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Frequency and Mortality Associated with Hyperglycemia in Critically Ill Children

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ABSTRACT

Objective: To determine the frequency of hyperglycemia in critically ill children admitted in PICU of a tertiary care hospital of Karachi and to compare the mortality of critically ill children with and without hyperglycemia.

Study Design: Cross-sectional study.

Place and Duration of Study: Paediatrics Intensive Care Unit (PICU) of National Institute of Child Health (NICH), Karachi, from November 2011 to April 2012.

Methodology: One hundred fifty critically ill children admitted to PICU were included. Patients who had fasting blood sugar levels more than 126 mg/dl within 48 hours of admission were included in the hyperglycemic group. The normoglycemic and hyperglycemic groups were followed till 10 days to determine the mortality associated with hyperglycemia.

Results: Out of 150 patients, 82 (54.7%) had hyperglycemia. Mortality rate was 48.7% (n=73/150). However, mortality rate was significantly high 57.3% (n=47) in hyperglycemic patients than non-hyperglycemic patients (p=0.019).

Conclusion: The presence of stress-induced hyperglycemia in critically ill patients is a well established marker of poor outcome, and a very high mortality rate. Normoglycemia was associated with favorable outcomes in terms of hospital stay and mortality.

Key Words: Hyperglycemia. Mortality. Critically ill children. Stress-induced hyperglycemia.

INTRODUCTION

Hyperglycemia is a common finding in critically ill patients. Hyperglycemia, during critical illness, results from a stress response that is modulated by the hypothalamic-pituitary-adrenal axis, the autonomic nervous system and the cytokines. Recent studies have shown that hyperglycemia in non-diabetic population has been associated with increased risk of mortality, increased length of hospital stay and increased risk of infections.¹

The association between stress and hyperglycemia was first described in the 19th century by Claude Bernard.² After Bernard's pioneering study, different terms such as stress diabetes, traumatic diabetes, diabetes of injury and critical illness hyperglycemia were used to describe the correlation between hyperglycemia and stress.³ All such studies revealed that stress had increased the release of counter regulatory hormones like glucagon, epinephrine, cortisol and growth hormone. These hormones, as a result, increase hepatic glucose production and decrease peripheral glucose uptake.⁴

Deleterious effects of hyperglycemia include free radical formation and abnormalities in white cell function like granulocyte adhesion defects, chemotaxis, phagocytosis, and superoxide formation. Hyperglycemia also impairs complement activity leading to a greater risk of infectious complications and affects the fluid balance by causing glycosuria and osmotic diuresis resulting in hypovolemia, electrolyte abnormalities and hyperosmolar non-ketotic coma. It also increases catabolism in skeletal muscles.

Studies in adults, using insulin to treat hyperglycemia and normalize blood glucose levels in large randomized controlled trials, have shown reduction in ICU mortality as a result of better glycaemic control.⁵ Moreover, glycaemic control is used in many adult ICU, however, it is still to be evaluated and implemented for the paediatric population. For purpose of the present research, the definition of hyperglycemia is based on the study conducted by Srinivasan *et al.*⁶ This study showed that non-survivors had more intense hyperglycemia during the first 48 hours as well as a longer duration of hyperglycemia. Furthermore, blood glucose level in hyperglycemic range was occurred in 86% of the patients during their PICU stay and associated with a 6-fold increase in mortality risk in the study population. An appropriate management of hyperglycemia may lead to an improved outcome in the future.⁷

The purpose of conducting this study was to find out the frequency of hyperglycemia in the PICU so that it may help in formulating recommendations.

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METHODOLOGY

It was a cross-sectional study conducted from November 2011 to April 2012 in Paediatric Intensive Care Unit (PICU) of National Institute of Child Health, Karachi. The estimated sample size was of 150 patients of either gender, aged from 1 month to 14 years of age, who were admitted for the Paediatric ICU. Patients were enrolled by non-probability sampling. All those patients who were admitted in PICU for at least 48 hours and having fasting blood sugar levels more than 126 mg/dl were included in the hyperglycemic group while those having blood sugar levels less than 126 mg/dl were followed in the normoglycemic group.⁸ Blood sugar levels were checked at admission and then twice daily for 48 hours by glucometer. The results were regularly calibrated and rechecked from laboratory. Both the groups were followed for 10 days for outcomes like mortality, shift out to step down or discharged. The severity of illness was assessed using Paediatric Risk of Mortality score (PRISM III) obtained from the PICU data sheet. A low score (< 10) is associated with greater chances of survival and higher (> 80) score associated with increased mortality.

