

# Hyperglycemia in critically ill children

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Objectives: To determine the incidence and study association of hyperglycemia with outcome of critically ill children. Setting and Design: This was a prospective observational study conducted in eight bedded pediatric intensive care unit (PICU) of a tertiary care hospital. Materials and Methods: One hundred and one critically ill non-diabetic children between ages of I month to 16 years were studied from the day of admission till discharge or death. Serial blood sugars were determined first at admission, thereafter every 12 hourly in all children. Blood glucose level above 126 mg/dl (>7 mmol/dl) was considered as hyperglycemia. Children with hyperglycemia were followed 6 hourly till blood glucose fell below 126 mg/dl. Hyper and non-hyperglycemic children were compared with respect to length of stay, mechanical ventilation, use of inotrops and final outcome. Survivors and non-survivors were compared in relation to admission blood glucose, peak blood glucose level and duration of hyperglycemia. Results: Seventy (69.3%) children had hyperglycemia. Requirement of ventilation [(23) 32.9% vs.(3) 9.7%], requirement of inotropic support [(27) 38.6% vs.(5) 16.1%], Mean length of stay in PICU (7.91 ± 5.01 vs. 5.58 ± 1.95 days) and mortality (28.6% vs. 3.2%) among hyperglycemic children was significantly higher (P < 0.05) than that of non-hyperglycemic. Logistic regression analysis showed Peak blood glucose level and duration of hyperglycemia has independent association with increased risk of death. Conclusion: Incidence of hyperglycemia is high in critically ill children and it is associated with high morbidity and mortality.

Keywords: Critically ill children, hyperglycemia, pediatric intensive care unit

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### Introduction

Abstract

Hyperglycemia is a stress response in critically ill patients<sup>[1]</sup>due to peripheral insulin resistance, relative insulin deficiency, impaired glucose metabolism<sup>[1,2]</sup> and often additional effects by medications like catecholamine, glucocorticoids and exogenous dextrose administration.<sup>[2]</sup> 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.<sup>[3-5]</sup>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).

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Department of Pediatrics, Wanless Hospital Miraj, <sup>1</sup>Bharati Vidyapeeth University Medical College, Sangli, Maharashtra, India

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Dr. Vinayak Krishnarao Patki, Indraprastha, 5<sup>th</sup> Lane, Nitave Colony, Jaysingpur - 416101, kolhapur, Maharashtra, India. E-mail: patkivinayak@gmail.com 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,<sup>[6]</sup> differences in co-morbid conditions<sup>[7]</sup> or age-dependant factors.<sup>[8]</sup>

Hyperglycemia may be less prevalent among children because diabetes mellitus is much less common in children.<sup>[9,10]</sup> However, duration of hyperglycemia and index of glucose variability are associated with increased mortality in critically ill children.<sup>[9,10]</sup> Among infants with necrotising enterocolitis, hyperglycemia is common and is associated with increased length of stay and increased mortality.<sup>[11]</sup> Hyperglycemia is an important negative prognostic factor in children with severe head injury,<sup>[12]</sup> gunshot wounds to the brain,<sup>[13]</sup> and multisystem trauma.<sup>[14]</sup> Stress hyperglycemia has been described in children with cystic fibrosis, sepsis, near drowning, falls, traumatic brain injury and following cardiac surgery.<sup>[15-21]</sup> This study was conducted to determine the incidence and association of hyperglycemia with outcome of critically ill children.

## **Materials and Methods**

This was a prospective cross-sectional analysis of the critically ill children admitted at eight bedded PICU at a tertiary care center over a study period of 1 year from 1<sup>st</sup> August 2007 to 31<sup>st</sup> July 2008. Two hundred and thirty six critically ill children admitted from age group 1 month to 16 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 also excluded from the study. By these exclusion criteria one hundred and one children were included in the study.

All children in the study were studied from day of admission and followed up till death or discharge.

