ORIGINAL RESEARCH PAPER

General Medicine

ROLE OF HBA1C & ADMISSION BLOOD SUGAR ON MORTALITY IN PATIENTS WITH ISCHEMIC STROKE

KEY WORDS:

Dr. Ismail M Haji Department Of Critical Care Medicine, Associate Professor ,institute Name : Yenepoya Medical College , Mangalore -575018.

Dr. Safdar Aftab A* Postgraduate Department Of General Medicine Institute Name: Yenepoya Medical College, Mangalore-575018 . *Corresponding Author

Dr Shaheen B. Associate Professor, Department Of Biochemistry Institue Name: Yenepoya Medical College, Mangalore-575018.

Dr Abdul Rehman Professor , Department Of General Medicine Institute Name: Yenepoya Medical College, Mangalore-575018

ABSTRACT

BACKGROUND: In ICU patients with ischemic stroke one of the common reasons for their mortality is found to be Hyperglycemia. Diabetes Mellitus itself is a risk factor that can initiate & propagate vascular events in conjunction with atherosclerosis in Ischemic stroke. The aim of this study was to evaluate relationship between admission blood sugar and HbA1c with mortality in patients with Ischemic stroke over a period of 28 days.

MATERIALS & METHODS: This is a retrospective study where data was collected from medical records of 50 diabetic patients admitted to ICU with ischemic stroke dated from April 2019 to September 2019.

Patients were further categorized depending upon their duration of stay in the hospital with cut-off of 10 days; Furthermore, a cut-off of "28 days- mortality" was taken into consideration.

Patients, who were already diagnosed with diabetes and who got admitted in medical ICU were taken as study subjects.

RESULTS: Mortality was significantly higher in patients with higher admission blood sugar values of more than 250mg/dl & lower when value was below 150mg/dl. It was noted that the survivors (72%) had their mean admission blood sugar values close to 260mg/dl whereas non-survivors (28%) mean admission blood sugar level was found to be 343mg/dl. It was also noted that patients with good glycemic control (HbA1C < 8) had better chances for survival. The survivors (72%) had mean HbA1c level of 9.06 and non-survivors (28%) had mean HbA1c level of 10.67. Both the mean values being so close to each other with difference of just 1% further emphasizes the fact that with each 1% increase in HbA1C the mortality risk rises by 10 fold.

CONCLUSION: A significant association was confirmed between admission blood sugar levels & mortality in diabetic patients with Ischemic stroke. Furthermore, this association was found to be affected by HbA1c i.e. chronic glycemic status.

INTRODUCTION

Hyperglycemia is associated with poor outcome & increased mortality in critically ill patients [1]

Hyperglycemia increases rate of infection, endothelial damage, mitochondrial damage in hepatocytes & tissue ischemia due to acidosis & inflammation. [2] Researches done previously have shown that hyperglycemia is associated with morbidity & mortality in ICU patients and further supported by the results showing correction of high blood sugar can improve mortality rates. [3,4]

Recent studies showed that the association between high blood sugar & mortality rate could be influenced by the presence of chronic hyperglycemia [5, 6]. American Diabetes Association has suggested HbA1c of 6.5% for diagnosis of diabetes. [7, 8] Other researches have also shown the importance of fasting blood glucose, fasting insulin levels & HbA1c levels on the stroke severity & outcome. [9,10,11]

There have been few studies done to understand the impact of HbA1c status on mortality & hyperglycemia among ischemic stroke patients. Few studies showed a linear relationship between HbA1c & death rate [12] whereas others have shown a J-shaped association, [13] but most of them have shown an increased risk of mortality when encountered with high HbA1c levels [13]. Hence HbA1c status is like a predictor for the association between chronic sugar control & patient mortality rate. It has been estimated that with each 1% increase in HbA1c concentration 15-20% cardiovascular risks increases. [14] Therefore, it can be said that HbA1c does play an important role in the severity & outcome of stroke in diabetes patients. Also 15-25% of ischemic stroke patients are known to be pre-diagnosed with diabetes thereby diabetes mellitus accounting for almost one-fourth of ischemic stroke patients. [15,16]

Thus the aim of this study was to investigate the association between admission blood sugar levels & mortality following ischemic stroke in critically ill diabetic patients under ICU care; Furthermore, also to evaluate the impact of HbA1c on mortality in these critically ill patients so that the importance of need of early sugar management can be understood better.

