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AN ANALYSIS OF HYPERGLYCEMIA & IT'S ASSOCIATION WITH OTHER PARAMETERS IN CRITICALLY ILL PAEDIATRIC PATIENTS

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ABSTRACT

INTRODUCTION : With increasing facilities for intensive care becoming available in India, a large number of Intensivists along with 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. Study was conducted to determine the incidence and association of hyperglycemia with outcome of critically ill childrens

METHODS: This Retrospective Analytical study involvd 100 paediatric patients who were grouped as hyperglycemic and non-hyperglycemic . Two groups were compared with each other with demographic variables like age, sex, weight, admission symptoms, nutritional status, final diagnosis, and vital signs at admission. Critical care illness variable like use of inotrope agents, requirement of mechanical ventilation, duration of ventilation, duration of stay in PICU, and final outcome was compared.

RESULTS: Both groups were comparable with respect to demographic variables like age, sex, weight, nutritional status, presenting complaints, disease pattern and severity of illness. Inotropic support , Mean stay in PICU & mortality was significantly higher in hyperglycemics . Mechanical Airway support & PRISM II score and peak glucose levels were higher in Non Survivors Peak blood glucose level and duration of hyperglycemia were independently associated with increased risk of death.

CONCLUSION: We have demonstrated that hyperglycemia occurs commonly in critically ill children and may be associated with poor outcome, glycemic control may confer survival advantage as it does in adults. Prospective, randomized, controlled trials related to glucose control in these children are needed.

INTRODUCTION

Hyperglycemia is a stress response in critically ill patients[1]due to peripheral insulin resistance, relative insulin deficiency, impaired glucose metabolism[1,2] and often additional effects by medications like catecholamine, glucocorticoids and exogenous dextrose administration.[2] In acute stress, hyperglycemia is considered adaptive, both by providing glucose-dependant organs substrate for energy needs and by preserving intravascular volume with increased serum osmolarity.[3-5]Though large number of studies revealed significant association between hyperglycemia and poor outcome in critically ill adults there is little knowledge about incidence of hyperglycemia and its effect in pediatric intensive care unit (PICU).

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. It is unclear whether hyperglycemia is a marker of critical illness in children or an etiological factor contributing to worse outcome. Hyperglycemia in pediatric population may have different effects on morbidity and mortality compared with adults as a consequence of different metabolic demands,[6] differences in co-morbid conditions[7] or age-dependant factors.[8]

Hyperglycemia may be less prevalent among children because diabetes mellitus is much less common in children.[9,10] However, duration of hyperglycemia and index of glucose variability are associated with increased mortality in critically ill children.[9,10]

Hyperglycemia is an important negative prognostic factor in children with severe head injury,[12] gunshot wounds to the brain,[13] and multisystem trauma.[14] Stress hyperglycemia has been described in children with cystic fibrosis, sepsis, near drowning, falls, traumatic brain injury and following cardiac surgery.[15-21]

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 consequences5 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 stroke18 as well as increased risks of dying after myocardial infarction1 and ischemic stroke18 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 managementincluding 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.

This study was conducted to determine the incidence and association of hyperglycemia with outcome of critically ill childrens

METHEDOLOGY

This Analytical study was retrospective in nature & involved Prior Consent from Hospital Authorities / Medical Superintendents of the Local Randomly selected Tertiary care hospitals to see the records of the patients from Medical Records Department (MRD). The study was conducted within ethical standards. The Paediatric Patients who were admitted in the ICUs of randomly selected tertiary care hospitals including Our Teaching Hospital in the city were selected for the study . Randomization was done using computer tables in selecting data. The hospitals selected were equipped with an emergency department and ICU of appropriate beds serving childrens and neonates , attending emergency physicians and residents , attending anesthesiologists who specialized in intensive care medicine. All Patients underwent standard clinical examinations, routine biochemical and haematological investigations,. Medical record numbers were used to generate the data for analysis. After delivery, those patients who required intensive care because of a postpartum cause complicating the delivery were admitted to the ICUs, where the intensive care medicine / Intensivist / Anesthesiologist assume the primary responsibility along with attending Paediatricians.