Relevant clinical details regarding age, gender, weight, family history of diabetes mellitus, past history, present diagnosis, vital parameters, treatment required in the form of IV fluids, inotropic support, length of stay in PICU, any operative procedure done, use of steroid, duration of mechanical ventilation if required, clinical outcome, and routine investigations performed were recorded for all 101 children. Severity of illness was measured byPediatric Risk of mortality score (PRISM II).

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.<sup>[22]</sup> 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.

Blood glucose paired values included both whole-blood bed side glucometer(Accu-check senor comfort-Brand Roche) and chemistry laboratory serum values (Chem well analyzer, awareness technology, Inc.). The bedside glucometer was calibrated and checked daily, and laboratory glucose analyzer was calibrated every 6 months and checked daily.

The study population of 101 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.

The data were presented as mean ± Standard deviation. Normally distributed continuous variables were compared with Student's t-test and categorical variables were compared with Chi-square test or Fisher's exact test. For non-normally distributed (skewed) data median was used instead of mean and was compared using "median test". For paired samples, degree of concordance was calculated by Kendall's W test. After determination of individual factors associated with mortality by univariate analysis, a binary logistic regression model of significant factors associated with mortality was developed. The results of regression model were presented as adjusted odds ratio with 95%Confidence intervals. Wald's chi square value was used to test unique contribution of each predictor.Regression model adequacy was tested by Omnibus test of model coefficients, Negelkerke R square and Hosmer and Lemeshow chi-sqare test. Receiver operating characteristic curve (ROC curve) was used to validate predicted probabilities of death. In all comparisons, P < 0.05 was considered significant. IBM SPSS software 19.0 was used for statistical analysis.

## Results

Total study population consisted of 101 children with median age of 2.2 years and median weight 12 kg.

Seventy (69.3%) were hyperglycemic and 31 (30.7%) were non-hyperglycemics. For the given effect size population, means of (196.2 Vs 107.6), SD (54.7 Vs 9.9), sample size (70 and 31) and alpha (0.05,2 tailed) 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 (99.2  $\pm$  1.7°F vs. 99.4  $\pm$  1.5°F), mean heart rate (123.5  $\pm$  33 vs. 117.4  $\pm$  27.80/min), mean respiratory rate (39.2  $\pm$  19.1 vs. 40.9  $\pm$  20.3/min), use of steroids and PRISM II score (8.32  $\pm$  3.07 Vs 8.03  $\pm$  3.68) were also comparable between the two groups [Table 1].

Male patient to female patient ratio in hyperglycemic children was 1.6:1. Incidence of hyperglycemia was 70.4% in the age group of 1 month-12 months, 64.3% in age group of 1 year to 5 years and 75% in above 5 years age group. There was no significant difference in the incidence of hyperglycemia among well-nourished (71%) and malnourished children (63.6% in children with grade I PEM, 72.7% in grade II PEM, 100% in grade III PEM). 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 64%, in diarrheal cases 62.5%, in neurological cases 71.4%, in infective cases 81.8%, and in miscellaneous cases 64%. Among hyperglycemic children 47 (67.2%) had hyperglycemia at admission and remaining 23 (32.8%) developed it eventually during their PICU stay. Median time to reach peak blood glucose level was 12 hrs. Median duration of hyperglycemia was 72 hrs.

Though the requirement of mechanical ventilation (32.9% vs. 9.7%) 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 also significantly higher (38.6% vs. 16.1) in hyperglycemics. Mean length of stay in PICU was significantly longer for hyperglycemics (7.91 ± 5.01 vs. 5.58 ± 1.95 days) than that of non-hyperglycemics.

Out of the total 101 children studied, 21 (20.8%) expired and mortality was significantly higher (28.6% vs. 3.2%)) in hyperglycemic children than non-hyperglycemics [Table 2].

