Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 08, 2024

STUDY OF ASSOCIATION BETWEEN GLYCOSYLATED HEMOGLOBIN AND ITS CLINICAL IMPLICATIONS IN ICU PATIENTS

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Received Date: 02/07/2024 Acceptance Date: 13/08/2024

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Abstract

Background: HbA1c is a marker of long-term glycemic control in patients with diabetes mellitus (DM) and allows clinicians to estimate the recent mean blood glucose concentration of a patient. In present study, we aimed to study association between glycosylated hemoglobin and its clinical implications in ICU patients at a tertiary hospital. **Material and Methods:** Present study was single-center, prospective, observational study, conducted patients of age above 18 years old, admitted to medical intensive care unit (ICU). We divided patients into two separate subgroups as patients with HbA1c < 6.5% & patients with HbA1c ≥ 6.5 %. **Results:** 137 patients (68.5%) have HbA1c < 6.5 and 63 patients (31.5%) have HbA1c≥ 6.5%. Amongst the 200 cases admitted in ICU, 157 (78.5%) patients are non-diabeticand43 (21.5%) patients are known cases of diabetes. Majority of patients 118 (59%) admitted in ICU were male and 82 (41%) were female. The association between glycosylated hemoglobin and length of stay in ICU is statistically not significant. (p =0.872). 93 (46.5 %) patients from group HbA1c < 6.5 % and 47 (23.5 %) patients from HbA1c > 6.5% group needed mechanical ventilation. The association between glycosylated hemoglobin and incidence of need of mechanical ventilation in ICU is statistically not significant. (p=0.33) The association between glycosylated hemoglobin and number of days on mechanical ventilation in ICU is statistically not significant (p=0.919). 33 (16.5 %) patients from group HbA1c < 6.5 % and 17 (8.5 %) patients from HbA1c > 6.5% group needed hemodialysis. The association between glycosylated hemoglobin and incidence of hemodialysis in ICU is statistically not significant (p =0.66). **Conclusion:** The present study does not reveal significant finding between glycosylated hemoglobin with various clinical aspects and outcome like mortality, need of mechanical ventilation and hemodialysis in critically ill patients.

Keywords: glycosylated hemoglobin, mortality, need of mechanical ventilation, critically ill patients, ICU care

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 08, 2024

Introduction

Diabetes has become a major healthcare problem in India. As per International Diabetes Federation, it is estimated that every fifth diabetic patient in the world would be an Indian. This immense public health problem will have a reflection on demographic of intensive care population. In a retrospective review 11% of all intensive care unit (ICU) admission in a general medical/surgical unit were diabetic.[1]

HbA1c is a marker of long-term glycemic control in patients with diabetes mellitus (DM) and allows clinicians to estimate the recent mean blood glucose concentration of a patient.[2] International expert committee appointed by American Diabetes Association recently introduced HbA1c as a diagnostic criterion for diabetes, suggesting that a level of ≥ 6.5 % is consistent with a diagnosis of diabetes and a level of 5.7% to 6.4% with a diagnosis of prediabetes.[3]

Hyperglycemia is a common complication of critical illness. Hyperglycemia may be due to preexisting and known diabetes or increased resistance to insulin due to stress of injury or critical illness. Initially it was considered to be part of the adaptive stress-response which is beneficial for survival. Glycosylated hemoglobin allows differentiation of patients with stress hyperglycemia from those with DM on admission and help the clinician to categorize patients metabolically.[4] It is deemed essential to differentiate the effects of premorbid diabetes on the outcome of critically patients unrelated to the degree of hyperglycemia on admission. In present study, we aimed to study association between glycosylated hemoglobin and its clinical implications in ICU patients at a tertiary hospital.

Material And Methods

Present study was single-center, prospective, observational study, conducted in Department of medicine, at MGM Medical College and Hospital, Aurangabad., India. Study duration was of 2 years (Sept 2021 to Aug 2023). The study was initiated after obtaining approval from the institutional ethics committee.

Inclusion criteria

- Age above 18 years old, admitted to medical intensive care unit (ICU), willing to participate in present study

Exclusion criteria

- Patients with previously diagnosed case of hemoglobinopathy.
- Patients with hemoglobin level < 10g/dl.
- Patients that have received more than or equal to two units of packed cell volume 48 hours prior to glycosylated hemoglobin sampling.

