was taken at the time of hospital admission for subsequent measurement of admission blood glucose level, HbA_{1c} level, and other routine examinations. After taking blood samples, all patients were sent for urgent NCCT head. Diabetic status was assigned on the basis of the history of diabetes or treatment with hypoglycemic agents or elevated HbA_{1c} or persistent/marked hyperglycemia. Patients were divided into three groups on the basis of HbA_{1c} levels. Group I having HbA_{1c} values <5.7%, i.e., (non-diabetic); Group II having HbA_{1c} values 5.7-6.4% (pre-diabetic), and Group III having HbA_{1c} values ≥6.5% (diabetic). The severity of neurologic impairment was evaluated by the National Institutes of Health Stroke Scale (NIHSS) score, on admission and after day 7/during discharge whichever was earlier. The functional status was evaluated by Modified Rankin Scale (MRS) on day 7/discharge which ever was earlier. Neurological outcomes were neurological improvement defined as four-point decrease in NIHSS during hospitalization or a 0 point status on NIHSS on day 7 or at discharge and neurological deterioration defined as ≥1 point increase in NIHSS during hospitalization. A poor functional outcome was defined as death (MRS 6) or dependency (MRS 2-5).

All continuous variables were expressed as mean ± standard deviation; all data were analyzed using *t*-test or the Chi-square test by the SPSS 13.0 software package. $P < 0.05$ was considered statistically significant. The HbA_{1c} level was

determined by high-performance liquid chromatography method.

RESULTS

The average age of the patients was 55.88 ± 11.67 years. 58 (64.4%) patients were males and 32 (35.6%) patients were females. The male to female ratio was 3:2. A total of 72 (80%) patients were present in 40-69 years age group. Out of this, maximum (28) were in 60-69 years age group. 42 (46.7%) patients were diabetic and 48 (53.3%) were non-diabetic. 18% patients were newly diagnosed and 21% were pre-diabetics out of total patients. The average HbA_{1c} value of AIS patients on admission was 6.61% ± 2.06%. 46.7% patients had HbA_{1c} value ≥6.5% (diabetic), 32% had <5.7% (non-diabetic), and 21% patients had 5.7-6.4% (pre-diabetic). There was no significant effect of gender on HbA_{1c} level in AIS patients ($P > 0.05$). HbA_{1c} level increased with increase in age of patients. There was no significant ($P > 0.05$) effect of gender on severity of stroke as assessed by NIHSS score on admission and day 7 and prognosis after 7 day of stroke. The severity of stroke (assessed by increase in mean NIHSS score) and poor prognosis and dependency (assessed by higher mean MRS score) increased for older age patients. On admission, severe stroke was present in diabetic patients, as there was significant ($P < 0.05$) increase in mean NIHSS score, and pre-diabetics had non-significant ($P > 0.05$) increase in mean NIHSS score, as compare to non-diabetic patients. On day 7/discharge, severe stroke was present in both diabetic and pre-diabetic patients as there was significant ($P < 0.05$) increase in mean NIHSS score as compared to non-diabetic patients. Both diabetic and pre-diabetic patients had significant ($P < 0.05$) higher mean MRS score as compared to non-diabetic patients. Neurological improvement was noted in non-diabetic group, as there was decrease in mean NIHSS score from admission to day 7. Neurological deterioration was noted in pre-diabetic and diabetic groups as there was increase in mean NIHSS score from admission to day 7. Poor functional outcomes as defined by higher MRS score on discharge were noted in pre-diabetic and diabetic patients. Higher admission HbA_{1c} levels were associated with raised blood pressure, dyslipidemia and raised blood sugar levels.

