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Average Inpatient Glucose Levels during the first 72 hours, Clinical Outcomes, and Length of Hospital Stay in Patients with Acute Ischemic Stroke

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Abstract
Although admission blood glucose (BG) in acute ischemic stroke (AIS) has been linked to increased morbidity, the impact of continuing hospital hyperglycemia is less clear. We examined mean blood glucose (MBG) during the first 72 hours, length of hospital stay (LOHS), and number of inpatient complications (NIC) in patients with AIS. The following data was retrospectively collected on 70 adult patients with AIS admitted to Palmetto Health Richland Hospital, Columbia, South Carolina, USA, over a 3-month period: age, gender, mean blood glucose during the first 3 days, LOHS, type of diabetes treatment, and NIC (death, myocardial infarction, angina, arrhythmia, deep vein thrombosis, urinary tract infection, urosepsis, pneumonia, and respiratory failure). Patients were divided into 3 groups based on their MBG in mg/dl: Group A <120 (n=33), Group B 121-180 (n=21), and Group C >180 (n=16). The average age was 67.8 years and 51.4%, had a known history of diabetes. The average LOHS per patient in the 3 groups was 6.12, 7.38, and 11.5 days with a statistically significant association with level of hyperglycemia ($p<0.05$). The average NIC per patient increased in the 3 groups (0.18, 0.29, and 1.0 respectively) and showed a significant relationship with MBG ($p<0.01$). In AIS, higher BG during the first 72 hours of hospitalization is associated with increased LOHS and NIC regardless of a history of diabetes. These findings do not necessarily imply causality. Optimal glucose targets in hospitalized patients with AIS are currently undetermined. Glycemic and nonglycemic interventions should be studied for their impact on clinical outcomes, LOHS, and cost.

Key Words: *cerebrovascular accident, acute ischemic stroke, diabetes, hyperglycemia, length of hospital stay*

Introduction

Atherosclerotic cerebrovascular disease is one of the leading causes of death among Americans.[1] The role of diabetes mellitus as a risk factor for acute ischemic stroke (AIS) is well-established. The Framingham study demonstrated that the risk of ischemic cerebrovascular accident (CVA) was higher in patients with diabetes than those without diabetes.[2] Transient ischemic attacks are 3 times more likely in diabetic patients, and the risk of stroke is twice as high.[3] Patients with elevated blood glucose (BG) levels on admission to the hospital, whether having known diabetes or not, have poorer recovery and more adverse outcomes after AIS than their non-diabetic counterparts.[4] Furthermore, intensive glucose control employing the aggressive use of insulin may protect the nervous system in critically ill patients.[5]

The state of South Carolina, USA, has a high prevalence of diabetes and stroke.[6,7] We conceived this study to assess the relationship between these two diseases in a large community teaching hospital by studying the association between glycemic status, hospitalization time, and adverse clinical outcomes. The primary purpose was to investigate the relationship between BG levels during the first 72 hours of hospitalization and length of hospital stay (LOHS) in patients with or without diagnosed diabetes admitted with AIS. The association between average glucose levels and morbidity and mortality in patients with AIS was examined, and the mode of therapy used for achieving glycemic control and its association with LOHS and the number of in-hospital complications (NIC) was evaluated. We subsequently reviewed the medical literature in order to glean evidence-based conclusions for glucose control in patients with AIS. We hoped that data obtained from the study would assist in addressing and implementing quality control measures for the inpatient setting and add to the current knowledge base for health care professionals who take care of patients with AIS that have co-morbid risk factors of hyperglycemia and diabetes.

Methods

We conducted an inpatient study and reviewed the relevant medical literature. The study population included adult patients (age >18 years) admitted to the Palmetto Health Richland Hospital (PHRH), a 649-bed community teaching hospital in Columbia, South Carolina, USA over a 3-month period. The project was done by a retrospective review and subsequent data analysis. The proposal and protocol were approved by the PHRH Institutional Review Board. Medical records of patients admitted to PHRH with documented AIS on brain imaging (CT, angiography, or MRI) were examined. They were categorized into 3 groups according to the degree of hyperglycemia and 3 groups according to the