Details of the study were explained to all patients in their own language and written informed consent was obtained from all. Patient demographics, medical history, past history of diabetes, patient previously suffering from hemoglobinopathy, whether received blood transfusion 48 hours prior to ICU admission and APACHE II score on ICU admission. All the patients were prospectively followed till death or discharge from ICU. During their stay in ICU, glycosylated hemoglobin was measured on admission and its impact on length of ICU stay, need of mechanical ventilation, number of days on mechanical ventilation and final outcome (death/ discharge) was prospectively observed.

A venous blood was obtained from each patient and was collected into EDTA-containing tube. Whole blood samples are hemolyzed on the VITROS 5, 1FS and VITROS 4600. Chemistry Systems and the VITROS 5600 Integrated System.

Data was collected and compiled using Microsoft Excel, analyzed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 08, 2024

variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

Results

137 patients (68.5%) have HbA1c < 6.5 and 63 patients (31.5%) have HbA1c≥ 6.5%. Amongst the 200 cases admitted in ICU, 157 (78.5%) patients are non-diabeticand43 (21.5%) patients are known cases of diabetes.

Table 1: Distribution of cases admitted in ICU

	No. of cases	**Percentage**
Glycosylated Haemoglobin		
HbA1c < 6.5%	137	68.50 %
HbA1c ≥ 6.5%	63	31.50 %
Diabetic Patients		
Yes	43	21.50 %
No	157	78.50 %

Majority of patients 118 (59%) admitted in ICU were male and 82 (41%) were female.

Table 2: Gender Distribution

Gender	**Glycosylated Haemoglobin**		**Chi-square P value**
	HbA1c < 6.5% (N1=137)	**HbA1c≥ 6.5% (N2=63)**	
Male (118)	84(42%)	34(17%)	0.3265
Female (82)	53(26.5%)	29(14.5%)	

More than half that is 107 (53.5 %) patients from HbA1c < 6.5 % and 47 (23.5 %) patients fromHbA1c≥ 6.5 % had LOS (length of stay) between 1-10days in ICU. 22 (11 %) patients from HbA1c < 6.5 % and 12 (6%) patients from HbA1c ≥ 6.5 % had LOS between 11-20 days in ICU. 7 (3.5 %) patients from HbA1c < 6.5 % and 3 (1.5 %) patients from HbA1c ≥ 6.5% had LOS between 21-30 days in ICU. Only 1 % of each group had LOS more than 31 days in ICU. The association between glycosylated hemoglobin and length of stay in ICU is statistically not significant. (p =0.872)

Table 3: Length of stay in ICU.

Length of Stay in ICU (in days)	**Glycosylated Hemoglobin**	
	HbA1c < 6.5% (N1=137)	**HbA1c≥ 6.5% (N2=63)**
1-10	107(53.5%)	47(23.5%)
11-20	22(11%)	12(6%)
21-30	7(3.5%)	3(1.5%)
>31	1(0.5%)	1(0.5%)
P value	0.872	

93 (46.5 %) patients from group HbA1c < 6.5 % and 47 (23.5 %) patients from HbA1c > 6.5% group needed mechanical ventilation. The association between glycosylated hemoglobin and incidence of need of mechanical ventilation in ICU is statistically not significant. (p=0.33)

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Table 4: Need of Mechanical Ventilation

	Need of Mechanical Ventilation	
Glycosylated Hemoglobin	Yes	No
HbA1c<6.5% (N1=137)	93(46.5%)	44(22%)
HbA1c≥ 6.5% (N2=63)	47(23.5%)	16(8%)
Chi-square test	0.3354	

More than half that is 117 (58.5 %) patients from HbA1c <6.5%and53(26.5%) patients from HbA1c≥ 6.5% were on mechanical ventilation between1-10 days in ICU. 14 (7 %) patients from HbA1c < 6.5 % and 8 (4 %) patients from HbA1c ≥6.5%wereonmechanical ventilation between 11-10days in ICU. 5(2.5 %) patients from HbA1c < 6.5 % and 2 (1 %) patients from HbA1c ≥ 6.5 % were on mechanical ventilation between 21-30 days in ICU. Only 1 % patients from HbA1c < 6.5 % and no patient from HbA1c ≥ 6.5 % was on mechanical ventilation for > 31 days in ICU. The association between glycosylated hemoglobin and number of days on mechanical ventilation in ICU is statistically not significant (p=0.919).

