GLYCEMIC PROFILE OF CRITICALLY ILL PEDIATRIC PATIENTS

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OBJECTIVE – To determine the frequency of glycemic abnormalities and association with outcome in critically ill children admitted to PICU.
STUDY SETTING – PICU of tertiary care hospital.
STUDY DESIGN:- Hospital based prospective cohort study.
METHODOLOGY:– All patients admitted to PICU in critical condition due to medical illness between age between 1 month to 18 years from September 2011 to October 2012 were enrolled for the study. Exclusion criteria was diabetes. Glucose monitoring of all patients was done. Within 1 hour of enrolment, venous sample for plasma glucose was taken and simultaneously finger stick capillary blood glucose measurement using glucometer was done. Subsequently, capillary glucose (finger stick) using glucometer was measured twice a day at fixed timings.
RESULTS - Out of the 200 patients included in the study, 134(67%) were males and 58 (29%) patients expired.The initial glucose value was >200 in 18% of the patients, maxima glucose value > 200 mg/dl in 25.5% of the patients during their stay period and mean glucose value was >200mg/dl in only 3.5% of the patients. All three parameters when >200 mg/dl were significantly associated with increased mortality. Hypoglycemia occurred in 6 (3%), out of the 200 patients in the study. Hypoglycemia was not associated with increased mortality or length of stay.
CONCLUSION - Hyperglycemia is common in critically ill children and is associated with increased mortality. The frequency of hypoglycemia is very less. It is not significantly associated with increased mortality and length of stay.

INTRODUCTION: Healthy individuals regulate blood glucose (BG) levels within a narrow range.[1] Critical illness is associated with disruptions of homeostatic mechanisms resulting in hyper- and hypoglycemia, both of which are associated with poor outcomes in critically ill neonates, children, and adults.[2–11]

With increasing facilities for intensive care becoming available in India, a large number of pediatricians are looking after critically ill children. The prevalence, consequences and management of hypoglycemia have been highlighted in pediatric literature but there is a lack of awareness regarding the prevalence and adverse effects of hyperglycemia among sick children.[12]

Hyperglycemia occurs frequently among critically ill adults, with prevalence rates reported from 3% to 71%.[13] During the acutely stressed state, hyperglycemia is thought to be advantageous,[14] providing the glucose-dependent organs such as the brain and blood cells adequate supply for their energy needs.[15,16] Hyperglycemia has also been postulated to compensate for volume loss by promoting the movement of cellular fluid into the intravascular compartment or liberating water bound to glycogen.[16] Despite potential positive effects, prolonged hyperglycemia in critically ill adults has been shown to be associated with a number of deleterious consequences[5] contributing to

greater risks of morbidity and mortality, even in the absence of pre-existing diabetes mellitus.[13,18,19] Elevated glucose concentrations have been associated with increased risks of congestive heart failure,[13] cardiogenic shock,[13] and poor functional recovery after stroke[18] as well as increased risks of dying after myocardial infarction1 and ischemic stroke[18] among nondiabetic patients. Even among non–critically ill adult patients admitted to general patient care units, patients with newly diagnosed hyperglycemia had a significantly higher mortality rate and a lower functional outcome compared with known diabetic patients or normoglycemic patients.[19]

In an era where goal directed therapies with clinical practice guidelines are gaining ease and popularity, safe glycemic control in PICU setting should be achievable. As ICUs worldwide grapple with the issues surrounding implementation of programs of intensive glycemic management-including especially questions of which groups of patients to target, and at what level hyperglycemia should be treated—the importance of determining the risk of glycemic abnormalities increases. However definite evidences regarding frequency, prognostic significance of glycemic abnormalities and safe glycemic targets are still awaited.

METHODS: The study was conducted in Pediatric Intensive Care Unit, Department of Pediatrics, Subharti Medical College and hospital from October 2011 to September 2012.It was a hospital based prospective cohort study. All patients admitted to Pediatric Intensive Care Unit between 1 month and 18 years were included in the study except those who had any exclusion criteria. Exclusion criteria where preexisting diagnosis of diabetes mellitus, newly diagnosed cases of diabetes mellitus were subsequently excluded from the analysis. Patients who stayed in the PICU for less than 24 hours were also excluded from the study so as to obtain an adequate number of glucose readings per patient. In order to estimate a difference of 15% in mortality between high and normal blood sugars with a precision of 5%, 400 subjects were needed, thus we proposed to take 200 subjects for this study.

