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Original Article

Internal Medicine Section

Analysis of Glycaemic Changes and their Outcome in Critically Ill Non-diabetic Patients Admitted to the ICU: A Cohort Study

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ABSTRACT

Introduction: Critical illness results in physiological and metabolic changes that lead to dysglycaemia, which is associated with morbidity and mortality. There exists a J- or U-shaped relationship between average glucose levels and mortality, emphasising the importance of evaluating glycaemic variability in critical illness.

Aim: To assess glycaemic changes in critically ill patients and their association with Intensive Care Unit (ICU) outcomes.

Materials and Methods: The prospective cohort study was conducted from August 2018 to August 2019. A total of 100 non-diabetic critically ill patients admitted to the ICU were observed for seven days. The severity of illness was evaluated using the Glasgow Coma Score (GCS) and Sequential Organ Failure Assessment (SOFA) scores. Plasma glucose levels were recorded every four hours in the ICU. Patients were followed for a maximum of seven days or until discharge or death. They were categorised into hypoglycaemia, normoglycaemia, or stress hyperglycaemia groups for analysis. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24.0.

Results: The study included 64 male and 36 female patients, with an average mean age of 55.90±16.51 years (range: 18-86 years). Among the 100 patients, 21 died within the seven-day hospitalisation period. Among these, two were in the hypoglycaemic group, 13 were in the normoglycaemic group, and six were in the stress hyperglycaemic group. The patients had a mean SOFA score of 11.55±2.20, which was significantly higher compared to patients without organ failure (mean score: 2.54±2.55), with a statistically significant association ($p<0.01$). Similarly, patients who died during hospitalisation had a very high SOFA score (mean score: 9.76±3.36), also statistically significant ($p<0.01$).

Conclusion: Critically ill patients in the stress hyperglycaemia and hypoglycaemia groups during their ICU stay had a worse prognosis compared to patients with normoglycaemia. Hypoglycaemia during the ICU stay was associated with the poorest outcome. Maintaining normoglycaemia can significantly reduce morbidity and mortality in critically ill non-diabetic patients; therefore, considering Continuous Glucose Monitoring Systems (CGMS) for more frequent glycaemic monitoring and reducing glycaemic variability may lead to better outcomes in the ICU.

Keywords: Hypoglycaemia, Stress hyperglycaemia, Sequential organ failure assessment score

INTRODUCTION

Any critical illness is often associated with many physiological and metabolic changes in the body that alter glucose metabolism. Stress hyperglycaemia is defined as an acute sustained rise in serum glucose levels during any acute illness [1]. It commonly occurs in patients who have not previously been diagnosed with diabetes mellitus and is frequently seen in critically ill patients [2]. Hyperglycaemia itself is independently associated with increased mortality in the ICU [3,4]. Therefore, intensive glycaemic monitoring in critically ill patients has become a standard of care in the ICU and remains a topic of research.

Several factors contribute to stress hyperglycaemia in critical illness, including excessive counter-regulatory hormones such as glucagon, growth hormone, catecholamines, glucocorticoids, as well as inflammatory cytokines such as IL-1, IL-6, and Tumor Necrosis Factor (TNF)-alpha. Additionally, exogenous administration of catecholamines, dextrose, and other nutritional support in the presence of relative insulin deficiency plays an important role [5]. Glycaemic variability is independently associated with adverse effects on vital organs and hospital mortality. Studies have shown a J- or U-shaped relationship between average plasma glucose and mortality [6-8].

Dysglycaemia in critically ill patients is associated with increased morbidity and mortality, as demonstrated in numerous studies [9]. While hypoglycaemia, hyperglycaemia, and increased glycaemic variability are associated with increased mortality in a critical care setting, the diabetic status of patients also greatly influences the final outcome [10]. Stress hyperglycaemia has been shown to worsen outcomes in critically ill patients [5]. Although a higher plasma glucose range is associated with a mortality benefit in diabetic patients compared to non-diabetic patients, hypoglycaemia affects mortality equally regardless of the underlying diabetic status [10]. Efforts to reduce glycaemic variability, thereby preventing both hypoglycaemia and hyperglycaemia, can significantly benefit the reduction of mortality in a critically ill patients [2].

