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Investigation of the Relation Between Hyperglycemia and Morbidity and Mortality Rates in Critically Ill Children in March 2013 to February 2014

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Abstract

Background: The purpose of this study is to determine the frequency of hyperglycemia in nondiabetic critically ill children and to investigate its relationship with mechanical ventilation, length of stay and mortality.
Methods: In this original retrospective study, data was (were) collected between 2013 and 2014 from the pediatric intensive care unit data base of Sheikh's Children Hospital in Mashhad, Iran (one hundred admitted children).
Results: From among 97 subjects, 49 subjects (50.5%) were hospitalized for more than 10 days, and the mean length of stay was 14 days. The overall mortality rate was 16 subjects (16.5%) and frequency of hyperglycemia was 24 subjects (24.7%). The median for blood glucose measurements was 100 mg/dl. Seventy three subjects (75.3%) had a mean blood glucose level in the normal range. Overall, 18 subjects (18.6%) had at least one blood glucose measurement of 180 mg/dL or higher. There was a significant association between hyperglycemia and mortality ($P < 0.001$). Linear regression analysis showed positive correlation between blood glucose level, length of stay and length of ventilation ($P \leq 0.001$). The maximum serum glucose concentration positively correlated with duration of mechanical ventilation and length of stay ($P < 0.001$).
Conclusions: Our study found that maximum serum glucose concentration positively correlated with the duration of mechanical ventilation, length of stay, and mortality.

Keywords: Hyperglycemia, Children, Mortality, Mechanical Ventilation, Length of Stay, Pediatric Intensive Care Unit

1. Background

Hyperglycemia is a normal response to stress in critically ill children, providing the glucose dependent organs such as brain and blood cells with their energy needs (1). A frequent event in critically ill children, hyperglycemia is associated with poor outcomes, including increased length of stay (LOS) higher infection rates, greater duration of mechanical ventilation, and higher mortality. Better glycemic control may improve survival (2, 3). Some causes, such as peripheral insulin resistance, relative insulin deficiency, impaired glucose metabolism, and medications such as catecholamine, glucocorticoids, and exogenous dextrose may also lead to hyperglycemia (4). Endogenous elevation of glucose production through gluconeogenesis and glycogenolysis can also cause hyperglycemia; This could happen as a result of an increases in regulatory hormones (including cortisol, catecholamines, glucagon, and growth hormone), combined with a decrease in insulin-stimulated uptake of glucose by peripheral tissues (2, 5).

Incidence of hyperglycemia in critically ill nondiabetic children was high (4). Mechanical ventilation and inotropic support, length of pediatric intensive care unit (PICU) stay, and mortality were significantly greater in hyperglycemic children than non-hyperglycemic children (4). It has been found that higher peak blood glucose levels and a longer duration of hyperglycemia were independently associated with mortality (6). It has also been reported in non-diabetic children admitted to a PICU, a maximum blood glucose concentration higher than 150 mg/dL within 24 hours combined with a peak blood glucose concentration higher than 120 mg/dL within 10 days of admission were correlate with in-hospital mortality (5). Hyperglycemia at 24 hours (present in 54 % of the subjects) was associated with 3.5 times higher mortality risk. A longer duration of hyperglycemia and a higher

peak blood glucose value during PICU stay were associated with an adverse outcome (5).

Recent studies indicate that hyperglycemia is a significant concern among physicians caring for critically ill children, and that glycemic management is routinely performed to improve outcomes and reduce morbidity and mortality (7-11). The purpose of this study is to determine the frequency of hyperglycemia in non-diabetic children and to investigate its relationship with mechanical ventilation, length of stay, and mortality.

2. Methods

This analysis was performed as a retrospective observational study. The study was conducted at Dr Sheikh Children's Hospital in Iran. Randomization was stratified by the center. Data were collected from the hospital's PICU database. The subjects were first admitted in 2013 from October to December; 100 medical records were selected and patients with even one hypoglycemic episode were excluded until finally 97 medical records remained.

The PICU unit was composed of a heterogeneous population of medical and surgical patients cared for by a team of pediatric intensivists. Children aged between 2 or 3 days to 13 years were first enrolled in the study between March 2013 to February 2014.