Informed written consent after explaining the parents as per patient information sheet was taken. Glucose monitoring of all patients admitted in PICU who had no exclusion criteria was done. Within 2 hours of enrollment, venous sample for plasma glucose was taken and simultaneously finger stick capillary blood glucose measurement using glucometer was done. Subsequently, capillary glucose (finger stick) using glucometer were measured twice a day at fixed timings of 10 a.m. and 10 p.m. Hypoglycemia was defined as glucose level less than 40mg/dl. Hyperglycemia was defined as glucose level more than 200mg/dl. Glucose parameters were Initial glucose level (glucose level at admission), Minimal and maximal glucose level during PICU stay, Mean glucose level during the PICU stay, Glucose variability index which is the mean of the difference of 2 sequential glucose readings divided by the time gap between them.

Data record included clinical parameters, age in months, sex, PRISM III score, GCS at the time of each glucose estimation, Final diagnosis, Treatment related: Intravenous fluids(rate of glucose infusion/kg/minute daily at time of glucose estimation) or enteral feeds(caloric intake/day) or both, Co-intervention related: any surgery done during this admission. Morbidities: shock, requirement for ionotropes, ventilation, duration of ventilation, blood transfusions were recorded. Outcome related discharge, transfer out or death, duration of stay in PICU.

Statistical analysis:

Mortality: Pearson's chi square test was used to compare mortality with various glycemic thresholds of mean, initial, minimal and maximal glucose levels. Mann Whitney test was applied to compare mortality with glycemic variability index as the data was not normally distributed. The various glycemic parameters were compared between survivors and non survivors using the Mann Whitney test.

Length of stay: Mann Whitney test was used to compare length of stay and mean, initial, minimal and maximal glucose values. Spearman's correlation coefficient test was used for length of stay and glycemic variability index.

RESULTS: Out of the 200 patients included in the study, 66 (33%) patients were females and 134(67%) were males. The length of stay was calculated in increments of 0.1 days. The mean length of stay of the patients in the study was 6.4 days, the median length of stay being 4.2 days and the range of length of stay being 1.0— 39.0 days. Out of the 200 patients included 58 (29%) patients expired. There was a linear rise of mortality with increasing severity of illness. As the PRISM III score increases the mortality also increases (p=0.000). The maximum PRISM III score recorded was 27; the average PRISM III score was 7.56; the median PRISM III score was 6 and the score ranged from 0-27. The initial glucose value was >200 in 18% of the patients, however 25.5% of the patients during their stay recorded a maxima glucose value >200 mg/dl. The mean glucose value was >200mg/dl in only 3.5% of the patients. All three parameters when >200 mg/dl were significantly associated with increased mortality, but only mean glucose >200 mg/dl was associated with significantly decreased length of

Glucose parameters during PICU stay		No. of patients	Survival	Mortality	P values	Length of stay Mean± S.D.	P value(m)
Initial glucose	≤ 200	164 (82%)	127(77.44%)	37 (22.56%)	0.000	6.5±6.3	0.245
	>200	36 (18%)	15(41.67%)	21 (58.33%)		5.9±6.3	
Maximal glucose	≤ 200	149 (74.5%)	121(81.20%)	28 (18.79%)	0.000	6.2±5.7	0.885
	>200	51 (25.5%)	21(41.17%)	30 (58.89%)		7.0±7.6	
Mean glucose	≤ 200	193 (96.5%)	142(73.58%)	51 (26.42%)	0.000	6.6±6.3	0.001
	>200	7 (3.5%)	0(0%)	7 (100%)		1.9±1.8	

Table 1: Correlation of hyperglycemia with survival, mortality and LOS using 200 mg/dl as a cutoff

stay (Table 1). Out of the 7 patients with mean glucose >200 mg/dl, the maximum mean glucose value recorded was 314 mg/dl and 2 of these had glucose value >250 mg/dl and required treatment. Severity of illness was more when glucose levels were more than 200mg/dl for all the glucose parameters initial, maximal and mean blood glucose level. For initial glucose< 200mg/dl need for