There are few studies evaluating non-diabetic subjects in a critical care setting, in which the assessment of glycaemic status at presentation and severity of illness scores are used [8,10,11]. Thus, there is a need for further studies to fill the gaps in existing knowledge, using expensive Continuous Glucose Monitoring Systems (CGMS) available in the market. However, due to the cost of CGMS systems, they cannot be used in a cost-free government hospitals. Therefore, this present study aimed to assess glycaemic changes, including hyperglycaemic and hypoglycaemic events, in critically ill patients in a tertiary care hospital in India using point-of-care glucometers. It also aimed to study the association between glycaemic events among critically ill patients and their ICU outcomes.

MATERIALS AND METHODS

This was a single-center prospective cohort study conducted at Command Hospital, Lucknow, India, over a period of one year, from

August 2018 to August 2019. Prior approval from the institutional ethical committee was obtained (Dated: 19th August, 2018).

Sample size estimation: was based on the reported incidence of stress hyperglycaemia among critically ill patients, which varies from 20% to 80% in different studies [11-13]. The present study aimed for a similar incidence (~60%), and a sample size of 100 was estimated using the formula suggested by Charan and Biswas [14]: n=C^2 * p * (1-p)/e^2. Here, 'p' represents the targeted incidence (60%), i.e., 0.60, 'C' is a constant at a certain confidence level (at 95% confidence limit and 80% power, its value is 1.96), and 'e' is the allowed error (taken as 10% or 0.10). Substituting these values in the equation, the authors get 92.1984, which rounds to 92. Therefore, the calculated sample size was 92. After accounting for a contingency of 10% and rounding off, the target sample size of 100 was chosen.

Inclusion criteria: All critically ill non-diabetic patients above 18 years of age, regardless of sex who presented during the study time period were included in the study. Non-diabetic patients were determined at admission by HbA1c <5.7%. The study also included patients with hypertension, Chronic Obstructive Pulmonary Disease (COPD), and other major illnesses such as bronchial asthma or thyroid disorders.

Exclusion criteria: Patients with baseline HbA1c levels >5.6% were excluded as they were considered to have prediabetes or overt diabetes mellitus. Additionally, patients with known diabetes mellitus on treatment, known hemoglobinopathies, postoperative patients, and those receiving glucocorticoids or immunosuppressive agents were excluded. Other exclusion criteria included patients with severe underlying co-morbidities like malignancy, connective tissue diseases, chronic renal failure, and cirrhosis. Finally, patients who died within 3 days of ICU admission were also excluded.

Procedure

A total of 117 patients were screened. Consent was refused by relatives of seven patients, and 10 patients did not meet the inclusion criteria. The demographic details and clinical profile of all the patients included in the study were recorded at the time of admission. Plasma glucose and HbA1c levels were measured upon admission. The severity of illness was determined using the GCS and SOFA scores [15]. Critical illness was assessed using the SOFA score, and patients with a SOFA score ≥4 at admission were admitted to the ICU. If not all parameters of the SOFA score were available, critical illness warranting ICU admission was considered in the presence of acute respiratory distress syndrome, refractory hypotension, a comatose state (GCS<9), or severe metabolic acidosis.

Random Plasma Glucose (RPG) levels were recorded once every four hours during the patients' stay in the ICU, and the average RPG for the day was calculated as the mean of all available RPG levels for that day. Patients were divided into three groups based on their RPG at admission: hypoglycaemia group (RPG <55 mg/dL), normoglycaemia group (RPG 55-180 mg/dL), and hyperglycaemia group (RPG >180 mg/dL) [16,17]. After initial detection of hypoglycaemia, the patients were given 100 mL of intravenous 50% dextrose and then received continuous 5% dextrose infusion or oral feeding to maintain their RPG in the range of 140-180 mg/dL. They underwent RPG monitoring every 1-2 hours to prevent recurrent hypoglycaemia until stable glycaemic control was achieved, at which point RPG monitoring continued every six hours. Similarly, patients with persistent hyperglycaemia >180 mg/dL on two occasions were managed with insulin infusion using a correction insulin protocol to maintain their RPG in the range of 140-180 mg/dL and prevent recurrent hyperglycaemia. They also underwent RPG monitoring every two hours to prevent subsequent hyperglycaemia until stable glycaemic control was achieved, at which point RPG monitoring resumed every six hours. The patients were classified into their respective subgroups based on RPG before the intervention was started.