METHODOLOGY

A total of 50 diabetic patients with ischemic stroke admitted in ICU were enrolled in this study. These patients were either on Oral Hypoglycemic Medications or on Insulin. Clearance from institutional ethical committee was obtained and data was collected from all diabetic patients admitted to ICU from April 2019 to September 2019.

Admission blood sugar and HbA1c was measured for all patients. Age, sex, duration of ICU stay, duration of DM, other co-morbidities, medication history was recorded for all patients. Other Risk factors like smoking, alcohol and hypertension history were also emphasized.

Furthermore all the 50 cases, mean admission blood sugar values and HbA1c of both Survivors and Non-survivors were compared. Mortality accounting up to 28 days was taken into consideration; Data was collected retrospectively & entered in the hospital based database.

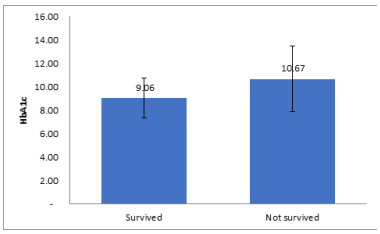
STATISTICAL ANALYSIS

The data was entered in the excel spread sheet. Descriptive statistics like frequency and proportions were used for qualitative data; mean & standard deviation were used for

quantitative data. Unpaired T test was used to test the significant difference between HbA1c and RBS levels with mortality. The level of significance was set at 5%

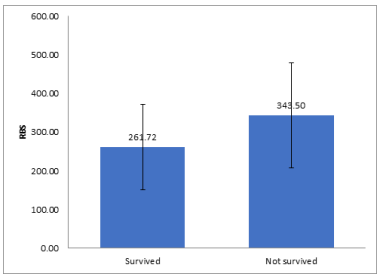
HbA1c Levels	Mortality after 28 days	N	Mean	Std. Deviation	Mean Difference	P Value*
	Survived	36	9.06	1.71	-1.607	0.017
	Non-survived	14	10.67	2.82		

*Unpaired t test



RBS values	Mortality after 28 days	N	Mean	Std. Deviation	Mean Difference	P Value*
	Survived	36	261.72	110.038	-81.778	0.032
	Non-Survived	14	343.50	135.714		

*Unpaired t test



RESULTS

- Total number of cases for the study :
- 50 diabetic patients with acute ischemic stroke.
- Out of the 50 cases, 44% of them had diabetes since 9-11years and were on treatment.
- Females were predominant accounting for 54% of cases, whereas males constituted 46% of study subjects.
- Predominant age group was between 51-60 years accounting to 26% of study subjects followed by 24% of study subjects whose age group was in the range of 61-70yrs.
- Our study showed that non-survivors had higher blood sugar values at the time of admission compared to those of survivors thus showing a significant relationship between admission blood sugar value & mortality rate.
- High mortality rate was seen when admission blood sugar levels were more than 250mg/dl & low mortality rate when admission blood sugar levels was less than 150mg/dl.

Mortality rates for the Admission blood glucose levels are as follows—

Admission blood sugar level	Mortality Rate
<150mg/dl	7%
150-200mg/dl	7%
200-300mg/dl	15%
>300mg/dl	71%

- Among the 50 cases, only 14% had good glycemic control (HbA1c <8) whereas 86% had poor glycemic control (HbA1c >8).
- Mortality rate for the patients with good glycemic control was 2% and for those with poor glycemic control was 98%.
- Mortality rates for the admission HbA1c levels are as follows-

Admission HbA1c level	Mortality rate
</=7	7%
7-8	7%
8-9	28%
>9	57%

The survivors (72%) had mean HbA1c level of 9.06 and non-survivors (28%) had mean HbA1c level of 10.67. Both the mean values being so close to each other with difference of just 1% further emphasizes the fact that with each 1% increase in HbA1C the mortality risk rises by 7 to 8 folds.

