Effect of Glycemic Variability on Mortality in ICU Settings: A Prospective Observational Study

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Abstract

Background: Evidence suggests a role of glycemic variability in intensive care unit (ICU) mortality. Objective: To assess effect of glycemic variability and ICU/in-hospital mortality. Design: Prospective, observational study. Setting: A 20-bedded medical/surgical ICU in a tertiary care hospital. Patients: Critically ill patients requiring life-support measures admitted to the ICU between November 1, 2015 and December 30, 2016 with hyperglycemia (random blood sugar (RBS) ≥200 mg%) and sequential organ failure assessment (SOFA) scores ≤9. Patients were put on predefined insulin infusion protocol, multiple glucose values were obtained, and mean blood glucose level (MGL) was calculated as their simple arithmetic mean. Standard deviation (SD) of MGL and coefficient of variation (CV) of glucose (derived as a percentage of SD to mean blood glucose) were then calculated for each patient and analyzed for all-cause death during hospitalization period. Results: A total of 123 patients having a mean age of 65.12 ± 16.27 years, mean SOFA score of 5.76 ± 1.76, and mean HbA1c of 6.22 ± 0.73% were included. MGL was 160.65 ± 24.19 mg/dl, SD 33.32 ± 15.08 mg/dl, and CV 20.74 ± 8.43. Deceased as compared to survivors had higher MGL (163.76 ± 24.85 vs 155.62 ± 22.43 mg/dl, P = 0.068) and higher glycemic variability (SD 38.92 ± 14.44 vs 25.06 ± 12.27 mg/dl, P < 0.001 and CV 23.69 ± 7.9 vs 15.98 ± 6.87, P < 0.001). Interestingly, more patients having higher CV at lower MGL (85.7%) died as compared to those having lower CV at higher MGL (55.6%). Conclusions: High glycemic variability is associated with increased ICU/in-hospital mortality. Outcome of patients having less glycemic variability even with slight hyperglycemia may be better than those having tight glycemic control but higher glycemic variability. Insulin protocols need to be in place for management of hyperglycemia in critical care setting aiming for adequate glycemic control as well as minimizing glycemic variability.

Keywords: Coefficient of variation of glucose, glycemic variability, mean blood glucose

Introduction

Hyperglycemia is a common occurrence in critical care setting (approximately 75% may have blood glucose concentrations >110 mg/dl; about 12% may have blood glucose >200 mg/dl at admission)[1,2] and it occurs in patients with critical illness having previously diagnosed or undiagnosed diabetes mellitus (DM) and due to stress hyperglycemia.[3] Hyperglycemia has been shown to have a strong and consistent relation with mortality.[3] A landmark single-center study[4] showed that intensive insulin therapy aiming at blood glucose levels of 80–110 mg/dl could reduce the morbidity and mortality of critically ill patients. Multiple studies thereafter investigated the effect of tight glycemic control on mortality and morbidity and reported contradictory results.[5-10] However, these studies have focused on average glucose concentration of the affected patients and did not emphasize much on the effect of hypoglycemia and glycemic variability on mortality and morbidity. Lately, three domains of glycemic control have emerged in the management of critically ill patients, i.e., hyperglycemia, hypoglycemia, and glycemic variability that must be addressed to achieve optimized outcome.[11,13] Recently, few studies have shown that glycemic variability is strongly associated with short-term intensive care unit (ICU) mortality.[14-17] However, the effect of glycemic variability needs to be further explored prospectively in a heterogeneous ICU population. Hence, we undertook this
Materials and Methods

This study was a prospective observational study conducted in the ICU (having round the clock availability of an intensivist) at a tertiary care hospital of Indian armed forces between November 1, 2015 and December 30, 2016. Twelve dedicated nurses in rotation collected data prospectively on every patient. Following thorough history and examination of the patient, blood samples were drawn under complete aseptic precautions for admission random blood glucose (RBG) by glucometer. An RBG of >200 mg/dl was reconfirmed with a second sample sent to the central lab. Patients were included after confirmation of RBG values ≥200 mg/dl from the lab. A diagnosis of DM was made in all patients known to have prior DM or having HbA1c >6.5% along with hyperglycemia. Samples were also drawn for biochemistry and HbA1c was tested if patients were included in the study. All patients ≥18 years old with hyperglycemia (RBG ≥200 mg/dl), Sequential Organ Failure Assessment (SOFA) score of ≤9, requiring life support and consenting to be subjects for the study were enrolled for the study. Exclusion criteria were SOFA score >9, patients not on life support, patients not meeting criteria for diagnosis of hyperglycemia, and unwillingness.