All cases were followed for a maximum of seven days or until death or discharge within seven days of hospitalisation. Their final outcome, including organ failure, death, or discharge from the hospital, was recorded. There was no specific follow-up of the studied patients to analyse their recovery and satisfaction levels after the pre-defined seven-day study period or after discharge from the hospital, whichever came earlier.

STATISTICAL ANALYSIS

The statistical analysis was conducted using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA). The values were presented as numbers (%) and mean±SD. Chi-square test, independent samples t-test, and Analysis of Variance were utilised to compare the data. A p-value less than 0.05 was deemed statistically significant.

RESULTS

Total 100 critically ill patients were recruited for the study, and their baseline demographic and laboratory parameters are shown in [Table/Fig-1,2].

Characteristics	Total N=100
Sex (Male:Female)	64:36
Age (years)	Mean 55.90±16.51years range 18-86 years
Background (Urban:Rural)	51:49 (1:1)
Smoker	45 (45%)
Tobacco chewer	35 (35%)
Alcohol consumer	19 (19%)
COPD	10 (10%)
Hypertension	12 (12%)

[Table/Fig-1]: Baseline demographic variables studied in the patients.

Baseline Values of variables (At admission/day 1)	Mean±SD (n=100)	Min-Max
Systolic blood pressure (SBP) (mmHg)	121.29±20.9	72-174
Mean arterial blood pressure (mmHg)	74.8±12.2	44-112
Haemoglobin (g/dL)	14.2±1.3	10.6-16.4
Random Plasma Glucose (RPG) (mg/dL)	110.64±26.6	36-182
HbA1c (%)	4.85±0.53	3.9-5.6
Total leucocyte count (per cmm)	10756.0±6291.3	3100-29100
Serum Sodium (mmol/L)	226.52±866.0	122-149
Serum Potassium (mmol/L)	4.49±0.56	3.4-6.2
Serum Creatinine (mg/dL)	1.22±1.35	0.1-7.4
Baseline SOFA score	3.53±3.8	0-16
Average plasma glucose (mg/dL)	115.22±27.84	32-184
ABG pH	7.37±0.07	7.10-7.59
ABG pO_2 (mmHg)	76.84±13.63	10.0-100.0
ABG pCO_2 (mmHg)	55.17±18.57	32.6-102.0

[Table/Fig-2]: Baseline laboratory variables studied in the patients.

The patients were divided into three glycaemic groups based on RPG at admission as follows: the hypoglycaemia group (2), the normoglycaemia group (83), and the hyperglycaemia group (15). A total of 21 patients (21%) died during the study. The first mortality was seen on day 4 of hospitalisation. By day 5, a total of thirteen patients had died, and by day 6, another seven patients had succumbed. One patient died on day 7 of hospitalisation. Among the patients who died, 11 (52.38%) had organ failure.

The mean age of the study population was 55.9 years (range 18-86 years). Among them, the majority (64%) were males, and females accounted for 36%. No significant co-morbidity was found in 73.0% of the patients, whereas 12% had a previous history of hypertension, 10% had COPD, and 5% had other major illnesses.

Among these, 45 (45.0%) were smokers, 35 (35.0%) were tobacco consumers, and 19 (19.0%) had a history of significant alcohol consumption. On admission, the mean RPG was found to be 110.64±26.6 mg/dL (range: 36-182 mg/dL). The mean SOFA score was found to be 3.53±3.8 (range: 0-16). Glucose levels were measured every four hours daily, and the mean glucose levels, as shown in [Table/Fig-2], were then compared with the baseline plasma glucose. The association between them was found to be statistically non-significant (p>0.05) [Table/Fig-3].

Glucose (mg/dL)	Mean±SD	Mean difference from baseline	p-value
Day-1	115.22±27.84	-	-
Day-2	117.46±27.79	-2.240	0.279
Day-3	115.22±31.12	2.740	0.205
Day-4	113.39±31.10	1.830	0.409
Day-5	113.79±26.93	1.011	0.591
Day-6	116.80±27.60	-0.831	0.659
Day-7	116.24±27.62	-0.277	0.878

[Table/Fig-3]: Distribution of mean blood glucose levels during hospital stay.

