

Glycaemic Variability in Critically ill Patients: Association with ICU Mortality and Length of Stay

Authors:

Dr. Mohammad Ashraf khan¹, Aanya Chawla², Aarushi Kashyap³

¹DMC- 51963, Associate Professor, Department of Medicine, at HIMSR & HAHC Hospital, Delhi.

^{2,3}MBBS 2022 Batch, Department of Medicine, at HIMSR & HAHC Hospital, Delhi.

Corresponding Author:

Aanya Chawla, MBBS 2022 Batch, Department of Medicine, at HIMSR & HAHC Hospital, Delhi.

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ABSTRACT

Background: Blood glucose (BG) homeostasis is frequently disrupted in critically ill patients. While hyperglycaemia and hypoglycaemia are established risk factors, Glycemic Variability (GV) the degree of glucose fluctuation is emerging as a critical independent predictor of mortality. **Objective:** To determine the incidence of hyperglycaemia, hypoglycaemia, and GV and to evaluate their specific associations with ICU mortality, length of stay (LOS). **Methods:** This prospective observational study followed 50 adult patients in a combined medical-surgical ICU at a tertiary care center at Hahc hospital, New Delhi. BG was monitored via arterial sampling. GV was defined as the presence of both hyperglycaemia (>180 mg/dl) and hypoglycaemia (<60 mg/dl) during the ICU stay. **Results:** Hyperglycaemia (60%), hypoglycaemia (68%), and GV (52%) were prevalent. Mortality was 46%. All non-survivors (100%) experienced hyperglycaemia, and 95.6% exhibited high GV. Statistical analysis showed a profound correlation between GV and mortality. **Conclusion:** GV is a superior predictor of mortality compared to mean glucose levels and is strongly associated with prolonged ICU stay and increased infection rates.

Keywords: Glycaemic Variability; Critical Illness; Intensive Care Unit; Hyperglycaemia; Hypoglycaemia; ICU Mortality; Length of Stay.

INTRODUCTION

Blood glucose (BG) has emerged as an important variable in critical care. In the past, this biological marker has been largely ignored or considered as adaptive marker to the stress conditions observed in critically ill patients(1). Disruption's in normal homeostasis of blood glucose are common in critically ill patients with unfavourable outcome. While the adverse effects of hypoglycaemia have been well documented in literature (2,3,4). It was not until the landmark study by Van den Berghe et al. that showed controlling hyperglycaemia with insulin was found to be associated with improved outcome in critically ill patients(5). Three domains of glycemic control, acute hyperglycaemia, hypoglycemia, and glycemic variability are an important marker of prognostication in critically ill patients. GV may be the confounding factor in the

various tight glycemic control studies in medical and surgical patients which did not take this domain of prognostication into account and measured mean blood sugar as their target variable(6,7,8,9,10).

The American Association of clinical Endocrinologists and American Diabetes Association task force on in patient glycemic control recommended targeting a BG level between 7.8 and 10.0 mmol/l (140 and 180 mg/dl) for the majority of ICU patients(11,12). Alterations in glucose metabolism occur during critical illness and are mediated by various factors, including increased insulin resistance, change in hormone production, and activation of cytokines(13). In critically ill patients a hypermetabolic state exists(27) with the predominant cause being the intense activation of counter regulatory hormones and cytokines, such as tumour necrosis factor- α (TNF- α), interleukin(IL)-1, and IL5-6, which may be

important mediators of insulin resistance and result in hyperglycemia(28). The vast majority of patients in intensive care have stress-induced hyperglycemia (SIH), which refers to transient hyperglycemia during illness and is usually restricted to patients without previous evidence of diabetes(14).