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type of anti-hyperglycemic therapy received. Their inpatient course with respect to average LOHS and morbidity/mortality data was reviewed. The following parameters were measured and entered for data collection: Age, Gender, and Mean Blood Glucose (MBG) during the first 3 days of hospital stay. The latter was the time period that, in a composite manner, reflected a) ambient (outpatient) preadmission hyperglycemia, b) the effect of the acute event and hospitalization on glucose levels, and c) the impact of anti-diabetic therapy, or lack thereof, during the initial days of hospitalization. MBG was calculated by ascertaining the average of daily blood glucose levels and using the mean of the daily averages. Both laboratory and fingerstick values were included in this calculation. Three patient categories were established on the basis of the MBG: Group A <120 mg/dl, Group B: 120-180 mg/dl, and Group C: >180 mg/dl. The Average Length of Hospital Stay (LOHS) in each group (in days) was determined. With respect to the type of diabetes treatment during the critical first 3 days of hospitalization, three broad categories were defined: 1) Non-pharmacologic Group (NPG): patients on no *scheduled* medications. (note: this group will also include patients who are on "sliding-scale insulin (SSI)" or "correctional insulin" *only*, as long as they are not on oral agents or regular doses of prandial or daily basal insulin), 2) Oral-Agent Group (OAG): those treated with oral medications, with or without SSI, and 3) Insulin Treated Group (ITG): patients who are treated with scheduled daily insulin, whether or not they are on oral agents (but excluding those on SSI only. Finally, the average number of in-hospital complications (NIC) per patient was ascertained: death, cardiac events (myocardial infarction, angina, and new arrhythmia), deep vein thrombosis, urinary tract infection, urosepsis, pneumonia, and respiratory failure. If the patient had a "placement issue" (for example, transfer to a nursing home or assisted living facility), the additional days of waiting were not counted in LOHS. The last day of hospital stay in these cases was when the patient was documented to be stable for discharge or transfer.

Statistical analysis was performed using the SPSS 11.0 statistical package. MBG, LOHS, and NIC were expressed as mean. Multiple stepwise logistic regression analysis was used to assess the effect of increasing MBG on LOHS and NIC. Statistical significance was defined as $p<0.05$ and all results were 2-tailed.

Finally, we reviewed the medical literature for current knowledge and recommendations regarding the management of hyperglycemia and diabetes in patients with stroke by performing a PubMed database search of the last 10 years.

Results

Seventy subjects with AIS (40 female, 30 male) were studied. The average age was 67.8 years. Based on their MBG, the 3 groups had the following number of subjects each: Group A (<120 mg/dl) = 33, Group B (120-180 mg/dl) = 21 and Group C (>180 mg/dl) = 16. There was a female preponderance in all groups. Forty-two subjects, or 60%, were African American (AA), while 28, or 40%, were Caucasian. Slightly more than half of the patients (36, or 51.4%) carried a previous diagnosis of diabetes mellitus upon admission to the hospital. As expected, there were more patients with known diabetes in Group C (14 of 16, or 87.5%) than in Group A (5 of 33, or 15%) or B (4 of 17, or 19%). Hemoglobin A_1c (HbA_1c) levels were ordered by the treating physicians in only a handful of patients (data not shown), even in those known to have diabetes or on glucose-lowering medications upon admission The 3 groups showed the following statistics respectively: patients treated with insulin 18.2%, 62%, and 94%, average LOHS in days 6.12, 7.38, and 11.5 ($p<0.05$), number of major medical complications as represented by total NIC 6, 6, and 16. The average NIC per patient increased progressively as the BG level increased (0.18, 0.29, and 1.0 respectively in the 3 groups, $p<0.01$). There were no deaths in patients with AIS during the time period studied. Thus a known history of diabetes, frequency of insulin use, time spent in the hospital and major medical complications all showed a correlation with higher average glucose levels measured during the first 72 hours of hospitalization.

Discussion

Our study reaffirms the association of hyperglycemia with inpatient morbidity in patients with CVA and AIS. Although prior studies have looked at the admission BG as a prognostic factor in stroke, our glucose data extends this to the average glucose during the first 3 days of hospital stay. Since the BG was an average of the first 72 hours of hospitalization, it likely represented in part, the ambient outpatient glycemia, implicating it as a risk factor for both the occurrence of AIS and hospital prognosis. The MBG also reflected the effectiveness of antihyperglycemic therapy during the first 3 days of hospitalization and its association with subsequent clinical course and NIC. However, causality can only be inferred and not proven, although it is tempting to speculate that intensive inpatient glycemic control could reduce adverse clinical outcomes, shorten hospital stay, and decrease cost of care.[8] It is interesting to note that in our study population, over half of acute strokes occurred in patients with diagnosed diabetes, while others with hyperglycemia may have also had previously undetected diabetes or hospital-induced acute hyperglycemia.