Table 5: Number of days on mechanical ventilation in ICU.

Days on Mechanical Ventilation	**Glycosylated Hemoglobin**	
	HbA1c<6.5% (N1=137)	**HbA1c≥ 6.5% (N2=63)**
0-10	117(58.5%)	53(26.5%)
11-20	14(7.0%)	8(4.0%)
21-30	5(2.5%)	2(1.0%)
>31	1(5.0%)	0(0.0%)
P value	0.9196	

33 (16.5 %) patients from group HbA1c < 6.5 % and 17 (8.5 %) patients from HbA1c > 6.5% group needed hemodialysis. The association between glycosylated hemoglobin and incidence of hemodialysis in ICU is statistically not significant (p =0.66).

Table 6: Incidence of hemodialysis in ICU

Glycosylated Hemoglobin	**Yes**	**No**
HbA1c<6.5% (N1=137)	33(16.5%)	104(52%)
HbA1c≥ 6.5% (N2=63)	17(8.5%)	46(23%)
Chi-square test	0.6603	

Amongst 200 patients in ICU, 137 are from HbA1c< 6.5% group from them101 were discharged (50.5%) and 36 (18%) patients succumbed to death. Another HbA1c ≥ 6.5% group had 63 patient, 39 (19.5%) were discharged and 24 (12 %) patients succumbed to death. The association between glycosylated hemoglobin and impact on mortality in ICU is statistically not significant (p =0.23).

Table 7: Mortality in ICU.

Glycosylated Hemoglobin	**Discharge**	**Death**
HbA1c < 6.5% (N1=137)	101 (50.5%)	36 (18%)
HbA1c≥ 6.5% (N2=63)	39 (19.5%)	24 (12%)
Total	140 (70%)	60 (30%)
Chi-square test	0.2381	

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Discussion

Glycosylated hemoglobin (HbA1c), the commonly used clinical test to estimate mean blood glucose levels, offers a reliable indication of glycemic control over the past 2 to 3 months. This correlation makes it a valuable tool for diagnosing diabetes and evaluating the effectiveness of treatment.[5] New red blood cells contain less glucose-bound hemoglobin when entering the circulation. A brief increase in blood glucose levels can cause nonenzymatic synthesis of aldimines, which proportional to glucose concentration.[6] Apart from diagnostic purposes, the HbA1c level also predicts diabetes complications because it reflects the more harmful glycation sequelae of diabetes, such as microvascular and macrovascular complications.[7] The association between hyperglycemia and mortality is thought to be influenced by the presence of diabetes mellitus (DM).

In order to clarify the observed association between HbA1c and various clinical implications in ICU patients in the present study, we divided patients into two separate subgroups as patients with HbA1c < 6.5% & patients with HbA1c ≥ 6.5 %.

Cases with HbA1c < 6.5 % were 137 (68.5%) and HbA1c>6.5%were63 (31.5%). In a study conducted by Kumar DS *et al.*,[8] out of 281 patients admitted to the ICU for more than 48 hours, 157 patients (55.9%) had an HbA1c level below 6.5%, while 124 patients (44.1%) had an HbA1c level above 6.5%.

In a study by Alghamdi AS *et al.*,[9] a positive correlation was reported between age and HbA1c levels. Mean age was higher in the group with HbA1c ≥ 6.5% (56.23 ± 10.03 years) compared to those with HbA1c < 6.5 % (52.14 ± 13.10 years), which was statistically significant.

The prevalence of diabetes increased significantly among elderly patients. Several factors may contribute to this age-related increase in HbA1c levels. As muscle mass decreases with age, the ability to metabolize glucose is affected, leading to increased insulin resistance and higher blood glucose levels. Consequently, HbA1clevels also rise with age.[10]

In our study amongst 200 patients in ICU, 36(18%) patients died from HbA1c< 6.5% group and 24 (12%) patients died from HbA1c ≥ 6.5%. The impact of glycosylated hemoglobin on mortality of ICU patient was found statistically insignificant.

