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Glycemic abnormalities and their outcome in critically ill pediatric patients admitted in pediatric intensive care unit of tertiary care hospital

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Abstract
Background: In normal healthy state, human body maintains homeostasis and normal glycemic levels, however in stress associated with any critical states, this control is impaired or lost. Hyperglycemia represents an extreme form of stress. There is no consensus about cut off blood glucose levels to be labeled as hyperglycemia in pediatric age group**.** Different studies considered different levels of blood glucose as hyperglycemia.
Aims & Objectives: To determine frequency of glycemic abnormalities and to correlate this abnormalities with outcome in critically ill children admitted in Pediatric intensive care unit.
Methodology: This was a prospective observational study. Total 61 number of cases in the age group of 1month to 17 years were enrolled in the study, by considering inclusion and exclusion criteria.
Results: Out of 61 patients, 50.8% were females and 49.2% were males. Out of 61 patients, 73.8% had Hyperglycemia, 24.5% had Euglycemia, 1.6% patient had Hypoglycemia. There was a statistically significant association between hyperglycemia and those cases requiring mechanical ventilation and on vasopressors. Outcome was poor in those cases which had hyperglycemia and the risk of death was 5.78 times more in them.
Conclusion: Prevalence of mean hyperglycemia was 80.3%, 72%, 31%, when cut off levels of blood glucose was considered as >126 mg/dl,>150 mg/dl, >200 mg/dl respectively. There was an increased morbidity and mortality in critically ill patients having hyperglycemia. As there are no definite cut off levels of hyperglycemia in critically ill patients, more studies and consensus is needed.

Keywords: Hyperglycemia, P.I.CU., euglycemia, blood glucose

Introduction
Human body in an otherwise healthy state is able to maintain a tight glycemic levels independent of ingested food or energy expenditure. Any form of stress that follows critical states may lead to profound impairments in this homeostasis [1] Hyperglycemia represents an extreme form of 'stress' in critically ill children. Initially, stress induced hyperglycemia during critical illness was thought to be an adaptive response that was either not important for improved survival [2]. However, it is no longer considered a physiological or benign condition as it results from a surge of endogenous counter-regulatory hormones, insulin resistance and other diabetogenic factors with the release of pro-inflammatory mediators, oxidative stress and therapeutic interventions such as exogenous dextrose infusion, glucocorticoids, vasopressors like dopamine, β- blockers, antibiotic solutions, overfeeding and bed rest [3, 4, 5] There is no consensus for cut off level of blood glucose above which hyperglycemia can be labeled [6] The more severe the hyperglycemia and or hypoglycemia, more severe the mortality [7]. This study aimed to find out the frequency of glycemic abnormalities, relationship between glycemic levels and critically ill children and duration of hospital stay as well as outcome.

Material & Methods: This was a prospective observational study, conducted in pediatric intensive care unit of tertiary care hospital. A total of 61 number of critically ill patients in the age group of one month to seventeen years were included in the study. Ethical clearance for conducting the study was obtained from institutional ethics committee. Information obtained during study was kept confidential. Parents of eligible subjects, who gave consent, were included in the study. Patients with pre-existing and newly diagnosed cases of Diabetes Mellitus. PICU stay for less than 24 hours, who had already received IV Glucose, those from outside hospitals, received drugs like Quinine, Chloroquine, Thiazide, Diuretics, Tacrolimus,

and Cyclosporine and patients / their parents refusing consent for enrolment in study were excluded. A detailed history, demographic data and thorough physical examination was performed. Patients were followed throughout, in terms of outcome and duration of PICU stay. A detailed history, demographic data and thorough physical examination was performed. Patients were followed throughout, in terms of outcome and duration of PICU stay. The details of patients on mechanical ventilation, vasopressors, infusions, steroids and medications, were also recorded. Other laboratory investigations such as CBC, ABG, and those required for PRISM III scores and other relevant investigations were performed as per requirement. Non hemolysed blood sample for estimation of glucose was performed by Trinder's method (Calibrated Erba XL machine model number -640) on initial sample subsequent samples obtained by Glucometer. (on-call plus model no. -103L124CBBT code no.-944 Glucometer). Glucose estimation was performed every 4 hourly for first two days and later, every 6 hourly for further three days thus a total of 24 sample was obtained over five days. Hypoglycaemia was considered as glucose level less than 40mg/dl, hyperglycaemia was considered as glucose level more than 126mg/dl [8] Euglycemia was considered as glucose level between 41-125 mg/dl. Prism III score was measured initially after admission and after four days in PICU to predict mortality and severity and to correlate it with blood glucose concentration, p value < 0.05 was taken as statistically significant test. Statistical analysis was performed with SPSS version 16. Other statistical test used in analysis were chi square test, ANNOVA and Tukey's Test.