We also found in our study that among the 72% of survivors, 54% of them stayed for less than 10 days in ICU, whereas among the 28% of non-survivors almost 20% of them had stayed in ICU for more than 10 days. Though this result seems promising regarding association between prolonged ICU stay and mortality, additional data is required for this particular context.

DISCUSSION

Diabetes mellitus is a well-known predisposing risk factor for Ischemic stroke. Initiating & further enhancing the atherosclerosis of intracranial & extra cranial arteries by diabetes is the generally accepted theory for ischemic stroke. Studies have shown that hyperglycemia exacerbates ischemic brain injury by accumulating lactate & acidosis in the penumbra tissue facilitating the brain infarction, brain edema formation thereby further disrupting the blood-brain barrier. [18] The mechanisms by which hyperglycemia affects outcomes could be due to suppressive effects on immune function and an associated increased risk of infection, endothelial damage, hepatocyte mitochondrial damage & potentiation of tissue ischemia due to acidosis or inflam mation. [2]

Laboratory studies done previously have shown that hyperglycemia causes injury to renal tubular cells, hepatocytes & various other types of cells that have insulin-independent glucose uptake. [31-32]

Our study showed that patient's admission blood sugars & HbA1c were correlated with mortality following ischemic stroke. The same is supported by numerous studies done previously that suggested strong associations between hyperglycemia and death rate in intensively ill patients. [20]

A retrospective study of 1826 patients admitted to ICU in Stanford revealed that survival rate was less among those with high mean blood glucose levels than those who survived. Mortality rate was 9.6% among those with a mean blood glucose level of 80-99mg/dl, 29.4% among those with 180-199mg/dl & 42.5% in patients with mean blood glucose of more than 300mg/dl, thereby concluding that a stepwise effect was seen causing increased mortality as mean blood glucose levels rose. [28]

In our study also, we could appreciate the same stepwise increase in mortality rate i.e. mortality rate was 7% among those with a mean blood glucose level of <150mg/dl, 7% among those with 150-200mg/dl, 15% among those with 200-300mg/dl & 71% in patients with mean blood glucose level of more than 300mg/dl.

Another study done in intensively ill patients showed that acute hyperglycemia is strongly related with high mortality in patients with previously uncontrolled hyperglycemia. [22]

Similar findings were seen in our study too, that is hyperglycemia and mortality association was influenced by previous hyperglycemia. In patients with HbA1c > 8 mortality

was significantly higher i.e. 98% as compared to patients with HbA1c level <7, only 2% was the mortality rate.

Similar positive associations are seen in many studies between HbA1c and mortality [23]. The possible mechanism for this is toxicity caused by advanced glycated end products, oxidants, hyper osmolality on tissues and changes in cell signaling pathways like alteration in kinases and phospholipids. Li W et al. showed that in Men with HbA1c >11% & in Women with HbA1c>10% mortality was signifi cantly higher as compared in patients with HbA1c level of 6.5-6.9%.[25] A risk adjusted analysis of 120 traumatic patients showed that patients with HbA1c>6% were 4.5times more likely to have poor outcomes than those with HbA1c<6% [26], this effect of preexisting hyperglycemia on mortality in critically ill patients could be due to high cytokine concentration that causes inflammation.
Furthermore Kizer et al [27], studied the relationship between HbA1c and stroke and emphasized that strict control of HbA1c might be a benefit for stroke prevention for the patients with diabetes. Similarly many other studies have shown that high HbA1c level has negative impact on DM patients admitted in ICU.