According to, Egi *et al.*,[11] demonstrated that higher mean glucose levels (>180 mg/dl) during ICU stay are associated with lower hospital mortality in patients with higher HbA1c levels (>7%) compared to those with lower HbA1c levels (<7%). Plummer *et al.*,[12] found that in critically ill patients, acute hyperglycemia increases mortality in those with previously adequate glycemic control but not in those with prior hyperglycemia. The predicted mortality curves were not significant for patients with HbA1c levels <6% and between 6% and 7%, likely due to the strong association between APACHE II scores.

According to study by Krinsley *et al.*,[13] the premorbid diabetic status impacts the relationship of the three domains of glycemic control to risk of mortality in critically ill patients. Study done by, Kumar D S *et al.*,[8] showed the overall mortality from the ICU was 38.07%. ICU mortality was higher in patients in the HbA1c ≥ 6.5% group compared to the HbA1c < 6.5%group. These findings were similar to the study by Farah R *et al.*,[14] They observed that 30-day all-cause mortality was significantly higher in patients with high levels of HbA1c (≥6%) levels.

Prior study done by, Kim HJ *et al.*,[15] found that the incidence of composite post-operative morbidity and mortality end points was higher in patients with HbA1c ≥ 7.0%.[(36)] In this study, 46.5 % of patients from group HbA1c <6.5 % and 23.5 % of patients from HbA1c > 6.5 % group needed mechanical ventilation. Need of mechanical ventilation and Glycosylated Hemoglobin of patients are independent to each other. In a study by Kompoti M. *et al.*,[16] it was observed that patients with elevated HbA1c levels required a longer

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duration of mechanical ventilation. The study indicated that a higher proportion of patientswithHbA1c levels above 6.5% needed mechanical ventilation, showing a significant correlation between mechanical ventilation use and elevated HbA1c.

Our study demonstrated that more than half that is 53.5% patients from HbA1c < 6.5 % and 23.5 % patients from HbA1c ≥ 6.5% stays 1-10 days in ICU. No statistically significant association between length of stay in ICU and Glycosylated hemoglobin was found. The association of HbA1c with length of hospital stay (LOS) has conflicting results.

In a study carried out by Almogati *et al.*,[17] showed that patients there was no significant difference in the total LOS in HbA1c < 7 % compared to HbA1c ≥ 7 % patients (P=0.367). Another study by M Sami Walid *et al.*,[18] showed contrasting results, there were significant differences in the LOS between the "No DM" and "Sub clinical" groups (P<0.05).

Elevated level of HbA1c has been identified as a significant risk factor for cardiovascular diseases and stroke. Even an increase of 1% in HbA1c concentration was associated with about 30% increase in all-cause mortality and 40% increase in cardiovascular or ischemic heart disease mortality.[19]

Similarly, Lee YS *et al.*,[20] reported that elevated HbA1c levels were linked to severe organ dysfunction and an increased need for vasopressors in diabetic patients with sepsis. This study also found a higher requirement for vasopressors in diabetic patients with elevatedHbA1c levels.

Prior study done by, Kim HJ *et al.*,[15] found that the incidence of composite postoperative morbidity and mortality endpoints was higher in patients with HbA1c ≥7.0% . Multivariable logistic regression analysis identified congestive heart failure, chronic kidney disease, moderate or greater mitral regurgitation, preoperative hemoglobin level and preoperative HbA1c ≥7.0% as independent factors associated with composite postoperative morbidity and mortality. The study suggests that an elevated preoperative HbA1c (≥7.0%), which reflects long-term glycemic control, negatively impacts outcomes.[21]

Conclusion

The present study does not reveal significant finding between glycosylated hemoglobin with various clinical aspects and outcome like mortality, need of mechanical ventilation and hemodialysis in critically ill patients. These negative correlations of current study are probably due to certain limitations. This study included a small sample size of 200 patients and out of which patients with HbA1c ≥ 6.5 were only 63 (31%). Comparative group of HbA1c ≥ 6.5 was significantly low as compared to HbA1c < 6.5. The cutoff value of HbA1c of 6.5 is considered as a good glycemic control, hence complication rates might be as good as non-diabetics. If we would have used cut off value of HbA1c of 8 or higher we might have got significant correlation of HbA1c with clinical aspects in ICU patients. The role of glycosylated hemoglobin in critically ill patients requires additional study with larger sample size and higher cutoff of HbA1c for accumulating evidence regarding its impact on morbidity and mortality in ICU patients.

Conflict of Interest: None to declare
Source of funding: Nil

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