In our retrospective study, the analized variables included age, gender, underlying diagnosis, weight, and days of ventilation, length of stay in hospital, mortality, and blood glucose levels. The blood glucose levels were divided into the following categories: (BG 40 to 120 mg /dL), mild-moderate hyperglycemia (BG 120 to 179 mg/dL) and severe hyperglycemia ($\geq$ 180 mg/dL) (7).

We defined hyperglycemia using the 2006 American Diabetes Association and World Health Organization definition of blood glucose level of $\geq$ 12 6 mg/dL .The duration of hyperglycemia was calculated as the time from a blood glucose value of > 126 mg/dL until the next blood glucose value that was < 126 mg/dL (1). We also divided children into five age groups: (a) younger than 3 months, (b) 3 to 6 months, (c) 6 to 9 months, (d) 9 to 12 months, and (e) older than 12 months. Organ dysfunction was defined as failure of all six categories diseases, e.g. renal, respiratory, cancer, septicemia, gastrointestinal, and neurological. Descriptive statistics were utilized to describe the demographic and descriptive data. Univariate analyses were used to assess the association between risk factors, hyperglycemia, mortality, total number of mechanical ventilation days, and length of stay in hospital.

For the outcome measurement, the KrusKal vallis test was utilized for independent variables. Univariate logistic regression was used for length of mechanical ventilation, and length of stay. We determined the significance of differences in responses between pediatric ICU centers with analysis (for categorical variables) and an independent student test (for continuous variables). The P value < 0.05 was considered statistically significant. Data were analyzed using SPSS software (version 11.0) because many of the variables were not distributed normally, chi-square root transformations of the data were applied. Comparisons in glucose groups used Pearson χ square test for dichotomous variables. Because sample sizes were not equal, the less significant result of the student test or the separate variance estimates was reported. Pearson correlations were reported as a descriptive statistic to describe strength of association.

Statistical comparisons were made using the Mann-Whitney U test. Linear regression analysis was used to determine whether glucose level was associated with mortality rate or LOS.

3. Results

A total of 97 patients admitted to the PICU (51.5 % boys and 48.5 % girls) were included in the study. Age ranged from first day to 156 months (Table 1). The details of the 97 subjects, including a confirmed diagnosis of underlying diseases, are summarized in Table 2. Major diagnoses included renal disease (n = 9), gastrointestinal disease (n = 61), neuro-developmental disorders (n = 14), respiratory conditions (n = 7), septicemia (n = 7), and cancer (n = 1). Forty nine subjects (50.5 %) were hospitalized for more than 10 days, and the mean and median length of stay was 14 and 10 days respectively (ranging from 2 to 66 days). The overall mortality was 16 subjects (16.5%). The frequency of hyperglycemia was 24 subjects (24.7%).The mean and median number of blood glucose measurements was 120 mg/dL and 100 mg/dL range, 28 - 730). Twenty four of subjects had blood glucose > 120 mg/dL at some stage during their admission. The frequency of patients in three groups of blood glucose is shown in Figure 1.

There was a significant association between hyperglycemia and percentage of death (16.5%), (P = 0.001). The blood glucose concentration was positively correlated with LOS and the length of dependence on mechanical ventilation (P = 0.002). The median length of ventilation was 2 days (ranging from 1 to 49 days). The distribution of LOS and length of ventilation is shown in Figures 2 and 3.

The hospital length of stay was significantly longer in surviving children with blood glucose levels of more than 120 mg/dL (P = 0.001). Furthermore, the average blood glucose level was significantly higher in the non-surviving children (P = 0 .001).

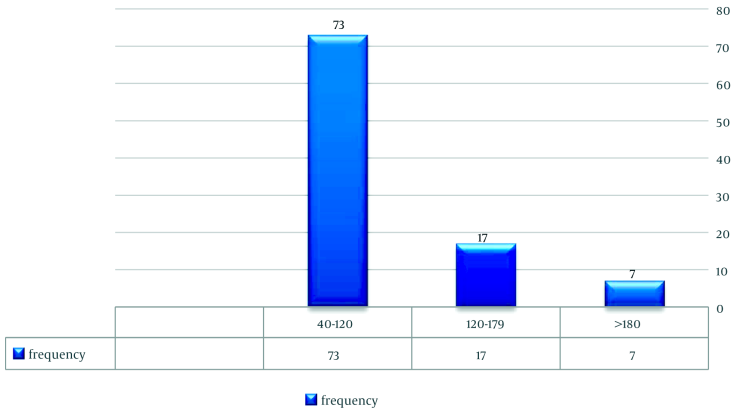

Figure 1. The Distribution Frequency of Mean Glucose Level in Each Category of Subjects