Result: Out of 61 patients, 50.8% were females and 49.2% were males; In the Age group analysis,14% were between 1-6 months, 16.0% were in 7-11 months, 19 31.1% were in 1-6 years, 31.1% were in 7-12 years and 13.1% were >12 years. The mean age (mean ± S.D.) of the patients was 6.11 ± 5.65 years with the range of 2 month – 17 years and the median age was 5years.Most of the patients were in the category of 1-12 year age group, (62.2%). Out of 61 patients, 73.8% had hyperglycemia, 24.5% had euglycemia, 1.6% patient had hypoglycemia. Mean blood glucose level on admission was 201.39 ± 80.12, median was 210 and Range was 36 – 384, whereas, mean hyperglycemia was in 80.3%, mean blood glucose was 177.30 ± 44.81, median being 187 & range 61.24 - 270.08 (when cut off blood glucose level for hyperglycemia was taken as >126mg/dl) during admission (Table -1).

Table 1: Distribution of Age of the patients

Level of blood Glucose (mg/dl)	Number	%	Mean ± s.d.	Median	Range
Hypoglycemia	1	1.6%	201.39 ± 80.12	210	36 – 384
Euglycemia	15	24.5%			
Hyperglycemia	45	73.8%			
Total	61	100.0%			

Out of the 61 patients 48(78.7%) had peak RBS levels >200 mg/dl. Mean of peak RBS level was 247.66 ± 72.30mg/dl. Median 250 and range was 88-412 mg/dl. Prevalence of Hyperglycemia at different cut off levels was 80.3% (126mg/dl), 72% (150 mg/dl) and 31% (200mg/dl). Since there is no consensus statement for cut off blood glucose levels to be considered as hyperglycemia, the prevalence of it varied according to different cut off values. Prevalence of euglycemia was 21%, 27%, 67% when cut off levels of blood glucose were considered as 125 mg/dl, 149 mg/dl & 199 mg/dl as normal levels respectively. Mean length of stay was 8.31 ± 3.78; median was 7.00; range of stay was 3.00 - 25.00 days. Out of 61 patients admitted in P.I.C.U. Majority of patients included in the study were of acute Congestive cardiac failure and severe bronchopneumonia each 13.5% followed by Meningitis, Septic shock, Status Epilepticus 11.5% and others.

Table 2: Distribution of Mean Blood glucose level during PICU stay

Time Interval	Mean ± S.D.	Median	Range
At Admission	201.39± 80.12	210	36 – 384
At 1st Day (at 4 hours interval)			
1st Hour	193.36±70.91	196	34 – 346
2nd Hour	193.21±74.12	200	16 – 386
3rd Hour	192.57±69.11	190	48 – 322
4th Hour	184.54±62.03	184	64 – 412
5th Hour	183.85±56.48	188	78 – 304
6th Hour	184.57±62.10	184	64 – 321
At 2nd Day (at 4 hours interval)			
1st Hour	181.38±63.44	187	32 – 320
2nd Hour	181.36±63.01	178	50 – 314
3rd Hour	184.59±50.98	188	70 – 310
4th Hour	187.41±59.66	192	68 – 311
5th Hour	185.52±60.38	184	48 – 342
6th Hour	184.00±59.73	182	54 – 334
At 3rd Day (at 6 hours interval)			
1st Hour	174.61±55.61	176	40 – 312
2nd Hour	175.11±48.40	184	64 – 296
3rd Hour	178.92±50.16	184	64 – 301
4th Hour	180.13±56.35	187	68 – 342