Though admission blood glucose (192.38 $\pm$ 59.08 mg/dL vs. 147.59  $\pm$  62.12 mg/dL) was significantly higher in non-survivors than in survivors, it was not associated

(Odds ratio 1.714,95% C.I. 0.649-4.725 and P = 0.33) with increased risk of death. Median time to reach peak blood glucose was also not significantly (p-0.053) different between survivor and nonsurvivors.

Peak blood glucose (198.43  $\pm$  51.17 mg/dL vs. 162.45  $\pm$  62.09 mg/dL), duration of hyperglycemia (79.2  $\pm$  42 h vs. 56.88  $\pm$  26.65 h), requirement of mechanical ventilation (52.4% vs. 18.8%), requirement of inotrops (57.1% vs. 25%) and PRISM II score (10.24  $\pm$  2.16 vs. 7.90  $\pm$  3.55) were significantly higher in non-survivors than in survivors [Table 5]. These factors were included as predictors in binary logistic regression model enter method to test their independent contribution for mortality. Values of Omnibus model coefficent (22.042.p, 0.000 at df = 5 Nagelkerke R square (0.306) and Hosmer and Lemeshow test (Chi-square 4.911 at df-8, sig. 767) indicated strong predictive value and overall fitness ofthe regression model.

Peak blood glucose level (odds ratio-8.256, wald-3.86, P = 0.049 at df-1) and duration of hyperglycemia (odds ratio-1.021, wald 4.833, P = 0.028 at df-1) were independently associated with increased risk of death. Mechanical ventilation (odds ratio-2.195, wald-1.596, P = 0.206 at df-1) and use of inotrops (odds ratio-1.494, wald-0.402, P = 0.526 at df-1) were not found as to be independent predictors of mortality while PRISM II (odds 1.229, wald-3.82, P = 0.051 at df - 1) score fell just short of statistical significance [Table 3] .The area under ROC curve for peak blood glucose (0.806 with sensitivity 90% and specificiy 67.5%) and for PRISM II score and mortality (0.736 with sensitivity 75% and specificity 68.7%) was higher than that for duration of hyperglycemia, (0.641 with sensitivity 40% and specificity 91.8%) [Table 4].

Kendall's W coefficient was (0.812,  $\chi$ 2-81.99, df 1) 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%.<sup>[23-25]</sup> We defined hyperglycemia as blood glucose level above above 126 mg/dl or (>7 mmol/l) as similar level considered in previous studies<sup>[9,26]</sup> and as per revised definition for diagnosis of diabetes (fasting blood glucose level >126 mg/dl) in children by WHO<sup>[22]</sup> 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.*,<sup>[9]</sup> Wintergerst *et al.*,<sup>[10]</sup> Allen *et al.*,<sup>[27]</sup> and Yung *et al.*<sup>[28]</sup> [Table 6]. 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.*<sup>[23]</sup>

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

Day *et al.*<sup>[29]</sup> found that among children with meningococcemia requiring mechanical ventilation, patients with lower blood glucose had less duration of ventilation required. Yates *et al.*<sup>[20]</sup> 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.*<sup>[24]</sup> and Day *et al.*<sup>[29]</sup>

Consistent with our findings Wintergerest *et al.*,<sup>[10]</sup> Faustino *et al*,<sup>[25]</sup> and Branco *et al.*,<sup>[24]</sup> 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.<sup>[28]</sup>In children, hyperglycemia is associated with worse outcome after severe sepsis<sup>[21]</sup> and traumatic brain injury.<sup>[12]</sup> Mortality in hyperglycemic children was significantly higher (28.6% vs. 3.2%) in our study. Similar findings were observed by Yung *et al.*,<sup>[28]</sup> Gupta *et al.*,<sup>[23]</sup> and Osier *et al.*<sup>[30]</sup>