A predefined insulin protocol was used in all patients for management of hyperglycemia. Point of care blood glucose measurements using glucometer were taken hourly till RBG stabilized between 150 and 200 mg/dl (three consecutive readings), then every 2 hourly for initial 24 h and 4 hourly thereafter for next 24 h. Insulin infusion was stopped when blood glucose was recorded to be <100 mg/dl, glucose tested hourly, and infusion was restarted when it was >150 mg/dl again. Hypoglycemia was defined as any blood glucose value <70 g/dl. Patients were switched to multiple subcutaneous insulin injections when they were hemodynamically stable and alert, accepting orally, blood glucose and insulin infusion rates stable for at least 48 h. Thereafter, blood glucose monitoring was done as a seven-point profile (pre- and 2 h postmeal and between 2 and 3 am).

Mean blood glucose level (MGL) was calculated as arithmetic mean of all recorded glucose values for the given patient. Standard deviation (SD) of MGL and coefficient of variation (CV) of glucose (derived as a percentage of SD to mean blood glucose) were calculated for each patient as described earlier.[4] The primary endpoint for the analysis was an all-cause hospital mortality (defined as death before hospital discharge).

Statistical analysis was performed on SPSS program performed for Windows, version 17.0 (SPSS, Chicago, IL, USA). Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t-test, whereas the Mann–Whitney U test was used for those variables that were not normally distributed. Categorical variables were analyzed using either the Chi-square test or Fisher’s exact test. For all statistical tests, a P value < 0.05 was taken to indicate a significant difference.

Results

A total of 479 patients were admitted in ICU from November 1, 2015 to December 30, 2016. Out of these, 351 were excluded (not meeting inclusion criteria, unwilling) and 128 were enrolled in this study. Five patients were dropped and finally 123 patients were included in the analysis.

Mean age of patients was 65.12 ± 16.27 years (range: 18–93 years, distribution in Table 1) and there were 86 (70%) males. At admission, mean HbA1c was 6.22 ± 0.73% (n = 95; range: 4.5–8.4%) and SOFA score was 5.76 ± 1.76 (range: 2–9). Mean stay in ICU was 4.3 ± 1.6 days and in hospital was 11.2 ± 3.3 days. A total of 76 (62%) patients died in ICU/in hospital. Mortality rate was not significantly different (P = 0.645) between males 52 (60.47%) or females 24 (64.86%). Age-wise distribution of patients along with their outcome is depicted in Figure 1.

During ICU stay MGL was 160.65±24.19 mg/dl (range: 102–216), SD of MGL was 33.32 ± 15.08 mg/dl (range: 10–73), and CV of glucose was 20.74 ± 8.43 (range: 7–38). Comparison of various parameters between alive and deceased patients is enumerated in Table 1. Both the parameters of glycemic variability, i.e., SD and CV were noted to be higher in deceased patients as compared to alive [Table 1].

MGL was higher in the deceased as compared to survivors (163.76 ± 24.85 vs 155.62 ± 22.43 mg/dl), though it did not reach statistical significance. However, none of the six patients having MGL >200 mg/dl survived. MGL was

| Table 1: Comparison of various parameters among alive and deceased patients |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| **Parameter**               | Alive (n=47)                | Deceased (n=76)              | P                      |
|                            | Mean±SD                     | Median (IQR)                | Mean±SD                     | Median (interquartile range) |                      |
| SOFA score                 | 5.47±1.93                   | 5 (4-7)                     | 5.95±1.62                   | 6 (5-7)                     | 0.088                  |
| HbA1c (%)                  | 6.14±0.66                   | 6.10 (5.80-6.30)            | 6.26±0.77                   | 6.20 (5.83-6.48)            | 0.298                  |
| MGL (mg/dl)                | 155.62±22.43                | 138 (156-172)               | 163.76±24.85                | 163 (148-182)               | 0.068                  |
| SD (mg/dl)                 | 25.06±12.27                 | 23 (15-30)                  | 38.42±14.44                 | 37 (26-49.75)               | <0.001                 |
| CV                         | 15.98±6.87                  | 16.00 (11-19)               | 23.69±7.97                  | 14.00 (26-30.50)            | <0.001                 |
High CV of glucose was associated with higher mortality across the MGL ranges in the patients having MGL ≤200 mg/dl [Table 3]. On further subgrouping as per CV tertiles [Table 4], it was seen that even within a given range of MGL, a higher CV was associated with higher mortality though statistical significance was not achieved. Interestingly, in the lower MGL tertile (<150 mg/dl), 85.7% patients who had a higher CV (>30) died as compared to 55.6% patients having a lower CV (<15) even in a higher MGL tertile (150–200 mg/dl). This finding suggests an adverse effect of higher CV even at relatively low MGLs. Four out of 13 (30.7%) patients having a combination of low MGL (<150 mg/dl) with low CV (<15) died as compared to 10 out of 12 (83.3%) having a combination of a relatively higher MGL (150–200 mg/dl) with high CV (>15).