It has been reported that pronounced hyperglycemia might lead to complications or a poor clinical outcome(15). Hyperperglycemia can cause polymorphonuclear neutrophil dysfunction(16), and decrease intracellular bactericidal(17,18) and opsonic activity(16,19) which plays a role in the increased incidence of infections in patients with hyperglycemia. High concentration of glucose in the cells can damage mitochondrial protein(20) exacerbate inflammatory pathway, modify the innate immune system, and impair endothelial function(21). High glucose concentrations also reduces vascular reactivity and endothelial nitric oxide production, which may compromise blood flow to the periphery(22). In addition, acute hyperglycemia enhances proteolysis(23) and is associated with an increased risk of cardiac complications, hemodynamic and electromyocardial disturbances, acute renal failure, and death(24,25). This study has been undertaken to find the incidence of hyperglycemia, hypoglycemia in critically ill patients and also to find the relationship between

GV and mortality in ICU, duration of ICU stay, in a tertiary care hospital.

METHODOLOGY

Study Design and Setting

This was a prospective observational study conducted at the Hakeem Abdul Hammad Centenary Hospital, New Delhi. The study focused on a combined medical and surgical ICU environment.

Inclusion and Exclusion Criteria

Inclusion

1. Adult patients aged greater or equal to 18 years.
2. Duration of ICU stay should be greater than 24 hours
3. Patients having at least six blood glucose samples in 24 hrs.

Exclusion

1. Patients aged < 18 years.
2. Patients having a duration of ICU stay < 24 hours.
3. Patients having < six blood glucose samples.
4. Patients who were readmitted to ICU within the same admission period.
5. Patients with pre-existing diabetes mellitus, hyperglycemic emergencies such as diabetic ketoacidosis, and hyperosmotic hyperglycemic syndrome or had blood glucose levels of greater than 500mg/dl.

Monitoring and Protocol

All patients underwent blood glucose testing by arterial blood sampling at the beginning of their admission, which were subsequently evaluated every 1 to 4 hours according to departmental protocol. If the blood glucose levels are greater than 180mg/dl, a protocol continuous intravenous insulin infusion were started to control the blood glucose level of 140- 180mg/dl. In case of hypoglycemia (blood glucose level less than 60 mg/dl), the insulin infusion protocol were aborted and the appropriate urgency management was commenced. All blood glucose levels were evaluated using a arterial blood gas analyser.(SIEMENS Rapidlab 1265) Patients characteristics such as Name, Medical record no., gender, Age, Diagnosis, Type of ICU admission (Medical or surgical), Blood glucose levels, Presence of infection at the time of admission, Hyperglycemia and Hypoglycemia, Type of infection during ICU stay, Insulin Infusion, Length of ICU stay and Mortality were collected and recorded. The mean blood glucose level (MGL) was calculated as the arithmetic mean of all recorded glucose values for the given patient. Standard deviation (SD) of MGL were calculated for each patient and analyzed for all-cause death and effect on duration of ICU stay.

Definitions

Glycemic Variability

Glycemic variability (GV), which refers to swings in blood glucose levels, has a broader meaning because it alludes to blood glucose oscillations that occur throughout the day, including hypoglycemic periods and postprandial increases, as well as blood glucose fluctuations that occur at the same time on different days. The broad definition of GV considers the intraday glycemic excursions, including episodes of hyperglycemia and hypoglycemia. (26)

Hyperglycemia

The term "hyperglycemia" is derived from the Greek hyper (high) + glykys (sweet/sugar) + haima (blood). Hyperglycemia is blood glucose greater than 125 mg/dL while fasting and greater than 180 mg/dL 2 hours postprandial. A patient has impaired glucose tolerance, or pre-diabetes, with a fasting plasma glucose of 100 mg/dL to 125 mg/dL. This activity reviews the pathophysiology of hyperglycemia, its presentation, complications and highlights the role of the interprofessional team in the evaluation and management of patients with this condition. (26)

Hypoglycemia

Hypoglycemia is often defined by a plasma glucose concentration below 70 mg/dL; however, signs and symptoms may not occur until plasma glucose concentrations drop below 55 mg/dL. (26)

Dysglycemia

Any abnormality in blood glucose stability.