To understand the clear-cut association between these 3 parameters i.e chronic hyperglycemia, acute hyperglycemia and mortality among ischemic stroke diabetic patients further more studies are to be done so that definitive conclusion can be reached thereby supporting the conclusion that has been made by previous studies.

CONCLUSION

Our study demonstrated that high Blood sugar levels during admission were associated with higher mortality rate. Furthermore this association was affected by chronic hyperglycemia. Higher mortality rate was seen in diabetic patients with poor glycemic control. Since both acute & chronic hyperglycemias are correctable abnormalities in the diabetic patients, they should be managed accordingly as a therapeutic target so as to improve the outcome in hospital admitted patients & reduce the mortality.

REFERENCES-

1. Donald E, Griesdale G, Russell J, de souza, Rob K, Heyland, et al. Intensive Insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009;180:821-27
2. Treggiari MM, Karir V ,Yanez ND, Weiss NS, Daniel S. Intensive Insulin therapy & mortality in critically ill patients. Crit care. 2008; 12:29-30.
3. Bochicchio GV, Sung J, Joshi M, Bochicchio K, Johnson SB, Meyer W, Scalea TM. Persistent hyperglycaemia is predictive of outcome in critically ill trauma patients. Journal of Trauma & Acute Care Surgery. 2005 May 1; 58(5):921-4
4. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control & mortality in critically ill patients. Jama. 2003 Oct 15; 290(15):2041-7
5. Sato H, Carvalho G, Sato T, Latterman R, Matsukawa T, Schricker T. The asspciation of preoperative glycaemic control, intra operative insulin sensitivity & outcomes after cardiac surgery. J Clin Endocrinol Metab. 2010; 95: 4338-44.
6. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycaemia- related mortality in critically ill patients varies with admission diagnosis. Crit Care Med. 2009;37:3001-9.
7. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan DM, Peterson CM; American Diabetes Association. Tests of glycaemia in diabetes. Diabetes Care. 2004; 27.91-S93.
8. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care. 2014; 37:14-80.
9. Hjalmarsson C, Manhem K, Bokemark L, Andersson B (2014), The role of pre-stroke glycemic control on severity & outcome of acute ischemic stroke. Stroke Res Treat 2014: 694569
10. Lawlor DA, Fraser A, Ebrahim S, Smith GD (2007) Independent associations of fasting insulin, glucose & glycated haemoglobin with stroke & coronary heart disease in older woman. PLoS Med 4 :e263
11. Roquer J, Giralt-Steinhauer E, Cerda G, Rodriguez-Campello A, Caudrado-Godia E, et al.(2015) Glycated haemoglobin value combined with initial glucose levels for evaluating mortality risk in patients with ischemic stroke. Cerebrovasc Dis 40:244-250
12. Barr EL, Bokyo EJ, Zimmet PZ, Wolfe R, Tonkin AM, Shaw JE. Continuous relationships between non-diabetic hyperglycemia & both cardiovascular disease and all-cause mortality: the Australian Diabetes, Obesity & Lifestyle study. Diabetologia. 2009; 52:415-424
13. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin , diabetes, & cardiovascular risk in nondiabetic adults. New England Journal of Medicine. 2010 Mar 4; 362 (9):800-11.
14. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL; Glycated hemoglobin, Diabetes & cardiovascular risk in nondiabetic adults. New England Journal of Medicine. 2010 Mar 4; 362(9): 800-11.
15. Michel P, Odier C, Rutgers M, et al. The Acute Stroke Registry and Analysis of Lausanne (ASTRAL): design & baseline analysis of an ischemic stroke registry including acute multimodal imaging. Stroke 2010; 41:2491-2498