The association between glucose levels in all three groups on all days compared to the baseline, as shown in [Table/Fig-4], was found to be statistically significant (p<0.01). The association between the hypoglycaemic and hyperglycaemic groups was found to be statistically significant on day 1, day 3, day 4, and day 5 (p<0.05). No significant association between the hypoglycaemic and hyperglycaemic groups was found on day 6 and day 7. No statistically significant association was found with different socio-demographic factors. Day-to-day changes in glucose levels at all days were compared with the severity of illness according to various variables, including the SOFA score.

Glucose level (mg/dL)	Hypoglycaemia (<55 mg/dL) (n=2)	Normoglycaemia (55-180 mg/dL) (n=83)	Hyperglycaemia (>180 mg/dL) (n=15)	p-value*	p-value**
Day-1	80.0±59.39	108.52±21.6	157.0±13.4	**<0.001**	**0.001**
Day-2	121.0±4.24	110.94±22.0	153.07±15.9	**<0.001**	0.051
Day-3	67.0±7.10	106.51±26.94	151.60±21.13	**<0.001**	**0.001**
Day-4	57.0±7.10 *First patient died	106.88±25.16	156.93±19.84	**<0.001**	**<0.001**
Day-5	84.0±39.67 *Second patient died	108.49±21.49 *Six patients died	156.27±20.22 *Five patients died	**<0.001**	**0.002**
Day-6	0	110.53±22.48 *Six patients died	109.92±22.15 *One patients died	**<0.001**	CND
Day-7	0	109.92±22.15 *One patients died	162.40±18.20	**<0.001**	CND

[Table/Fig-4]: Distribution of day-to-day changes in glucose level during hospitalisation and its association with baseline hypoglycaemia, normoglycaemia and hyperglycaemia. CND: Cannot be determined

This study observed that the patients who recorded any form of organ failure during hospitalisation had a mean SOFA score of 11.55±2.20, which was much higher than patients who did not have any organ failure (mean score 2.54±2.55), and the association between them was found to be statistically significant (p<0.01) [Table/Fig-5].

ICU outcome		SOFA score	p-value
Organ failure	Yes (n=11)	11.55±2.20	**<0.001**
	No (n=89)	2.54±2.55	
Final outcome	Discharged (n=79)	1.87±1.43	**<0.001**
	Death (n=21)	9.76±3.36	

[Table/Fig-5]: Association between mean SOFA score at baseline with ICU outcomes.

Similarly, patients who died during hospitalisation had a very high SOFA score (mean score: 9.76±3.36), suggesting a statistically significant association with the final outcome (p<0.01).

In the studied groups, two ICU outcomes were noticed: organ failure and the final outcome (discharge/death). The association of these outcomes with glycaemic events (hyperglycaemia, hypoglycaemia, and normoglycaemia) was also observed [Table/Fig-6], and both outcomes were found to be statistically significant (p<0.05). The association of the final outcome and organ failure after day 7 of hospitalisation was also statistically significant [Table/Fig-7].

ICU outcomes		Random Plasma Glucose (RPG)			Total	p-value
		Hypoglycaemia (<55 mg/dL) (n=2) (%)	Normoglycaemia (55-180 mg/dL) (n=83) (%)	Hyperglycaemia (>180 mg/dL) (n=15) (%)		
Organ failure	Yes	1 (50.0)	6 (7.2)	4 (26.7)	11 (11.0)	**0.018**
	No	1 (50.0)	77 (92.8)	11 (73.3)	89 (89.0)	
Final outcome	Discharge	0 (0.0)	70 (83.3)	9 (60.0)	79 (79.0)	**0.002**
	Death	2 (100.0)	13 (15.7)	6 (40.0)	21 (21.0)	

[Table/Fig-6]: Distribution of association between glycaemic changes and ICU outcomes.