Abbreviations

GV - Glucose variability

BG- Blood Glucose

MGL -Mean glucose level

RBS -Random Blood sugar

GLI -Glycaemic lability index

SD -Standard deviation

CV -Coefficient of variation

O/E- Mortality ratio

o/d- Odds ratio

SIH - Stress induced hyperglycaemia

TNF- α -Tumour necrosis factor- α

IL - Interleukins

G6PD - Glucose-6-phosphate

DHEA - Dehydroepiandrosterone

ICU - Intensive care unit

mg/dl - Milligram per decilitre

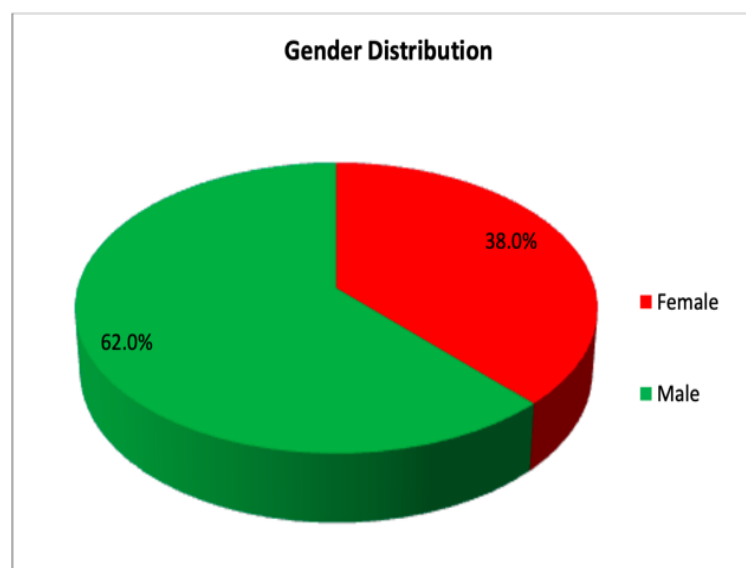
Statistical Analysis

Data were described in terms of range; mean $\pm$ SD, frequencies (number of cases) and relative frequencies (percentages) as appropriate. To determine whether the data were normally distributed, a Kolmogorov-Smirnov test was used. Comparison of quantitative variables between the study groups was done using the student t-test and Mann-Whitney U test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, the chi-square test (χ^2) test was performed and the exact test was used when the expected frequency is less than 5. A probability value (P value) < 0.05 was considered statistically significant. All statistical calculations were done using (statistical package for the social sciences) SPSS 21 version (SPSS inc., Chicago, IL, USA) statistical program for Microsoft Windows.

RESULTS

Demographic and Clinical Data

The study population (n=50) was 62% male and 38% female. Medical patients showed a significantly higher incidence of hyperglycaemia (85.7%).

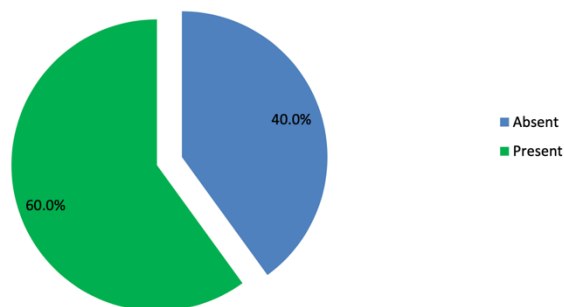


Incidence of Dysglycemia

The data revealed a high burden of glucose dysregulation:

- Hyperglycaemia (>180 mg/dl): 60%

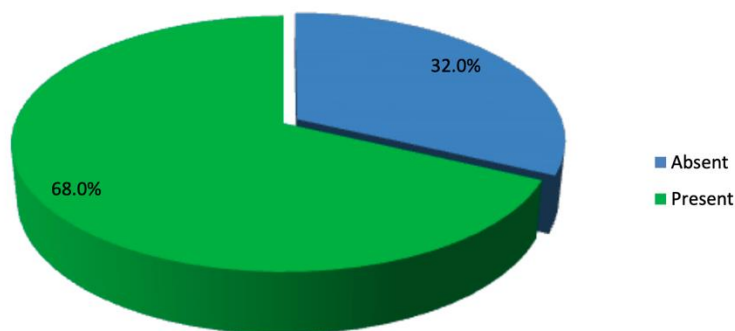
Hyperglycemia



Hyperglycemia	No. of cases	Percentage
Absent	20	40.0%
Present	30	60.0%
Total	50	100.0%

- Hypoglycaemia (<60 mg/dl): 68%

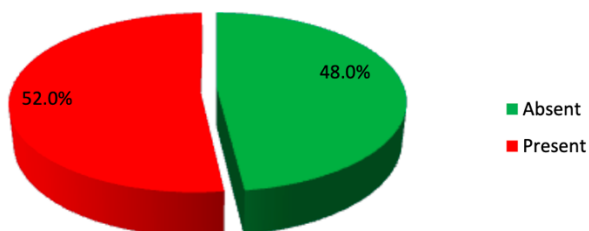
Hypoglycemia



Hypoglycemia	No. of cases	Percentage
Absent	16	32.0%
Present	34	68.0%
Total	50	100.0%

- Glycemic Variability (GV): 52%

Glucose Variability

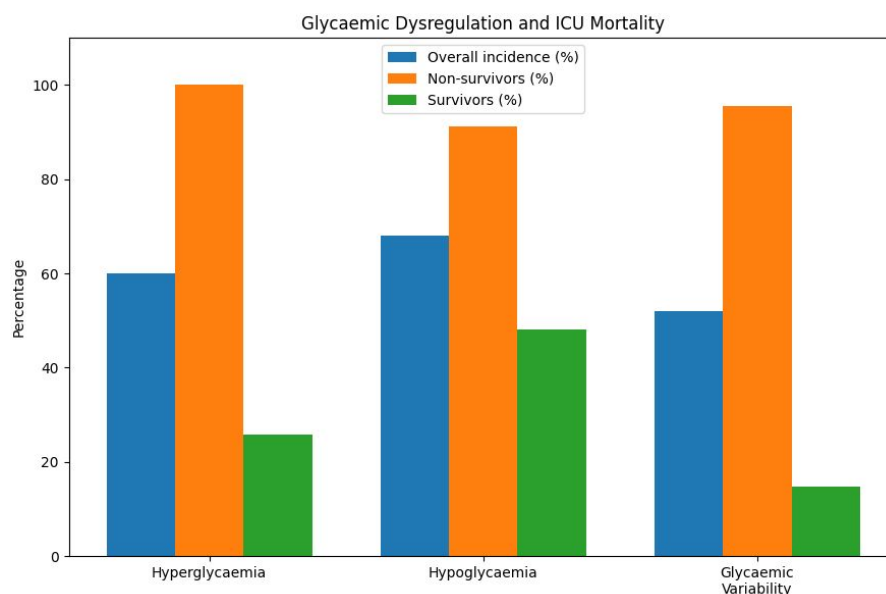


Glucose variability	No. of cases	Percentage
Absent	24	48.0%
Present	26	52.0%
Total	50	100.0%

Primary Outcome: Mortality

The association between GV and mortality was the most significant finding.

- Survivors (n=27): Only 14.8% experienced GV.
- Non-Survivors (n=23): 95.6% experienced GV.