For the purpose of the present study, 100 of the randomly selected Paediatric patients (candidates / study subjecs) who seeked care for delivery at the emergency department and who were admitted to the ICU between Nov 2019 to March 2020 were retrospectively identified. 100 critically ill children admitted from age group 1 month to 14 years during study period. Children who were on long term steroid, beta agonist or intravenous glucose therapy before their arrival or those with history of diabetes mellitus were excluded. Children who expired in less than 24 h of admission were also excluded. In addition, all post-operative cardiac surgery children who were cared for in separate cardiac intensive care units were also excluded from the study. By these exclusion criteria one hundred patients were included in the study.

The medical records for these patients were reviewed for the collection and classification of data including the patient characteristics, history, the preexisting medical disorders and the causes that necessitated admission to the ICU. The data collected included the demographics and medical history, including admitting diagnosis . The ICU-related data included the critical illness severity scores , Severity of illness was measured byPediatric Risk of mortality score (PRISM II). organ failures, any sepsis, treatment given during ICU admission, including mechanical ventilation, inotropic support, and the ICU stay.

Hyperglycemia was defined as a blood glucose level of >126 mg/dL (>7.0 mmol/L). This was based on report of a WHO consultation on diagnosis and classification of diabetes mellitus.[22] Serial blood glucose levels were monitored first at admission, and thereafter every 12 hourly in all children. Children with hyperglycemia were followed with 6 hourly blood glucose monitoring till blood glucose fell below 126 mg/dl, and this period in PICU was defined as duration of hyperglycemia. Highest blood glucose value measured during PICU stay after first measurement was defined as peak blood glucose. All patients received dextrose containg IV fluids but no patient in this study had undergone insulin infusion for glucose control.

The study population of 100 patients were grouped as hyperglycemic (those with peak blood glucose >126 mg/dL) and non-hyperglycemic (those with peak blood glucose ≤126 mg/dL). Two groups were compared with each other with demographic variables like age, sex, weight, admission symptoms, nutritional status, final diagnosis, and vital signs at admission. Critical care illness variable like use of inotrope agents, requirement of mechanical ventilation, duration of ventilation, duration of stay in PICU, and final outcome was also compared.

Actual time spent from intubation till extubation was defined as 'ventilator days' and duration in PICU excluding ventilator days was considered as "ventilator free days". As ventilator days may appear short in cases of death of patients occurring in short duration after admission, both "ventilators days" along with "ventilator free days" were considered for comparing duration of ventilation. Survivors and non-survivors were compared in relation to admission blood glucose, peak blood glucose and duration of hyperglycemia.

Continuous data were expressed as mean ± standard deviation (SD). The data were analyzed by IBM SPSS Statistics 23. Overall, < 0.05 was proposed to represent statistical significance after correction.

RESULTS

Total study population consisted of 100 children with median age of 2.8 years and median weight of 12.72 kg. 68% were hyperglycemic and 32 % were non-hyperglycemics. For the given effect size population, means of sample size (68 and 32) and alpha power was 1.00. Both groups were comparable with respect to demographic variables like age, sex, weight, nutritional status, presenting complaints, disease pattern and severity of illness. Vital parameters at admission like mean temperature (99.3 ± 1.8 °F vs. 99.5 ± 1.3 °F), mean heart rate (121.5 ± 29 vs. 115.4 ± 25.8 /min), mean respiratory rate (38.7 ± 17.3 vs. 39.9 ± 20.7 /min), use of steroids and PRISM II score (8.12 ± 3.07 Vs 8.03 ± 3.48) were also comparable between the two groups [Table 1]

Table 1: Comparative demography in hyperglycemic verses non-hyperglycemic children