Exclusion criteria included diabetic children, hepatic failure, renal failure requiring dialysis and those having glucose infusion rate more than six, or patients on steroids. Data analysis was done using SPSS version 16. Categorical variables like gender, hyperglycemia, PRISM scores, mortality and shift to step down were computed in frequency and percentages. Continuous variables like age, weight, days on mechanical ventilation were estimated in mean and standard deviations. Comparison of mortality between hyperglycemic and normoglycemic groups were done using chi-square test. The results were considered statistically significant when $p < 0.05$.

RESULTS

A total of 150 patients were included in this study. Most of the patients were below 3 years of age. Their age, weight, PRISM score and random blood sugar are presented in Table I. Out of the 150 cases, 56.7% (n=85) were male and 43.3% (n=65) were female children. Mild (PRISM score < 10) was seen in 58% (n=87) cases and 42% (63) were moderate (PRISM score 11 to 79). There were 37.3% children on ventilation and the average stay on ventilation was 3.27 ± 1.45 days.

Frequency of hyperglycemia in critically ill children was observed in 82 patients (54.7%). Overall mortality rate was 48.7% (n=73/150). However, it was significantly high in hyperglycemic patients than non-hyperglycemic patients – 57.3% (47/82) vs. 38.2% (26/68) $p=0.019$. Age was not significantly associated with hyperglycemia ($p=0.27$, Table II). Mortality rate was significantly high in male patients with hyperglycemia (n=85, $p=0.002$) than

females (n = 65, $p=0.93$). Mortality was significantly high in 10.1 - 15 kg children with hyperglycemia ($p=0.02$, Table III). While high PRISM score were significantly associated with hyperglycemia (n=44/63, $p=0.001$).

Table I: Descriptive statistics of characteristics of patients.

| Variables | 95%CI | Median (IQR) | Max-Min |
|-----------------------------------|-----------------|--------------|----------|
| Age (months) | 28.95 - 40.83 | 24 (38) | 147 - 1 |
| Weight (kg) | 9.38 - 11.47 | 9 (7) | 35 - 2 |
| PRISM III score in first 24 hours | 8.39 - 10.62 | 9 (12) | 27 - 0 |
| Blood glucose level (mg/dl) | 156.78 - 194.65 | 145 (97) | 650 - 22 |

Table II: Comparing mortality of critically ill children with and without hyperglycemia with respect to age.

| Age In months | Alive Hyperglycemia | | Dead Hyperglycemia | | p-value |
|---------------|---------------------|----|--------------------|----|---------|
| | Yes | No | Yes | No | |
| 1 - 12 | 13 | 9 | 22 | 8 | 0.37 |
| 13 - 36 | 13 | 22 | 12 | 11 | 0.29 |
| 37 - 60 | 3 | 3 | 5 | 3 | 0.99 |
| 61 - 144 | 6 | 8 | 8 | 4 | 0.27 |

Table III: Comparing mortality of critically ill children with and without hyperglycemia with respect to weight.

| Weight | Alive Hyperglycemia | | Dead Hyperglycemia | | p-value |
|--------------|---------------------|----|--------------------|----|---------|
| | Yes | No | Yes | No | |
| < 5 kg | 4 | 3 | 18 | 10 | 1.00 |
| 5.1 <10 kg | 20 | 21 | 12 | 9 | 0.59 |
| 10.1 <15 kg | 4 | 12 | 8 | 3 | 0.02 |
| 15.1 < 20 kg | 6 | 5 | 7 | 2 | 0.37 |
| > 20 kg | 1 | 1 | 2 | 2 | 0.99 |

DISCUSSION

Hyperglycemia occurs frequently among critically ill patients, with prevalence rate reported from 3% to 71%.⁹ However, there has not been a census statement on the cut-off value to define significant hyperglycemia. Different studies have used different values and thus have reported separate prevalence rates. Studies revealed a significant association between hyperglycemia and increased morbidity and mortality rates among adult patients, both diabetic and non-diabetic, in the ICU. In particular, hyperglycemia has been shown to be a risk factor for poor outcomes in a variety of clinical settings, including trauma,¹⁰ cardiac,¹¹ surgical, head injury and stroke. Moreover, controlling hyperglycemia greatly improves the risk of morbidity and death among such critically ill adult patients.