DISCUSSION

Recent studies in the ICU setting have found detrimental effects of GV on ambulating diabetic patients. In acute settings, rapid fluctuations can lead to oxidative stress, neuronal damage, mitochondrial damage, and increase coagulation activity- all of which hamper the outcome of these patients and hence increase mortality. We studied the effects of GV on ICU mortality and length of stay, out of the 527 patients admitted to the ICU during the study period 50 met the inclusion criteria. A total of 2565 blood glucose samples were collected and MGL and SD were calculated as a measure of GV. The mean age of our study population is 47 $\pm$ 16.8 years. Our study looks at a combined medical and surgical ICU and 72% of our admissions were surgical. A total of 23(46%) patients died in the ICU which is similar to what the previous studies have reported (Manjit singh et al, Subash Todi et al and Kinsley JS). Our study established a significant association between GV and mortality in ICU ($p=0.0001$). MGL in our study was around 145 mg/dl with an SD of 51.5 MGL. Non-survivors had a higher MGL than survivors (149.21 mg/dl, SD 60.074 vs 137.92 mg/dl, SD 31.2) with a p -value of 0.024.

Just like mortality, the duration of ICU stay seemed to be linked with the MGL. The mean duration of ICU stay was 8.5 $\pm$ 4.8 days. As per our study patients with GV had greater lengths of stay in the ICU than patients without GV (10.04 $\pm$ 5.16 vs 6.92 $\pm$ 3.94 days) with a p -value of 0.021.

In our study, the incidence of hypoglycemia (BG <60 mg/dl) was 68% and that of hyperglycemia (BG > 180 mg/dl) was 60%. This is higher than the previous studies and may be explained by the smaller sample size and a single center of study. We discovered a relation between hyperglycemia or hypoglycemia with mortality at 76.6% and 61.8% respectively. Hyperglycemia was also related

to the development of infections like UTI, VAP, bloodstream infection, etc.

Our study firmly establishes the association of GV with ICU mortality and duration of ICU stay. The effects of GV on mortality is believed to be because of oxidative stress, neuronal damage, mitochondrial damage, and coagulation abnormalities; nevertheless, the exact mechanism for the same is not completely understood. We acknowledge the limitations of our study which include small sample size, single-center study, and inability to use a continuous monitoring system.

Strengths of the Study

The study used a prospective observational design to evaluate glycaemic variability in critically ill patients. It included both medical and surgical ICU patients and assessed clinically relevant outcomes, including mortality and length of ICU stay. Regular blood glucose monitoring and the use of standardised glucose measurement procedures were additional strengths of the study.

Limitations of the Study

The study was limited by its small sample size and single-centre design, which may restrict the generalisability of the findings. Continuous glucose monitoring was not used, and intermittent blood glucose measurements may not have captured all glycaemic fluctuations. The observational design also limits the ability to establish a causal relationship between glycaemic variability and adverse clinical outcomes.

Future Directions

Future studies should include larger, multicentre patient populations to validate the association between glycaemic variability and ICU outcomes. The use of continuous glucose monitoring and standardised

measures of glycaemic variability may provide a more comprehensive assessment of glucose fluctuations. Further research should also evaluate the potential role of glycaemic variability in predicting mortality and prolonged ICU stay.

CONCLUSION

Glycemic variability is a critical, independent marker of poor prognosis in the ICU. It is more closely linked to mortality and infection than either hyperglycaemia or hypoglycaemia alone. Future research should focus on automated, continuous glucose monitoring (CGM) systems to minimize GV and improve survival in critically ill patients.

Declarations

Ethics Approval and Consent to Participate

The details of Institutional Ethics Committee approval and informed consent should be provided in accordance with the study records.

Consent for Publication

Not applicable, unless identifiable patient information is included in the manuscript.

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To be confirmed by the authors.

Conflicts of Interest

To be confirmed by the authors.

Author Contributions

All authors should specify their respective contributions to the study conception, data collection, analysis, manuscript preparation, and final approval.

Data Availability Statement

The data supporting the findings of this study may be made available by the corresponding author upon reasonable request, subject to institutional policies and applicable ethical requirements.

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Use of Artificial Intelligence

The authors declare that no artificial intelligence (AI)-assisted tools were used in the preparation of this manuscript.

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