At 4th Day (at 6 hours interval)			
1st Hour	176.00±54.93	196	46 – 284
2nd Hour	174.31±62.00	190	12 – 312
3rd Hour	166.72±56.34	172	30 – 288
4th Hour	167.43±49.65	176	54 – 264
At 5th Day (at 6 hours interval)			
1st Hour	165.85±45.70	184	52 – 254
2nd Hour	164.84±50.13	168	70 – 348
3rd Hour	168.84±49.32	180	64 – 310
4th Hour	169.44±46.79	174	46 – 308

Table -2 shows distribution of mean blood glucose levels, accordingly Mean blood glucose level decreased subsequently during PICU stay, as compared to on admission. Out of 61 patients 41(67.2%) required mechanical ventilation, whereas 20 (32.8%) did not required ventilation. Hyperglycemia was found in 37(90.0%) who required mechanical ventilation, Euglycemia was found in 4 (9.8%), who did not require mechanical ventilation. A statistically significant association was found between requirement of mechanical ventilation and mean blood glucose level of the patients (p<0.05). Test of proportion showed that, requirement of mechanical ventilation was significantly higher for hyperglycemia (Z=6.78; p<0.05). Hyperglycemia was found in 27(73.0%) patients which required vasopressor support. Euglycemia was found in 10 (27%) patients, who did not require vasopressor support. Corrected Chi-square (χ^2) association between requirement between requirement of vasopressor support and mean level of blood glucose was found to be highly significant (p<0.0001) as depicted in Table -3.

Table 3: Correlation of Mean blood glucose level with requirement of Mechanical Ventilation and Requirement of Vasopressors

Mean Level of Blood Glucose	Requirement of Mechanical ventilation		p Value	Requirement of Vasopressors		p Value
	Yes	No		Yes	No	
Euglycemia	4(9.8%)	8(40.0%)	0.031	2(8.3%)	10(27.0%)	<0.0001
Hyperglycemia	37(90.2%)	12(60.0%)		22(91.7%)	27(73.0%)	
Total	41(100.0%)	20(100.0%)		24(100.0%)	37(100.0%)	

An association between PRISM III Score and Glycemic status of patients was assessed (between day 1 and on day 4), increase in PRISM III score in 55(90%) patients out of 61 patients was noticed. Out of 55 patients 43(78.2%) had developed Hyperglycemia, in whom PRIM III score was increased. Corrected Chi-square (χ^2) test showed that there was a significant association between PRISM-III Score and glycemic status (p<0.05). Also there was an increase in PRISM III score in comparison of Euglycemia with Hyperglycemia and it was statistically significantly (p<0.05) as depicted in Table-4 below.

Table 4: Comparison of Glycemic Status with PRISM III score during PICU stay (on day 1 & on day 4)

Mean Level of Blood Glucose	Comparison of PRISM III score during PICU stay (on day 1 & day 4)			p Value
	Decreased	Remains Same	Increased	
Euglycemia	0(0.0%)	0(0.0%)	12(21.8%)	0.042
Hyperglycemia	2(100.0%)	4(100%)	2(100.0%)	

Out of the 16 patients admitted in P.I.C.U. 37(60.7%) patients survived and 24 (39.3%) died.

Correlation of Hyperglycemia and outcome of patients is depicted in Table -5 below

Table 5: Hyperglycemia (as per Mean blood glucose level) and Outcome in PICU

Hyperglycemia	Outcome in P.I.C.U.		p Value	Odds Ratio
	Died	Survived		
Yes	20(83.3%)	29(78.4%)	0.044	5.78
No	4(16.7%)	8(21.6%)		
Total	24(100.0%)	37(100.0%)		

Chi-square (χ^2) test showed that there was a significant association between Hyperglycemia and Outcome in PICU (p<0.05). The risk of death was 5.78 times more among the patients with hyperglycemia as compared to the patients without hyperglycemia [OR-5.78(1.02, 12.38); and the risk was significant (p<0.05).