The sample recruited 150 children which included predominantly boys (56.7%). Some 54.7% (n=82) of critically ill children had hyperglycemia. The mortality rate was also high 57.3% in this group. Further, mortality of critically ill children with hyperglycemia was statistically significant ($p=0.019$). Hyperglycemia, seen more in boys, could be explained because we had more male patients than females, as no studies have shown any gender association of hyperglycemia so far. We also

found that frequency of hyperglycemia in critically ill patients in respect to age and gender was non-significant but severity of illness was significant. In contrast, the study done by Srinivasan *et al.*¹² who had also inducted a total of 150 patients, having the same criteria of > 126 mg/dl to define hyperglycemia, found 86% of critically ill children having hyperglycemia. He had also showed that duration and intensity of hyperglycemia was higher in non-survivors.

In a prospective randomized study, Van den Berghe *et al.*¹³ reported on 1548 patients admitted to an adult surgical ICU that during the admission, intensive treatment with intravenously administered insulin to control hyperglycemia (target range: 80-110 mg/dl) for both diabetic and non-diabetic patients reduced the risk of death in the ICU by 42%, the overall in-hospital mortality rate by 34%, the sepsis rate by 46%, the acute renal failure rate by 41%, and the median number of red blood cell transfusions by 50%. With less-stringent criteria for glycemic control (target range: 80 - 140 mg/dl), Krinsley also reported that control of hyperglycemia greatly improved morbidity and mortality risks among critically ill adult patients.¹⁴ That study, in contrast to the predominantly postoperative, cardiothoracic, surgical population in the study by Van den Berghe *et al.*, was a historical control trial that included both medical and surgical patients.¹⁵ Van den Berghe *et al.* reported the results of a similarly designed, prospective, randomized study focusing on the effects of glycemic control (target range: 80 - 110 mg/dl) among medical, rather than surgical ICU patients. Unlike the surgical ICU study, tight glycemic control did not reduce the overall in-hospital mortality rate significantly. The mortality rate was reduced among patients with ICU admissions of >3 days. However, there was also a significant reduction in the morbidity rate, regardless of the number of days in the ICU. Less is known about the incidence of hyperglycemia and its effects in the PICU.

Hyperglycemia is an important negative prognostic factor and an indication of poor neurologic long-term outcomes among paediatric patients with traumatic head injuries.¹⁶ Among infants, diagnosed as having necrotizing enterocolitis, hyperglycemia is common and is associated with longer length of stay (LOS) and increased rate of late death in the NICU.¹⁷ In a study conducted by Jennifer *et al.*, glucose control protocol was used by using insulin therapy, achieved normoglycemia and severe hypoglycemia did not occur.¹⁸ On the contrary, a study conducted in PICU of Brazil and in Cambridge, UK¹⁹ has shown that normoglycemia is difficult to achieve. It is evident that glycemic control is associated with increased incidence of hypoglycemia and use of insulin is not without risk.²⁰

The presence of stress-induced hyperglycemia in critically ill patients, especially in those without evidence

of antecedent diabetes, is a well-established marker of poor outcomes.²¹ Similarly, this study in children found that 54.7% of critically ill children have hyperglycemia. Further, mortality of critically ill children with and without hyperglycemia was statistically significant. Two large single-center studies, comparing the standard strategy of permissive hyperglycemia to use intravenous insulin to achieve a blood glucose between 80 and 110 mg/dl (intensive insulin therapy), demonstrated overall clinical benefit with the intensive insulin therapy. However, more recent studies of insulin therapy in critically ill patients have yielded conflicting results.²² In addition, a growing awareness of the potential risk of hypoglycemia, which can occur more frequently when using intravenous insulin therapy, has raised concerns over the best way to control glucose. Despite this, reverting back to allowing hyperglycemia to continue unchecked, is unlikely to be the correct approach either.

The main weakness of the study was use of cross-sectional study design, as the cross-sectional study is unable to comment on the causative association between predictor and outcome. The selection of non-probability sampling limits generalizability of the study results and findings. Although study sample size was scientifically calculated, the selection of an epidemiological study warrants a large sample size to provide true estimation of frequency and prevalence.

There are many strengths of this study. First, the simple and single objective determination based on single outcome and complete, simple, well defined exposure and outcome variables in measurable terms, reduces and controls bias and confounders. The scientific apriori calculation of sample size provides rigor in our sample. The stringent inclusion and exclusion criteria and stratification at the level of analysis not only limit the bias and confounders but also control the effect modification in the study. These strengths also increase the generalizability of these findings and worthiness of the study.

CONCLUSION

A high proportion of severely or critically ill children not only had hyperglycemia but also a very high mortality rate as compared to normoglycemic children. The authors emphasize the need for blood glucose monitoring in all patients admitted in intensive care units.

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