Our data also reveals a direct and significant relationship between degree of BG elevation and average LOHS. This observation is likely a consequence of the reported association between hyperglycemia and poor clinical outcomes in inpatients that lead to increased hospital stay.[4] It would be intuitive to conclude that increased complications and prolongation of hospital stay result in increased cost of care, adding to the economic burden of diabetes on society. Our data shows that African Americans with AIS had worse glycemic control and longer and more complicated hospital course than Caucasians, a disparity previously pointed out in other studies of the effect of race on diabetes-related outcomes.[9]

Although our analysis has the limitations of being a

Table 1: Data on 70 patients admitted with acute stroke

Parameter	Mean Blood Glucose (MBG) in mg/dl			Association with hyperglycemia (p value)
	Group A <120	**Group B 120-180**	**Group C >180**	
Number of Subjects	33	21	16	-
Race:				
African American (60%)	16	15	11	-
Caucasian (40%)	17	6	5	
Other	0	0	0	
Average Age (overall av. 67.8)	68.2	67.4	67.6	-
Female (57%)	19	11	10	
Male (43%)	14	10	6	-
Mean Blood Glucose (MBG) in mg/dl	103.3	149.2	213.6	-
Known diabetes (36/70, or 51.4%)	5	17	14	-
Anti-hyperglycemic Therapy:				
Non-pharmacologic Group (NPG)	20	5	1	
Oral-Agent Group (OAG)	7	3	0	-
Insulin Treated Group (ITG)	6	13	15	
Average Length of Hospital Stay (LOHS) per patient in days	6.12	7.38	11.5	<0.05
Total Number of In-hospital Complications (NIC)*	6	6	16	-
Average NIC per patient	0.18	0.29	1.0	<0.01

Table 2: Association between hyperglycemia and acute stroke*

Established Points

- Admission hyperglycemia, whether or not with known diabetes, is closely associated with adverse clinical outcomes in stroke patients
- Hospital-induced blood glucose elevations ("stress hyperglycemia") is strongly linked to a poor inpatient prognosis as well
- Higher average daily glucose levels lead to longer hospital stay and increase cost of care
- An intravenous insulin drip used in critically ill patients with stroke can lower blood glucose more effectively than subcutaneous or 'sliding scale' insulin

Areas of Controversy or Ongoing Research

- What are the desirable blood glucose targets to be aimed for in patients with acute stroke?
- What are the pathophysiologic mechanisms, concomitant risk factors, and the relative contributions of glycemic and nonglycemic interventions on stroke outcomes during hospitalization?
- A clear mortality benefit of aggressive insulin therapy has yet to be determined, including the therapeutic time window, what level to intervene at, and how long to use it for

Guidelines for Clinicians who manage Stroke Patients in the Hospital

- Elevated admission glucose in acute stroke patients should alert providers to possible increased morbidity, longer hospital stay, and presence of underlying undiagnosed diabetes
- Glycosylated hemoglobin (HbA_1c) should be obtained in all patients presenting with hyperglycemia (>180 mg/dl) to detect undiagnosed diabetes, assess outpatient glucose control, and plan future therapy
- The American Diabetes Association blood glucose goals should be used in stroke patients *(generally <180 mg/dl).* However, more aggressive lowering in the ICU (less than 110 mg/dl) can increase the risk of hypoglycemia and death
- Insulin is the drug of choice for hospitalized patients with stroke
- Intravenous insulin protocols can be used in an ICU setting to reduce glucose effectively but are relatively labor-intensive and may increase the risk of hypoglycemia.

retrospective review, it reemphasizes the impact of glucose intolerance and diabetes on the development of atherosclerotic cerebrovascular disease and the hospital course of patients with AIS. An important observation was that patients with higher glucose levels, many of whom had an already established diagnosis of diabetes, were more likely to be treated with insulin during early hospital stay, albeit not very successfully. Factors related to the latter may have included "carry-over" of outpatient hyperglycemia, possibly aggravated by the stress of illness and requiring a

period of dose adjustment in subjects with diabetes naïve to insulin, and lack of a target-oriented basal-bolus approach with insulin. Use of sliding scale insulin alone with its known disadvantages likely makes this scenario worse; notably, such subjects were excluded from the ITG based on the study criteria. Other factors that we did not measure in our analysis (hypertension, dyslipidemia, smoking, etc) may co-segregate with worse diabetes control in a particular individual and play a pathophysiologic role in AIS occurrence and outcomes.

