

Alteration of Homeostasis: Prevalence, Effect of Therapy and Outcome in Pediatric Intensive Care Unit at a Tertiary Care Centre

Sushma U Save¹, Maaz Ahmed², Anandini Suri³

ABSTRACT

Introduction: Many factors influence outcome in children admitted to the Pediatric Intensive Care Unit (PICU), including hyperglycemia, hypoglycemia and glucose variability. We conducted a study to determine the prevalence of hyperglycemia, hypoglycaemia and glucose variability in children admitted to the PICU and their association with mortality and morbidity.

Material and methods: A prospective observational study was conducted over an 18-month period in the PICU of a teaching public hospital in Mumbai. 113 children aged 29 days to 12 years admitted to the PICU were enrolled in the study. Hyperglycemia, hypoglycemia and glucose variability were recorded. Insulin by infusion was given for children with hyperglycemia. The outcome measures were recorded in terms of duration of PICU, discharge and death.

Results: A total of 113 eligible patients who were enrolled in the study. Hyperglycemia was significantly associated with increasing length of PICU stay (χ^2 , $p=0.045$). Hypoglycemia was not associated with significant mortality (p value 0.66) or increase in length of stay ($p=0.351$). Increased glucose variability was associated with increased morbidity in terms of length of PICU stay (χ^2 , $p=0.005$, $p=0.038$; standard deviation and coefficient of variance respectively). Insulin infusion was used in children with hyperglycemia ($p=0.025$) associated with mortality.

Conclusion: Our study also confirms to the existing evidence that hyperglycemia and glucose variability prolongs the length of PICU stay. Hence we suggest a closer watch on blood glucose variability. Though our study shows increased mortality in children in whom insulin infusion was started; more data and large randomised control trials are required to evaluate the effect of tight glycemic control on critically ill children.

Keywords: Alteration of Homeostasis, Pediatric Intensive Care Unit

INTRODUCTION

Many factors influence outcome in children admitted to the Pediatric Intensive Care Unit (PICU), including hyperglycemia, hypoglycemia and glucose variability.^{1,2} Glucose being an important substrate for energy; maintenance of its blood levels is of critical importance. Till recently, great amount of attention has been paid to avoidance and early treatment of hypoglycaemia.³ As hyperglycemia was considered to be an adaptive response to stress; scant attention was paid to its occurrence, prevention or treatment (1). The situation seems to be changing slowly.^{4,5} Variability in glucose levels is being increasingly recognized as an important factor influencing the outcome in terms of prolonged hospital stay, prevalence of organ dysfunction and mortality. However, there is a paucity of data regarding the occurrence of variability in glucose levels in children in Indian PICU settings.^{4,5} Although, increasing attention is being paid to the occurrence, prevention and control of hyperglycemia.¹ The opinion regarding use of tight control over blood glucose levels

in critically ill children continues to be divided.⁴

Hence, we conducted a study to determine the prevalence of hypoglycaemia, hyperglycemia and blood glucose variability in children admitted to the PICU and their association with mortality and morbidity.

MATERIAL AND METHODS

A Prospective observational study was conducted over an 18-month period beginning March 2012 in the PICU of a teaching public hospital in Mumbai after being approved by the Institutional Ethics committee. Children aged 29 days -12 years admitted to the PICU were enrolled in the study after receiving a written informed consent from parents.

Sample size: Sample size was calculated after determining the prevalence of glycemic variation in our PICU. The prevalence was determined to be 8.8% on the basis of available records. The sample size thus calculated was 113.

Baseline blood glucose levels (both venous and capillary) were recorded on admission to the PICU. Venous blood (0.5 ml) was used for measurement of random blood sugar. Capillary blood sugar (one drop by bold finger prick/ heel prick) reading was taken with the help of a calibrated glucometer (optiumxceed™). Children with diabetes mellitus were excluded.