ventilation was in 42.7% and for >200mg/dl it was 72.2% (p =0.001). For maximal glucose< 200mg/dl need for ventilation was in 39.6% and for >200mg/dl it was 72.5% (p =0.000). Similarly for mean glucose< 200mg/dl need for ventilation was in 46.4% and for >200mg/dl it was 100% (p =0.000). PRISM score for initial glucose< 200mg/dl was 6.59 ± 4.36 and for >200mg/dl it was 11.97 ± 7.00(p =0.000). PRISM score for maximal glucose < 200mg/dl was 6.26 ± 4.07 and for >200mg/dl it was 11.35 ± 6.69 (p =0.000). PRISM score for mean glucose < 200mg/dl was 7.35 ± 5.17and for >200mg/dl it was 13.29 ±7.15 (p =0.018). Hypoglycemia occurred in 6(3%), out of the 200 patients in the study. Mortality occurred in 2 (33.3%) out of 6 patients with hypoglycemia where as patients with blood glucose >40mg/dl had 28.86% mortality (p = 0.678). Length of stay for blood glucose <40mg/dl was 13.1 ± 12.8 and for blood glucose > 40mg/dl it was 6.2 ± 5.9 (p = 0.062). Thus hypoglycemia was not associated with increased mortality or length of stay. Increased glycemic variability was significantly associated with increased mortality, survivors had glycemia variability index of 2.50±1.14 whereas non survivors had 4.52±3.21 (p =0.000). Glycemic variability index was significantly associated with decreased Length of stay (p =0.000).

DISCUSSION: There are no definite criteria for diagnosing hyperglycemia among patients without diabetes. We defined hyperglycemia as blood glucose >200 mg/dl, based on the WHO criteria and adult studies. A part from the absolute value of glucose, the major problem is in determining which of the different glucose parameters (initial, maximal, mean) are more predictive of outcome.

Faustino et al (2005) conducted a retrospective study including 942 critically ill non diabetic children. They also used three parameters; initial and maximal glucose within 24 hours and within 10 days duration. The initial glucose was >200 mg/dl in 16.7% of patients. The maximal glucose values within 24 hours of admission were >200 mg/dl in 22.3%. The maximal glucose value within 10 days of admission was >200 mg/dl in 26.3%. They did not find significant association between initial glucose and mortality. For maximum glucose within 24 hours their mortality rate was 6.7% at >200 mg/dl. Mortality rates for maximal glucose within 10 days was 8.1% at >200 mg/dl respectively.

Wintergerst et al (2006) conducted a retrospective study in 1094 pediatric patients. They used maximal glucose value as a parameter for measuring hyperglycemia. They found a frequency of 35.2% for >200 mg/dl, he also demonstrated a significant association of hyperglycemia with mortality 9.9% at glucose level of >200 mg/dl (p <0.001, chi square test). However their total mortality in the study population was 4.6% as compared to our mortality rate of 29.0%. Mortality rates in the PICUs in the developed countries are much lower due to early arrival of patients, better nutritional status of patients and better staffing and facilities in PICUs.

Bhisitkul et al (1994) found 3.8% of children visiting emergency department had glucose >150 mg/dl. These were all emergency cases and not necessarily requiring PICU admission and so incidence was much lower. These studies have found a slightly variable prevalence of hyperglycemia as compared to our study with few readings being more and others less using different cut off values. This may be due to the retrospective nature of their study. Their PICU did not have a glucose monitoring protocol during the study period. Thus patients, who were considered to be at higher risk for hyperglycemia might have been more closely monitored, compared to those thought to be low risk.

The mean glucose level was used as a parameter in an adult retrospective study conducted by Krinsley et al (2004) on 1826 critically ill adults. The lowest mortality 9.6% occurred among patients with mean glucose values between 80 and 99 mg/dl. Further increases in mean glucose had a progressively deleterious association with mortality, increasing to 37.5% for glucose between 200 - 249 and 42.5% for glucose >300 mg/dl.

Siamak Shiva at al (2012) studied 362 critically ill children and found Mortality rate (P=0.001) and need for mechanical ventilation (P=0.02) were higher in the hyperglycemic patients. The results of this study are similar to our study both in terms of disease severity and need for mechanical ventilator support with hyperglycemia in children.

Faustion EV et al(2010) found hypoglycemia blood sugar <40mg/dl in 2.2% critically sick children and blood sugar <60mg/dl in 7.5% of the patients, the results of his study are similar to ours in terms of incidence of hypoglycemia, but they found a significant association between hypoglycemia and mortality unlike our study.

Egi et al (2006) conducted a study to find the association of blood glucose variability and short term mortality in 7049 critically ill adult patients. They found that the S.D. of glucose concentration is a significant independent predictor of mortality. The S.D. of blood glucose was significantly higher in non survivors as compared to survivors. 3 ± 1.6; 1.7 ± 1.3 mmol, respectively). In our study also mean of SD of glucose values in patients who died was significantly higher than those who survived suggesting that glucose variability affects mortality.

CONCLUSIONS: Based on this study, we conclude that hyperglycemia is common in critically ill children. Hyperglycemia is significantly associated with increased mortality. The frequency of hypoglycemia was very less. It occurred in only 6 (3%) of the patients. It was not significantly associated with mortality and length of stay. Non survivors had significantly more fluctuating glucose values as compared to survivors.

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