**Table 2:** Comparison of outcome with CV of glucose as per HbA1c levels

| HbA1c value | Outcome | P       |
|-------------|---------|---------|
|             | Overall | Alive   | Deceased |
|             | Mean±SD | Mean±SD | Mean±SD  |
| HbA1c <6.5 (n=95; 77%) | 156.11±23.81* | 152.42±23.36* | 158.56±24.61* | 0.220 for * |
|             | MGL     |         |         |
|             | CV      | 21.69±8.65** | 16.79±7.29** | 24.96±7.96** | <0.001 for ** |
| HbA1c ≥6.5 (n=28; 23%) | 176.54±6.82** | 169.11±18.06* | 179.57±18.63* | 0.181 for * |
|             | MGL     | 176.07±18.76* | 169.11±18.06* | 179.57±18.63* | 0.181 for * |
|             | CV      | 176.54±6.82** | 169.11±18.06* | 179.57±18.63* | 0.181 for * |

P <0.001 for * (MGL) and 0.021 for ** (CV) comparison.

* and ** have been used for comparison of MGL and CV in overall series respectively (result shown at the bottom of the table). * used for MGL and ** used for CV comparison as per HbA1c values. * and ** have been used for comparison of MGL and CV between alive and deceased group respectively (result shown in the rightmost column of the table). * used for MGL and ** used for CV comparison as per HbA1c values. * and ** have been used for comparison of MGL and CV between alive and deceased group respectively (result shown in the rightmost column of the table). * used for MGL and ** used for CV comparison as per HbA1c values.

**Discussion**

We studied the effect of glycemic variability on mortality in patients admitted to the ICU irrespective of cause and excluded patients with higher SOFA score so as to eliminate the confounding effect of severity of illness on mortality. In this prospective study, we have demonstrated that in critical care settings, both higher glycemic variability and higher mean blood glucose were associated with higher mortality. Deleterious effects of glycemic variability persist even with lower ambient MGL and a combination of high glycemic variability with high mean glucose seems most detrimental. Interestingly, patients having less glycemic variability at relatively slightly higher MGL (150–200 mg/dl) had better outcome than those having higher glycemic variability at lower MGL (<150 mg/dl).

Hyperglycemia is a common occurrence in critical care setting and can result from the combination of factors such as increased hepatic gluconeogenesis, increased secretion of the catabolic hormones, and resistance to hepatic and peripheral actions of the insulin.[12,13] Literature suggests that higher ambient blood glucose levels are associated with higher mortality.[14,15] and similar trend was seen in our study though it did not reach a statistical significance. This could be attributed to relatively smaller sample size, use of a standardized insulin infusion, and round the clock availability of an intensivist in the ICU. However, unfortunately, all six patients having MGL >200 mg/dl died.

A trend was noted where higher glycemic variability was found to be associated with a poorer outcome, a finding that is in accordance with the published literature.[14-17] It is not clear yet whether this is an epiphenomenon or there is a causal relationship between glycemic variability and mortality in critically ill patients. Putative mechanisms include increased oxidative stress, neuronal damage, mitochondrial damage, and coagulation abnormalities[12-15] induced by fluctuating glucose levels. An interesting observation was that slight hyperglycemia with less glycemic variability was associated with better results as compared to more stricter glycemic control with high variability. It has been shown that induced
fluctuations of glucose levels may result in apoptosis more than sustained hyperglycemia.14 Also, the adaptive cell mechanisms that are initiated in case of constant hyperglycemia are possibly overwhelmed when the hyperglycemia is varying in intensity. Whether low glycemic variability can have a protective effect also needs to be examined separately.

The strengths of our study are being prospective analysis, insulin delivery through intravenous route as per predefined protocol, mandatory round the clock availability of an intensivist, and use of already described indices of glycemic variability such as SD and coefficient of glycemic variation. Shortcomings of our study include a small sample size, single-center study, exclusion of patients with higher SOFA score, and inability to use continuous glucose monitoring system.

**Conclusions**

We have demonstrated that glycemic variability is strongly associated with mortality in critically ill patients, and patients having slight hyperglycemia with less glycemic variability fare better than those having strict glycemic control with higher glycemic variability. These findings need to be confirmed by larger multicentric trials preferably using continuous glucose monitoring system. Whether management of glycemic variability improves the outcomes or not is also needs to be elucidated in future studies; however, we recommend that institutionalized protocols should be in place for management of hyperglycemia in critically ill patients emphasizing both good glycemic control and simultaneously minimizing glycemic variability.

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**Conflicts of interest**
There are no conflicts of interest.

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