DISCUSSION

The mechanism by which poor glycemic control before onset is associated with unfavourable outcome of ischemic stroke is unclear. There is possible hypothesis regarding the association between HbA_{1c} level and outcomes. Persistent hyperglycemia is thought to be associated with the expansion of infarct volume and worse functional outcome.[10] Admission hyperglycemia has been independently associated with outcome both in patients with and without diabetes.[11] One of the proposed mechanisms is that hyperglycemia itself probably results in neurotoxicity and induces a procoagulant state.[12]

Our study showed, a significant association between glycated hemoglobin level and neurological and functional outcomes. As the HbA_{1c} level increased from non-diabetic to diabetic, neurological improvement decreased and neurological deterioration increased. Similarly, poor functional outcomes were noted for higher HbA_{1c} levels. After adjusting age and sex, neurological severity, blood sugar, dyslipidemia and hypertension, in HbA_{1c} level increased from nondiabetic to diabetic groups. Other studies also support our results. A study done in Japan,[6] patients were categorized into four groups based on their pre-stroke glycemic control (PSGC) status defined by glycated hemoglobin level: Excellent (HbA_{1c} on admission <6.2%), good (6.2–6.8%), fair (6.9-8.3%), and poor (≥8.4%). The age- and sex-adjusted odd ratios for neurological improvement decreased substantially as PSGC status became poorer. In contrast, signs of neurological deterioration increased with poorer PSGC status. The probability of achieving neurological improvement was significantly lower, and the risk of a neurological deterioration was significantly higher in both the fair and poor PSGC groups than in the excellent PSGC group. In other study,[13] HbA_{1c}, but not glycemia was significantly correlated with acute stroke severity. In a Chinese study,[14] a higher blood HbA_{1c} levels were found to have more serious neurological impairment and the prognosis was worse after 3 months. In one of the Indian study from Baroda,[15] most patients with a better prognosis as determined by their lower NIHSS score had a lower HbA_{1c} level, and most with a worse prognosis as per their higher NIHSS score had a higher HbA_{1c} level. Tables 1 and 2, shows the significance of neurological and functional outcomes in our study and other similar studies. In contrast to other studies, our study had more number of diabetic (HbA_{1c} ≥6.5) patients, i.e., 42 (46.7%). This higher number in diabetic patients may be due to the fact that our institute is the only tertiary care center for Chhattisgarh state. Limitation of our study is short term (7 days) follow-up after AIS.

CONCLUSION

Diabetes is a known risk for poor neurological and functional outcomes, which was again confirmed by this study but pre-diabetes had also poor neurological and functional outcomes as compared to non-diabetes in AIS patients. Hence, HbA_{1c} level should be determined in every AIS patients to know the prognosis and for further treatment plan after stroke.

Table 1. HbA_{1c} level and mean NIHSS score on admission & on day 7/discharge and mean MRS score on discharge in Acute Ischemic Stroke (AIS) patients

Group	HbA_{1c} level (%)	Mean NIHSS score on admission	Standard deviation	T test	P value
I (Non diabetic) N=29	<5.7	6.51	± 3.9		*
II (Prediabetic) N=19	5.7-6.4	7.52	± 2.8	1.46	0.164
III (Diabetic) N+9 = 42	≥6.5	10.66	± 4.2	4.15	<0.001
		Mean NIHSS score on day 7/discharge			
I (Non diabetic) N=29	<5.7	4.10	± 4.1		*
II (Prediabetic) N=19	5.7-6.4	8.15	± 4.8	3.09	0.003
III (Diabetic) N=42	≥6.5	12.73	± 5.4	7.19	<0.001
		Mean MRS score on discharge			
I (Non diabetic) N=29	<5.7	1.8	± 1.0		*
II (Prediasbetic)N=19	5.7-6.4	3.1	± 1.2	3.99	<0.001
III (Diabetic) N=42	≥6.5	3.9	± 1.0	8.21	<0.001

*Group I patients (nondiabetic) were taken as reference for comparing group II (prediabetic) and group III (diabetic) patients.

Table 2. Several studies with P values of neurological and functional outcome

Studies	P value of Neurological outcome by NIHSS score	Remark
Masahiro Kamouchi, et, al,	<0.001	Highly significant
Clara Hjalmarsson et al,	0.042	Significant
Guo Shuangxi1, et al,	0.019	Significant
Suresh Hirani et al,	0.018	Significant
Our study	<0.001	Highly significant
	P value of Functional outcome by MRS score	
Masahiro Kamouchi, et, al,	<0.001	Highly significant
Clara Hjalmarsson et al,	0.024	Significant
Guo Shuangxi1, et al,	0.028	Significant
Our study	<0.001	Highly significant

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