As there is no standard cut-off for defining hyperglycemia, proportion of children having blood glucose levels in excess of 110mg/dl, 150mg/dl and 200mg/dl during the entire PICU stay was calculated. Hypoglycaemia was defined as any single blood glucose level ≤ 50 mg/dl and for hyperglycemia >200 mg/dl during the entire hospital stay. If the child required intervention, the reading were repeated hourly for initial titration of the therapy and subsequently two hourly followed by six and twelve hourly monitoring as per the therapy response and patient status. Repeated readings done for monitoring purpose were taken by the glucometer which was calibrated and calibration was checked every day. Any reading showing <50 mg/dl or > 200 mg/dl on the glucometer was confirmed by venous glucose and therapy changed according to the venous glucose.

Hyperglycemia and hypoglycemia was treated as per our standard PICU protocol. Insulin by infusion was given for

¹Associate Professor, ²Specialty Medical Officer, ³Junior Resident, Department of Pediatrics, Topiwala National Medical College and BYL Nair Hospital, India

Corresponding author: Maaz Ahmed, Department of Pediatrics, First Floor, College Building, Topiwala National Medical College and BYL Nair Hospital, India

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hyperglycemia (>200mg/dl). Glucose variability was defined if the child had both hypoglycemia and hyperglycemia episode during the PICU stay, which was calculated using the glucose variability index. The glucose variability index was calculated for each patient as a measure of variability, by dividing the absolute difference of successive glucose values by the difference in time of collection. For each subject the

variability index is formed by the mean of the ratios, which uses the standard deviation and coefficient of variance of all glucose values.^{2,6} The outcome measures were recorded in terms of death and discharge. The duration of PICU stay was also recorded. Figure-1 shows protocol for glucose monitoring.