Table 1. Background Characteristics of 97 Children

Patient (n = 97)		
Characteristic		
Gender	Male	50
	Female	47
Age (mo)	< 3	56
	3 - 6	10
	6 - 9	10
	9 - 12	1
	> 12	20
LOS		14 (2 - 66)[a]

Abbreviation: LOS, length of stay (calculated with range in days).
[a]Mean (range).

Table 2. Classification of Underlying Diseases

Characteristic	Values
Renal	9
Gastrointestinal disease	58
Neuro-developmental disorders	14
Respiratory disorders	7
Sepsis	7
Cancer	1

Observed associations between hyperglycemia, length of ventilation and Mortality rate andrate of death were significant (P = 0.001). The length of stay in PICU was significantly longer in children with blood glucose levels of more than 120 mg/dL. Linear regression analysis showed the relationship between blood glucose level, LOS and length of ventilation (P = 0.001).

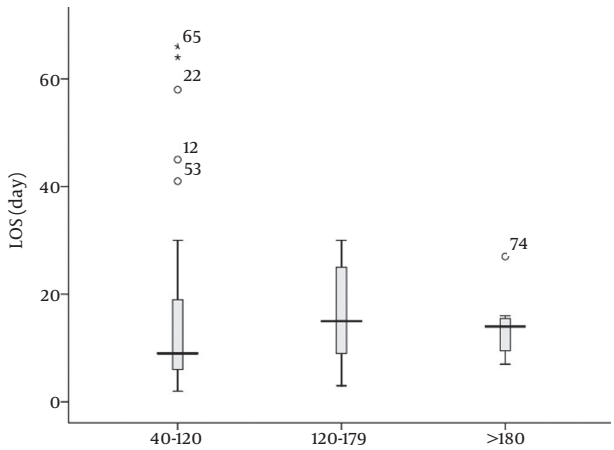

Figure 2. The Comparison of Length of Stay (LOS) Between 40 - 120 and 120 - 179 and > 180 Groups

4. Discussion

This study demonstrates the significance of increased mean glucose levels $\geq$ 120 mg/dL over a one-week stay in a PICU. In hospitalized adults, the definition of stress hyperglycemia has been challenged over the past several years based on at least one large trial, which demonstrated a survival benefit to maintaining a glucose target of less than 110 mg/dL in the intensive care unit (7). However, there is a paucity of studies regarding the impact of mild or moderate hyperglycemia on the outcomes in pediatric populations (7).

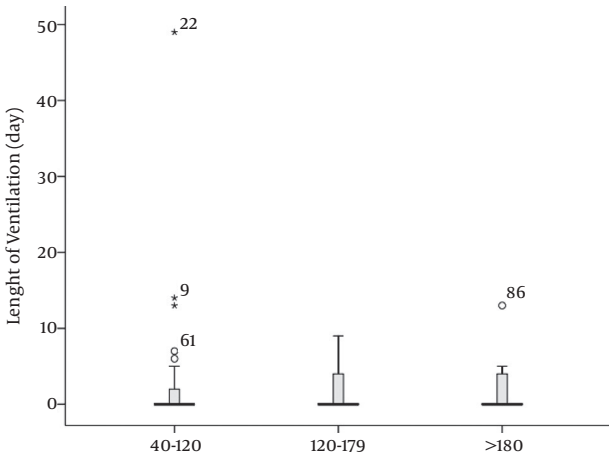

Figure 3. The Comparison of Length of Ventilation Between 40 - 120 and 120 - 179 and > 180 Groups

4.1. Mortality

The mean level of blood glucose in this study was 126 mg/dL, and the overall frequency of children with a glucose level above 180 mg/dL was 24%. This study found significant associations between hyperglycemia and requirements for mechanical ventilation, LOS, and mortality.