Organ failure	Final outcome		Total (n=100)	p-value
	Discharged (n=79)	Deaths (n=21)		
Yes	0 (0.0)	11 (52.4)	11(11.0)	**<0.001**
No	79 (100.0)	10 (47.6)	89 (89.0)	

[Table/Fig-7]: Association of final outcome and organ failure of patients after day 7 of hospitalisation.

DISCUSSION

This was a prospective cohort study conducted in a tertiary care teaching hospital for a period of one year. Similar observational studies have been previously conducted by Goldberg PA et al., Finney SJ et al., Holzinger U et al., Singh V et al., and Zochios V et al., [18-22]. The advantage of an observational study is that it is inexpensive, captures multiple variables at the time of data collection, and can prove or disprove assumptions.

In this study, a total of 100 non-diabetic critically ill adult patients were observed for a period of seven days, with a similar sample size as the studies conducted by Holzinger U et al., and Singh V et al., [20,21]. However, the study by Finney SJ et al., had a larger sample size of 531 patients due to variations in the inclusion and exclusion criteria of the studied population [19].

In this study, all adult patients were included, with an age range of 18-86 years (mean age 55.90 years), and 64% of them were male. This is consistent with the findings of Finney SJ et al., where 72.8% of the patients were male, and the median age was 64 years [19]. Wernly B et al., also reported a mean age of 69 years in their study, with an age range of 58-77 years, and 61% of the patients were male [23]. Singh V et al., reported a mean age of 70.02 years in their study, but they had a majority (57.2%) of female participants [21].

In this study, 73% of the patients had no significant co-morbidities, while 12% had hypertension, 10% had COPD, and 5% had other systemic illnesses. Smoking history was documented in 45% of the patients, and a total of 19% were alcohol consumers. Singh V et al., also reported hypertension (56.02%), CAD (47.80%), and smoking (22.16%) among their patients [21].

In this study, the RPG at admission was 110.64±26.6 mg/dL, with an HbA1c level of 4.85±0.53%. Umpierrez GE et al., reported a mean blood glucose level at admission for their study patients as 227±65 mg/dL, which was higher than the levels observed in this study because they included diabetic patients [24]. However, this study excluded diabetic patients, which is why a non-significant

association was observed between the glucose concentration on the first day and the last day of hospitalisation (p>0.05) [24].

While it is generally accepted that stress hyperglycaemia is associated with increased morbidity and mortality, it remains uncertain whether tight glycaemic control is beneficial or even harmful for critically ill patients [17,25]. Regardless of the selected blood glucose target range, the randomised clinical studies conducted by Finfer S et al., and Brunkhorst FM et al., did not achieve the predefined target range in the majority of patients, resulting in an increased rate of severe hypoglycaemia [17,25]. Earlier studies by Krinsley JS and Grover A, and Vriesendorp TM et al., investigated the consequences of hypoglycaemia under tight glycaemic control in critically ill patients, revealing conflicting results [26,27]. However, these studies primarily focused on mortality and morbidity. The present study, which focused on ICU survivors, is the first to explore the effects of hypoglycaemia and hyperglycaemia during ICU treatment.

Finney SJ et al., reported a mean SOFA score of 5 on day 1, which is very close to our finding of a mean SOFA score of 3.53±3.8 [19]. In the present study, a total of 21 patients died during the seven days of hospitalisation. By day 5, thirteen patients had died, seven more succumbed by day 6, and one patient died on day 7. Organ failure was observed in 11 patients who died within these seven days of observation. The association between organ failure and death in the reported patients was found to be statistically significant (p<0.01). This demonstrated that mortality was difficult to control in patients with organ failure, and glucose levels were also inherently difficult to control. Thus, patients spent considerable periods of time with glucose levels outside the target range. This is likely due, at least in part, to the multitude of variables that impact blood glucose levels, including feeding regimen, catecholamine administration, stress response, insulin administration, inherent bioavailability, and possibly a lack of concern about a variable that may be considered relatively minor by clinical staff [1].