16. Fuentes B, Castilo J, San Jose B et al. The prognostic value of capillary glucose levels in acute stroke : the glycaemia in Acute Stroke(GLIAS) study. Stroke 2009; 40:562-568.
17. Kasner SE, Chalela JA, Luciano JM, et al. Reliability and validity of estimating the NIH stroke scale score form medical records. Stroke 1999; 30:1534-1537.
18. Kidwell CS, Alger JR, Saver JL. Evolving paradigms in neuroimaging of the ischemic penumbra. Stroke 2004; 35:2662-2665.
19. Song EC, Chu K, Jeong SW, et al. Hyperglycemia exacerbates brain edema & perihematomal cell death after intracerebral hemorrhage. Stroke 2003; 34: 2215-2220.
20. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, Bailey M. Blood glucose concentration and outcome of critical illness: The impact of diabetes. Critical Care medicine. 2008 Aug 1; 36(8): 2249-55.
21. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 Diabetes. New England Journal of Medicine. 2008 June 12; 358(24): 2560-72.
22. Plummer MP, Bellomo R, Cousins CE, Annink CE, Sundararajan K, Reddi BA, Raj JP, Chapman MJ, Horowitz M, Deane AM. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. Intensive care medicin. 2014 Jul 1; 40(7):973-80.
23. Andersson C, Van Gaal L, Cttaerson ID, Weeke P, James WP, Couthino W, Finer N, Sharma AM, Maggioni AP, Torp-Pedersen C. Relationship between HbA1c levels & risk of cardiovascular adverse outcomes and all-cause mortality in over-weight and obese cardiovascular high-risk women and men with Type 2 diabetes. Diabetologia. 2012 Sep 1 ;55(9): 2438-55.
24. Zhang Y, Hu G, Yuan Z, Chen L. Glycosylated hemoglobin in relationship to cardiovascular outcomes and death in patients with Type 2 Diabetes: A systematic review and meta-analysis. 2012; 31; 345-361.
25. Li W, Katzmarzyk PT, Horswell R, Wang Y, Johnson J, Hu G. HbA1c and all-cause mortality risk among patients with Type 2 Diabetes. International journal of cardiology. 2016 Jan 1; 202:490-6.
26. Lionel KR, John J, Sen N. Glycated hemoglobin A: A predictor of outcome in trauma admissions to intensive care unit. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine. 2014 Jan; 18(1):21.
27. Kizer JR, Wiebers DO, Whisnant JP, Galloway JM, Welty TK, et al. (2006) Glycemic level and future stroke in Type 2 DM : The strong heart study. Circulation 114:444-446.
28. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogenous population of crirtically ill patients. Mayo Clin Proc 2003; 78: 1471-1478 (PMID : 14661676 DOI: 10.4065/78.12.1471)
29. Kaukonen KM, Bailey M, Egi M, Orford N, Glassford NJ, Marik PE, Bellomo R. Stress hyperlactatemia modifies the relationship between stress hyperglycemia and outcome: A retrospective observational study. Crit Care Med 2014; 42: 1379-1385.
30. Green JP, Berger T, Garg N, Horeczko T, Suarez A, Radeos MS, Hagar Y, Panacek EA. Hyperlactatemia affects the association of hyperglycemia with mortality in nondiabetic adults with sepsis. Acad Emerg Med 2012; 19: 1268-1275.
31. Vanhorebeek I, Gunst J, Ellger B, Boussemaere M, Lerut E, Debaaveye Y, Rabbani N, Thornalley PJ, Schetz M, Van den Berghe G. Hyperglycemic kidney damage in an animal model of prolonged critical illness. Kidney Int 2009; 76: 512-520
32. Boonen E, Van den Berghe G. Endocrine responses to critical illness: novel insights and therapeutic implications. J Clin Endocrinol Metab 2014; 99:1569-1582.
33. Groop PH, Forsblom C, Thomas MC. Mechanisms of disease: pathway-selective insulin resistance & microvascular complications of diabetes. Nature Reviews Endocrinology. 2005 Dec; 1(2):100.
34. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic in the diabetes control & complications trial. Arch Opthalmol B. 1998; 116:874-86.