Over the course of the first week of life Hperglycemia has been associated with increased risk of death (7). Furthermore, Umpierrez et al reported that patients in medical and surgical units with newly discovered hyperglycemia (fasting glucose level > 126 mg/dL, and/or random glucose > 200 mg/dL on two occasions) had a higher inpatient mortality rate (16%) compared to that of patients with a prior history of diabetes (3%) or subjects with normoglycemia (1.7%). In addition, newly hyperglycemic patients have been shown to have a longer length of hospital stay, a higher admission rate to intensive care, and less chance of being discharged to home, frequently requiring transfer to a transitional care unit or a nursing home compared with patients with a prior history of diabetes (12). Faustino and Apkon found subjects had a 2.5 times greater risk of dying if the maximum glucose level obtained within 24 hours of admission to the PICU was greater than 150 mg/dL, and a 5.68 times increased mortality risk if the maximum glucose obtained within 10 days of admission to the PICU was greater than 120 mg/dL (6).

4.2. Mechanical Ventilation

In our study the median length of mechanical ventilation was 2 days and the maximum serum glucose concentration positively correlated with the length of dependency on mechanical ventilation.

Recently, investigators reported cumulative hyperglycemia rates of 89% in mechanically ventilated patients in a PICU (using a single blood glucose level of greater than 110 mg/dL to define hyperglycemia) (13, 14). Elsewhere it has been reported that 86% of patients in a PICU requiring mechanical ventilation or vasopressors developed hyperglycemia, although the study did not further analyze subgroups (15). Subjects requiring mechanical ventilation or vasopressor infusions also have a very high incidence of critically deleterious hyperglycemia. In a study of one PICU, Preissig et al. showed patients requiring mechanical ventilation, vasopressor infusions, or both developed persistent blood glucose levels greater than 140 mg/dL at rates of 60%, 90%, and 93%, respectively (16). Researchers also found that among children with meningococcemia requiring mechanical ventilation, patients with lower blood glucose required a lower duration of ventilation (17). Research also shows prolonged hyperglycemia to be associated with increased duration of mechanical ventilation (18).

4.3. Length of Stay

We found that the length of stay in PICU was significantly longer in surviving subjects with blood glucose levels of more than 120 mg/dL, demonstrating a positive association between hyperglycemia and LOS. A previous study found that length of stay was increased if the maximum blood glucose obtained within 10 days of admission to the PICU was greater than 120 mg/dL (6). It has also been reported that infants with glucose maximums greater than 11.9 mmol/L (214 mg/dL) more frequently required a stay of greater than 10 days compared to those with lower glucose maximums (10). In a similar study, Wintergersat et al shown, there was a significant increase in both PICU and total hospital stays with increasing maximum glucose levels. Death was associated with greater maximal glucose level and those patients were found to have the lowest PICU LOS and total hospital LOS values, as well as no deaths (19).

4.4. Conclusions

Because of the high frequency of hyperglycemia in critically ill children, and the associated morbidity and mortality, investigating this issue is very important. If blood glucose measurement had been done regularly, for example, every 6 hours, this study would have been more accurate. It has been clearly shown that careful glycemic control with intravenous insulin improves morbidity and mortality in adult diabetic and non-diabetic patients during periods of critical illness (17). Similar evaluation of treatment in critically ill children appears to be necessary.

Our study shows associations between hyperglycemia and length of ventilation and mortality. There was no

statistically significant association between blood glucose level and LOS in the PICU, but the hospital length of stay was significantly longer in subjects with blood glucose levels of more than 120 mg/dL. The maximum serum glucose concentration was therefore positively correlated with the length of dependence on mechanical ventilation, LOS, and mortality.

Careful glycemic control may improve morbidity and mortality in adult diabetic and non-diabetic patients during periods of critical illness. Regular glycemic control in critically ill children could be similarly helpful.

The major limitations of this study are the retrospective design of the study and the lack of long term outcome data, and because of the retrospective nature of the study, we were unable to adjust for all of the potential confounders such as administration of total parenteral nutrition, insulin administration and glucose load. Despite these limitations, these data provide new information regarding the incidence and risk factors for hyperglycemia in children during hospitalization.

Footnote

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