We found that the admission blood glucose level was significantly higher in non-survivors than in survivors as in the Ruiz Margo *et al.*<sup>[26]</sup> study. But in contrast toYung *et al.*<sup>[28]</sup> 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.*<sup>[9]</sup> Branco *et al.*<sup>[21]</sup> and Yates *et al.*<sup>[20]</sup> like our study. Odds ratio for peak blood glucose level in our study (8.25) was comparable with Branco *et al.*,<sup>[21]</sup> (6.1) but it was much higher than that of Srinivasan *et al.*,<sup>[9]</sup> (1.2). Area under ROC curve (0.806) for peak blood glucose with high sensitivity (90%) and moderate specificity (67.5) in our study was comparable with Branco *et al.*,<sup>[21]</sup> (AUC 0.754, sensitivity 71.4% and specificity 72.4%). Peak blood gluose level as independent predictor of death has comparable AUC with PRISM II (0.736) 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.*<sup>[20]</sup> and Srinivasan *et al.*<sup>[9]</sup>

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 specificity (91.8%).

| Table 1: | Comparative   | demography | in hyper | glycemic v | verses |
|----------|---------------|------------|----------|------------|--------|
| non-hyp  | erglycemic ch | ildren     |          |            |        |

| Parameter                       | Hyperglycemic<br>(n=70) | Non-hyperglycemic<br>(n=31) | P value |
|---------------------------------|-------------------------|-----------------------------|---------|
| Male/female                     | 43/27                   | 22/9                        | 0.4852  |
| Mean temperature (°F)           | 99.2+1.7                | 99.4+1.5                    | 0.5736  |
| Mean heart rate (/min)          | 123.5+33                | 117.4+27.8                  | 0.3718  |
| Mean respiratory<br>rate (/min) | 39.2+19.1               | 40.9+20.3                   | 0.6866  |
| Steroids used n (%)             | 2 (2.8%)                | 3 (9.7%)                    | 0.3370  |
| PRISMII score                   | 8.32±3.07               | 8.03±3.68                   | 0.683   |
| DDICMUL D. IS & DOLL OCK        | A . I. C II             |                             |         |

PRISMII: Pediatric Risk Of Mortality Score II

# Table 2: Comparison of morbidity and mortality between hyperglycemics and non-hyperglycemics

| Parameter                          | Hyperglycemic<br>(n=70) | Non-hyperglycemic<br>(n=31) | P value |
|------------------------------------|-------------------------|-----------------------------|---------|
| Mean length of stay (days)         | 7.91±5.01               | 5.58±1.95                   | 0.0140  |
| Ventilation required $n$ (%)       | 23 (32.8)               | 3 (9.6)                     | 0.0271  |
| Inotrop infusion<br>required n (%) | 27 (38.5)               | 5 (16.1)                    | 0.0451  |
| Mortality n (%)                    | 20 (28.6)               | l (3.2)                     | 0.0086  |

#### Table 3: Multivariate analysis of factors associated with mortality by logistic regression

| Variable                  | Wald  | df | P value | Odds ratio |
|---------------------------|-------|----|---------|------------|
| Peak blood glucose level  | 3.860 | I  | 0.049   | 8.256      |
| Duration of hyperglycemia | 4.833 | 1  | 0.028   | 1.021      |
| PRISM II score            | 3.820 | 1  | 0.051   | 1.229      |
| Inotrops                  | 0.402 | I. | 0.526   | 1.494      |
| Mechanical ventilation    | 1.596 | Ι  | 0.206   | 2.195      |

PRISM2: Pediatric Risk Of Mortality Score II; df: Degree of freedom

| Table 4: ROC curve analysis of factors associated with mortality |       |        |         |                |                 |                 |           |
|--|-------|--------|---------|----------------|-----------------|-----------------|-----------|
| Variable   | AOC   | SE     | P value | 95%CI          | Sensitivity (%) | Specificity (%) | Criterion |
| Peak blood glucose level   | 0.806 | 0.0501 | 0.000   | 0.715 to 0.878 | 90.0            | 67.5            | >0.1614   |
| PRISM II score   | 0.736 | 0.0586 | 0.001   | 0.638 to 0.819 | 75              | 68.7            | >0.2018   |
| Duration of hyperglycemia  | 0.641 | 0.0783 | 0.052   | 0.516 to 0.753 | 40              | 91.8            | >0.3007   |