In an attempt to provide meaningful points and "take-home messages" for practicing clinicians on the subject, we reviewed the recent medical literature (past 10 years) for guidelines regarding management of elevated blood glucose in hospitalized patients with acute stroke. As mentioned above, hyperglycemia as a poor prognostic factor after AIS and its association with adverse clinical outcomes have been well-documented.[8,10,11] Surprisingly, there is a paucity of interventional data and recommendations on treatment targets for blood glucose and optimal methods to achieve them. A meta-analysis suggested that mortality could be reduced if blood glucose could be normalized after acute stroke.[12] A large British trial concluded that a "Glucose-Potassium-Insulin" infusion protocol significantly reduced plasma glucose concentrations and blood pressure in post-stroke hyperglycemia, but was not associated with significant clinical benefit.[13] The study was, however, underpowered and alternative results could not be excluded. Lately, Bruno et al. showed that an intravenous insulin protocol corrected hyperglycemia during acute cerebral infarction significantly better than usual care without major adverse events.[14] More recently, the Glycemia in Acute Stroke (GLIAS) Study concluded that a glucose level $\geq$ 155 mg/dL at any time within the first 48 hours after stroke onset, was associated with poor stroke-related outcomes independently of stroke severity, infarct volume, diabetes, or age. [15]

Of note, data on HbA_1c was too sparse to be gathered and reported in our study. Although more than half of the patients had known diabetes, very few had HbA_1c levels ordered or drawn. The admission HbA_1c level can assist in assessing the degree of outpatient glycemic control, uncover possible pre-existing and undiagnosed diabetes, and guide inpatient therapy.[16] It can also prove useful in discharge planning and choosing the appropriate home-going pharmacologic regimen. More importantly, a high HbA_1c can alert the clinician to the presence of suboptimally treated hyperglycemia within the past 3-4 months and its association with a poorer prognosis and a longer hospital course in patients with stroke.

It is important, however, to keep two caveats in mind. First, association does not imply a cause-and-effect relationship. The connection between elevated BG level and poor outcomes is provocative and hypothesis-generating, but does not prove causality. Second, the optimal range of blood glucose levels in hospitalized patients is yet to be determined and remains controversial. The recently reported findings from the multinational Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial are particularly relevant.[17] The study compared intensive and conventional glycemic control in 6104 patients in the intensive care unit. Intravenous insulin was used to achieve a blood glucose level of 81 to 108 mg/dl in the intensive group and 144 to 180 mg/dl in the conventional group. Rather surprisingly, there was an absolute increase in the rate of the primary end point, death at 90 days, with intensive glucose control vs. with conventional control (27.5%, vs. 24.9%), although neurologic complications were lower in the intensive arm (21.7%) compared to conventional control (25.8%). As expected, there was a significantly higher rate of severe hypoglycemia in the intensive-control group than in the conventional-control group (6.8% vs. 0.5%). It is, therefore, unclear whether hyperglycemia is a pathophysiologic factor or simply a marker for adverse outcomes in hospitalized patients, including those with acute stroke. Observational data supports lowering of extremely uncontrolled glucose levels, but caution should be exercised in overly enthusiastic attempts at attaining euglycemia in critically ill patients.

A summary of knowledge and recommendations from recent data and detailed reviews on the subject [10,11,15,16,17, 18, 19] are shown in Table 2.

Conclusions and Practical Points (Table 2)

Both diabetes and atherosclerotic stroke are major health concerns in communities worldwide. Our analysis at a large community teaching hospital shows the average BG level during early hospitalization, regardless of a known diagnosis of diabetes, to be a significant risk factor for length of time spent in the hospital and major inpatient medical complications in patients with AIS. A higher level portends a worse clinical prognosis and longer inpatient stay. Although many questions remain unanswered in the medical literature, hyperglycemia in acute stroke patients should alert clinicians to the presence of underlying undiagnosed diabetes and the possibility of increased complications and longer hospital stay. HbA_1c should be obtained in all patients presenting with hyperglycemia (random BG >180 mg/dl) to look for undiagnosed diabetes, evaluate outpatient glucose control, and plan treatment. While consensus on optimal glucose levels in stroke patients is still evolving, it is prudent to follow the American Diabetes Association blood glucose goal of less than 180 mg/dl for hospitalized patients. Insulin is the preferred medication for attaining glucose targets for inpatients. In the ICU setting, intravenous insulin drip can reduce glucose better than other therapies but requires expertise and may increase hypoglycemia risk and mortality. Based on the results of the NICE-SUGAR study released recently, aiming for a target BG of less than 110 mg/dl in the ICU is controversial, and may even be detrimental.

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