Parameters	Hyperglycemic (n=68)	Non Hyperglycemic (n=32)	P value
Male / Female	41 – Males 27 – Females	19 – Males 13 – Females	0.568
Mean Temperature	99.3 ± 1.8 °F	99.5 ± 1.3 °F	0.386
Mean Heart rate	121.5 ± 29	115.4 ± 25.8 /min	0.492
Mean Respiratory rate	38.7 ± 17.3	39.9 ± 20.7 /min	0.521
PRISM II Score	8.12 ± 3.07	8.03 ± 3.48	0.752

There was no significant difference in the incidence of hyperglycemia among well-nourished and malnourished children . Hyperglycemia was almost similar in all the disease categories without significant preference to a particular system. Incidence of hyperglycemia in children with respiratory disease was 66.17%, in diarrheal cases 63.2%, in neurological cases 70.5 %, in infective cases 86.7%, and in miscellaneous cases 61.7%. Among hyperglycemic children , 46 (67.65 %) had hyperglycemia at admission and remaining 22 (32.35 %) developed it eventually during their PICU stay. Median time to reach peak blood glucose level was about 12 hrs. Median duration of hyperglycemia was about 72 hrs.

Though the requirement of mechanical ventilation among hyperglycemic children was significantly higher than that of non-hyperglycemic, there was no significant difference between median duration of ventilator days or ventilator free days among the two groups.

Inotropic support requirement was significantly higher in hyperglycemics (36.7% vs. 18.7) . Mean length of stay in PICU was also significantly longer for hyperglycemic (7.91 ± 5.01 vs. 5.58 ± 1.95 days) than that of non-hyperglycemic.

Out of the total 100 children studied, 16 expired and mortality was significantly higher (19.11 % vs 9.3%) in hyperglycemic children than non-hyperglycemics .

Though admission blood glucose (190.18 ± 59.08 mg/dL vs. 145.39 ± 52.12 mg/dL) was significantly higher in non-survivors than in survivors, it was not associated (Odds ratio 1.694 , P = 0.33) with increased risk of death.

Median time to reach peak blood glucose was also not significantly (p = 0.062) different between survivor and non survivors.

Peak blood glucose (195.13 ± 50.7 mg/dL vs. 160.75 ± 61.59 mg/dL), duration of hyperglycemia (78.6 ± 40.58 hours vs. 55.88 ± 25.15 hours), requirement of mechanical ventilation (51.72% vs. 17.75%), requirement of inotrops (54.2 % vs. 24.8%) and PRISM II score (10.34 ± 2.56 vs.7.08 ± 3.75) were significantly higher in non-survivors than in survivors . These factors were included as predictors in binary logistic regression model enter method to test their independent contribution for mortality.

Peak blood glucose level (odds ratio-8.35, wald-3.91, $P = 0.047$) and duration of hyperglycemia (odds ratio-1.131, wald 4.833, $P = 0.019$) were independently associated with increased risk of death.

Mechanical ventilation (odds ratio-2.395, wald-1.596, $P = 0.206$) and use of inotrops (odds ratio-1.6, wald-0.402, $P = 0.56$) were not found as to be independent predictors of mortality along with PRISM II (odds 1.24, wald-3.82, $P = 0.06$) score was also not significant .The area under ROC curve for peak blood glucose and for PRISM II score and mortality was higher than that for duration of hyperglycemia.

Kendall's W coefficient was significant ($P < 0.000$) for paired values of glucose in this study.

DISCUSSION

The findings of our studies emphasize higher incidence of hyperglycemia in critically ill children. Some authors in the past have defined hyperglycemia as blood glucose level above 150 mg/dl or above 200 mg/dl and found incidence ranging from 16.7% to 56%.[23-25] We defined hyperglycemia as blood glucose level above above 126 mg/dl or (>7 mmol/l) as similar level considered in previous studies[9,26] and as per revised definition for diagnosis of diabetes (fasting blood glucose level >126 mg/dl) in children by WHO[22] Ninety six (95%) out of 101 acutely ill children were in the fasting state for >12 hours and remaining 5 (5%) were in fasting state for >10 hrs. Higher incidence of hyperglycemia in our study was comparable with studies like Srinivasan *et al*.,[9] Wintergerst *et al*.,[10] Allen *et al*.,[27] and Yung *et al*.[28]. This strikingly higher incidence in our critically ill study population underscores the need to recognize that hyperglycemia is common in such acutely ill children.