In this study, the association between glucose levels in all three groups on all days was found to be statistically significant (p<0.01). The association between hypoglycaemia and hyperglycaemia was found to be significant on day 1, day 4, and day 5 (p<0.05). However, on day 6 and day 7, the correlation between the hypoglycaemia and hyperglycaemia groups could not be found as there were no patients in the hypoglycaemic range, and only mortality was observed in the normal glucose range on day 7. The association between organ failure and the final outcome, along with their respective SOFA scores, was found to be statistically significant (p<0.01). This data suggests that hyperglycaemia is the relevant variable determining the outcome. These findings are in agreement with other investigators' results and other observational data indicating that the level of RPG at admission represents an independent risk factor for long-term prognosis, especially after myocardial infarction and in women following coronary artery bypass graft surgery, even in those without diabetes [28-30].

In this study, two ICU outcomes were observed: organ failure and the final outcome (discharged/death). The correlation of these outcomes with initial glycaemic levels (hyperglycaemia, hypoglycaemia, and normoglycaemia) was also found to be statistically significant (p<0.05). While it is generally agreed that adequate glycaemic control is an essential part of critical care, there are still differences among experts. There is no standard definition of normoglycaemia during ICU stay for optimal outcomes, and the only recommendation, as per the NICE-SUGAR trial, is to maintain plasma glucose between 140 to 180 mg/dL [17]. Therefore, it is very difficult to determine the best protocol in terms of results and clinical effort.

Various studies conducted since 2001 by Bryer-Ash M and Garber AJ, as well as Inzucchi SE and Rosenstock J, have suggested that although proper management of hyperglycaemia improves outcomes, the precise target blood glucose level, optimal mode of administration, type of insulin used, and the subset of patients most likely to benefit remain uncertain [31,32]. The response of optimal glycaemic control immediately after acute myocardial infarction and in septicaemia is highly erratic [23]. Critically ill patients tolerate hypoglycaemia poorly and may remain asymptomatic during periods of severe hypoglycaemia [26].

In recent years, one of the most controversial topics in intensive care medicine has been how to treat critically ill patients with hyperglycaemia [33]. Several protocols are available for insulin therapy in the ICU, although there is great variability regarding the initiation and titration of insulin [12,28,34]. Some recommendations apply to hospitalised patients with newly diagnosed hyperglycaemia, although some patients may no longer require glucose-lowering therapy after they have recovered from acute illness. This study has not taken into consideration the use of insulin, even at suboptimal doses, and other treatment modalities in hyperglycaemic-range patients. Hence, the correlation between the influence of insulin and other modalities with outcomes cannot be commented upon and is outside the purview of the present study.

Hyperglycaemia is common in critically ill patients, even those without diabetes mellitus [35]. However, if both hyperglycaemia and increased administration of insulin are associated with an increased risk of death, can manipulation of blood glucose to lower levels with infusions of soluble insulin reduce mortality? Published evidence suggests that such a strategy is effective in certain groups of patients [28]. The apparent contradiction between the adverse effects of hyperglycaemia and increased administration of insulin provokes debate about the most appropriate target for glucose control.

Limitation(s)

The limitations of this study include being a single-centre study, which means it represents an analysis of manually acquired data that is susceptible to inherent inaccuracies. It cannot be certain that bias did not occur as plasma glucose results deviated from the required range and more observations were made. Another limitation is the absence of using CGMS, which could have provided better accuracy for assessing glycaemic status. Nonetheless, the study attempted to mitigate this possibility by time-weighing its observations. Additionally, it did not consider the impact of insulin usage, even at sub-optimal doses, on the final outcome of the study group.

CONCLUSION(S)

Critically ill patients with stress hyperglycaemia during their ICU stay have a worse prognosis compared to patients with normoglycaemia. Hypoglycaemia during the ICU stay has an even worse outcome than stress hyperglycaemia. Stress hyperglycaemia and hypoglycaemia in critical care have a significant impact on patient mortality and outcomes. Normoglycaemia can significantly reduce these negative outcomes, but consistently achieving it as an expected outcome of critical care remains clinically elusive.

This overview has examined the current performance of clinical glycaemic control studies in critical care, focusing on the differences in emerging model-based approaches that utilise a variety of computational and emerging sensor technologies, as well as current ad-hoc clinical methods. With limited published studies, it is still an emerging field rather than a mature area of research. Hence, it is recommended that in the future, clinical research should be able to determine the true impact of glycaemic variability in critically ill patients, as well as consider new technologies like CGMS to optimise plasma glucose monitoring in the ICU.

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