Null hypothesis area=0.5, criterion based on predicted probability, AOC: Area under curve; SE: Standard error; PRISM2: Pediatric risk of mortality score ii; CI: Confidence interval; ROC: Receiver operating characteristic

|  | Table 5: | <b>Comparisons of</b> | survivors and | non-survivors |
|--|----------|-----------------------|---------------|---------------|
|--|----------|-----------------------|---------------|---------------|

| Variables                      | Survivors<br>(n=80) | Non-survivors<br>(n=21) | P value |
|--------------------------------|---------------------|-------------------------|---------|
| Age in years                   | 4.04±3.92           | 4.54±3.89               | 0.503   |
| Weight in kg                   | 13.75±8.97          | 14.05±6.712             | 0.888   |
| Sex n (% of male)              | 52 (65)             | 13 (61.9)               | 0.792   |
| Use of steroid n (%)           | 4 (5)               | I (4.8)                 | 0.964   |
| Malnutrition present n (%)     | 34 (42.5)           | 5 (23.8)                | 0.117   |
| PRISM2 score                   | $7.90 \pm 3.55$     | $10.24 \pm 2.16$        | 0.003   |
| Mechanical ventilation n (%)   | 15 (18.8)           | 11 (52.4)               | 0.004   |
| Inotrops use n (%)             | 20 (20)             | 12 (57.1)               | 0.008   |
| Admission blood gluose         | 147.59±62.12        | 192.38±59.08            | 0.003   |
| (in mg/dl) mean                |                     |                         |         |
| Admission hyperglycemia n (%)  | 35 (43.75)          | 12 (57.14)              | 0.273   |
| Peak Blood glocose (in mg/dL)  | $162.45 \pm 62.09$  | 198.43±51.17            | 0.0163  |
| mean                           |                     |                         |         |
| Overall hyperglycemia n (%)    | 50 (62.5)           | 20 (95.2)               | 0.004   |
| Duration of hyperglycemia mean | 56.88±26.65         | 79.2±42                 | 0.0035  |

PRISM II: Pediatric risk of mortality score ii

# Table 6: Comparison of incidence of hyperglycemia with previous studies

| Author and year                          | Hyperglycemia defined as blood glucose (mg/dL) | Incidence<br>(%) |
|--|--|------------------|
| Srinivasan et al (2004) <sup>[9]</sup>   | >126   | 86               |
| Faustino et al (2005)[25]                | >120   | 75               |
|  | >200   | 16.7             |
| Wintergerst et al (2006) <sup>[10]</sup> | >110   | 86.5             |
| 0  | >150   | 61               |
|  | >200   | 35.2             |
| Allen et al (2008) <sup>[27]</sup>       | >110   | 95               |
| Yung et al (2008)[28]                    | >110   | 89               |
| Present study                            | >126   | 69.7             |

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. The eventually included patients also received steroids and vasopressors. So the difference between included and excluded patients may be only the phase of stabilization. Inclusion of these patients could have reduced the bias with improvement in validity of our study.

As 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.

### Conclusion

Incidence of hyperglycemia in critically ill non-diabetic children was high in a selected cohort. 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.

### **Recommendations**

Close monitoring of blood sugar levels is required in critically ill children, especially those who require ventilation and inotropic support.

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Announcement

#### iPhone App



A free application to browse and search the journal's content is now available for iPhone/iPad. The application provides "Table of Contents" of the latest issues, which are stored on the device for future offline browsing. Internet connection is required to access the back issues and search facility. The application is Compatible with iPhone, iPod touch, and iPad and Requires iOS 3.1 or later. The application can be downloaded from http://itunes.apple.com/us/app/medknow-journals/ id458064375?ls=1&mt=8. For suggestions and comments do write back to us.