Discussion: Critical illness was defined as any condition leading to malfunction of one or more organ system requiring support to maintain vital function either with mechanical or pharmacological aids [9]. There is no definite cut off value to designate hyperglycaemia in literature, neither there is any consensus statement for hyperglycaemia in children. In particular, both the peak hyperglycemia and duration of hyperglycemia have been found to be poor prognostic factors, predict longer lengths of hospital stay and mortality in the diabetic and non diabetic adults [10, 11]. Different studies have taken different cut off levels of blood glucose to define hyperglycaemia. In present study, cut off

level of hyperglycaemia was considered as glucose level more than 126mg/dl & hypoglycaemia was considered as glucose level less than 40mg/dl. Prevalence of hyperglycemia in PICU varies depending on cut off levels considered for hyperglycemia in different studies.

Table 6: Prevalence of hyperglycemia in PICU in different studies

Author and Year	Hyperglycaemia Cut Off Blood Glucose level (mg/dL)	Prevalence (%)
In this study	>126	80.3
	>150	72
	>200	31
Srinivasan *et al.* (2004) [2]	>126	86
Patki *et al.* (2008) [5]	>110	95
Faustino *et al.* (2005) [7]	>200	16.7
Wintergerst *et al.* (2006) [10]	>110	86.5
Allen *et al.* (2008) [12]	>150	61
Yung *et al.* (2008) [13]	>200	35.2
Jain *et al.* (2016) [14]	>126	58

Prevalence of Hyperglycemia in this study was 80.3%, 72%, 31% when cut off levels of blood glucose was considered as >126 mg/dl, >150 mg/dl, >200 mg/dl respectively. Chi-square test (χ^2) showed that there was a significant association between hyperglycemia and Outcome in PICU (p<0.05). The risk of death was 5.78 times more among the patients with Hyperglycemia as compared to the patients without Hyperglycemia [OR-5.78(1.02, 12.38); and the risk was significant (p<0.05). Various studies showed significant association between hyperglycemia and type of disease. Branco *et al.* [15] found a significant association of hyperglycemia and mortality was found with septic shock, burns, traumatic brain injury, post cardiac surgery, and trauma. Hyperglycaemia was associated with worse mortality in severe sepsis and traumatic brain injury in Chiaretti *et al.* [16], whereas, in this study, no significant association between mortality and hyperglycemia was found with any particular type of disease. On comparing association of morbidity and mortality with hyperglycemia, a statistical significant relation (p<0.05) was found with mechanical ventilation requirement, vasopressor support requirement and mortality, prolonged duration of ventilation and increased vasopressor support was required with prolonged hyperglycemia, similar correlation was also observed in study of Patki *et al.* [5]. Prolonged hyperglycemia was associated with increased duration of mechanical ventilation in Branco *et al.* [15], Yates *et al.* [17], Srinivasan *et al.* [18] studies. In present study out of 61 patients, hyperglycemia was found in 49 (80.3%) patients, Out of 49 patients, 22(45%) patients died; whereas, 27(55%) of patients survived thus, there was a significant association between Hyperglycemia and mortality (p<0.05), the risk of death was 5.78 times, as odds ratio was 5.78 when cut off level for hyperglycemia was >126mg/dl in this study. Different rate of risk of mortality was observed in different studies ranging from 2.5 to 11.1 as the cut off levels for hyperglycemia and size of samples also varied in various studies. There was only one patient of hypoglycaemia in this study. Limitation of this study was enrolment of small number of patients compared to other studies.

Conclusion

Prevalence of mean hyperglycaemia in this study was 80.3%, 72%, 31%, when cut off levels of blood glucose was considered as >126 mg/dl, >150 mg/dl, >200 mg/dl respectively. There is a significant association between duration of hyperglycemia in critically ill patients and increased morbidities such as increased requirement of ventilation and vasopressors. Mortality also increased in critically ill patients with duration of hyperglycemia. As there is no uniform cut off levels for hyperglycemia and as hyperglycemia is associated with increased morbidity and mortality in various studies, there is a need for a consensus statement for cut off level of Hyperglycemia.

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