No significant difference in incidence of hyperglycemia was found in children with different age groups, systemic diseases and nutritional status which was consistent with Gupta *et al*.[23]

Very high incidence of hyperglycemia was documented in ventilated children by Srinivasan *et al*.,[9] Branco *et al*.,[24] Allen *et al*.,[27] and Yung *et al*.[28] as in our study which could be explained by systemic and pulmonary effects of hyperglycemia.[24].

Day *et al*.[29] found that among children with meningococcemia requiring mechanical ventilation, patients with lower blood glucose had less duration of ventilation required. Yates *et al*.[20] found that prolonged hyperglycemia was associated with increased duration of mechanical ventilation. We could not find such association of duration of mechanical ventilation with hyperglycemia.

We found children with hyperglycemia had higher requirement of inotropic agents. This association could be explained by higher severity of illness in this group. Similar significant association was found by Branco *et al*.[24] and Day *et al*.[29]

Consistent with our findings Faustino et al, [25] and Branco et al.,[24] observed that increase in peak blood glucose levels were significantly associated with increase in ICU length of stay.

Hyperglycemia has been implicated as a predictor of adverse outcome after cardiac surgery.[28]In children, hyperglycemia is associated with worse outcome after severe sepsis[21] and traumatic brain injury.[12] Mortality in hyperglycemic children was significantly higher in our study. Similar findings were observed by Yung *et al*.,[28] Gupta *et al*.,[23] and Osier *et al*.[30]

We found that the admission blood glucose level was significantly higher in non-survivors than in survivors as in the Ruiz Margo *et al*.[26] study. But in contrast toYung *et al*.[28] there was no independent association of admission hyperglycemia with death in our study.

Association of Peak blood glucose with mortality has been documented by Srinivasan *et al*.,[9] Branco *et al*.,[21] and Yates *et al*.[20] like our study. Odds ratio for peak blood glucose level in our study was comparable with Branco *et al*.,[21] (6.1) but it was much higher than that of Srinivasan *et al*.,[9] (1.2). Area under ROC curve for peak blood glucose with high sensitivity and moderate specificity in our study was comparable with Branco *et al*.,[21] . Peak blood gluose level as independent predictor of death has comparable AUC with PRISM II score in our study.

Duration of hyperglycemia was significantly higher in non-survivors than in survivors. It was also an independent risk factor for death in our study with odds ratio comparable with that of Yates *et al*.[20] and Srinivasan *et al*.[9]

Area under ROC curve (0.641) for duration of hyperglycemia was lower as compared to that of peak blood glucose level with very low sensitivity (40%) and high specifi city (91.8%).

The association of peak blood glucose levels and duration of hyperglycemia with mortality was independent of severity of illness, inotrops use, mechanical ventilation or steroid use, suggesting that hyperglycemia may not be just an epiphenomenon, but a maladaptive response to stress. Over estimation of risk of mortality due to hyperglycemia was possible in our study related to limitation of the study design. We have excluded sizeable group of children who were on IV glucose infusion, inotropes and steroid before admission to our PICU as per our exclusion criteria.

CONCLUSION

We have demonstrated that hyperglycemia occurs commonly in critically ill children and may be associated with poor outcome, glycemic control may confer survival advantage as it does in adults. Prospective, randomized, controlled trials related to glucose control in these children are needed. Incidence of hyperglycemia in critically ill non-diabetic children was high . Requirement of ventilation and inotropic support, length of PICU stay and mortality were significantly higher in hyperglycemic children. Peak blood glucose levels and longer duration of hyperglycemia were independently associated with mortality so close monitoring of blood sugar levels is required in critically ill children, especially those who require ventilation and inotropic support.

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