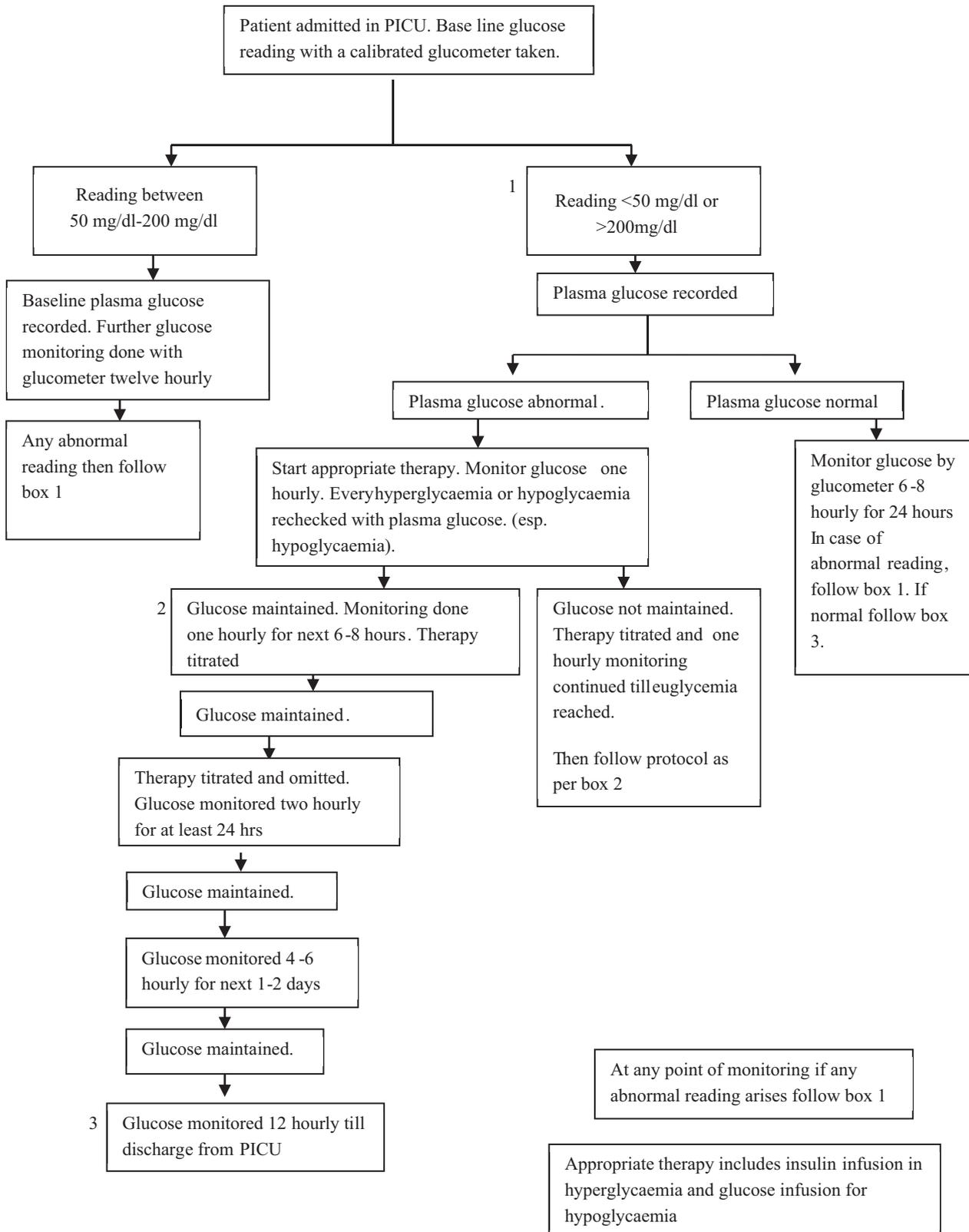


Figure-1: Protocol for Glucose Monitoring.

Hyperglycemia (Quantiles)	Length of stay (hrs)				Total
	< 24 [^]	24 to 72 [^]	72 to 120 #	>= 120 #	
<110	5	32	26	20	83
111-150	0	6	7	8	21
151-200	0	4	0	1	5
>200	1	2	0	1	4
Total	6	44	33	30	113

[^], # Row and Column data pooled and Chi-Square Test applied. df: 2 p value = 0.045

Table-1: Association among the cases between Hyperglycemia (Quantiles) and Length of stay.

Standard deviation of glucose values (Quantiles)	Length of stay (hrs)	
	< 72 ^a	>= 72-120 ^a
0.71-8.27	21	8
8.28-12.04	11	17
12.05-25.61	8	20
25.61-152.08	10	18
Total	50	63
Coefficient of variance of Glucose (Quantiles)	< 72 ^b >=72-120 ^b	
	< 72 ^b	>=72-120 ^b
0.73-9.20	20	9
9.21-13.86	11	17
13.87-21.19	10	18
21.20- 81.66	9	19
Total	50	63

a: Column data pooled and Chi-Square Test applied. df:6 p = .0055
b: Column data pooled and Chi-Square Test applied. df:6 p= 0.038

Table-2: Association of Glucose variability with Length of PICU stay.

Insulin infusion	Outcomes		Total
	Expired	Discharged	
Yes	8	4	12
No	32	69	101
Total	40	73	113

Fischer's exact test applied; p = 0.025

Table-3: Association of insulin infusion and outcome

STATISTICAL ANALYSIS

Statistical analysis was done with the help of PSPP version 3. Prevalence of hyperglycemia was studied by dividing the mean glucose into quantiles. The association between episode of hypoglycaemia, hyperglycemia and glucose variability index in the form of mortality and length of stay was calculated on the basis of Chi-square test or Fischer's test. Binary logistic regression was used to find correlation between glucose variability by coefficient of variation and length of stay.

RESULTS

A total of 113 (Boys: 63, 55.8%; Girls: 50, 44.2%; M:F= 1.26:1) eligible patients were enrolled in the study. Sixty nine (61.1%) were less than 3 years of age. The mean age of the study population in the study was 2.92 ± 3.59 years. Percentage mortality was 40 (35.4%) without any significant association with age or sex. 41 (36.3%) required mechanical ventilation, and 34 (30.1%) required vasopressor. Seven (6.2%) children had surgical intervention. None of these contributed significantly to glycaemic variations. The mean glucose on admission in the non survivors was 111.15 ± 62.79. Four children (3.5%) of study population had mean glucose >200 mg/dl. The association of

hyperglycemia to outcome was studied, although hyperglycemia was not associated with increased mortality, it was significantly associated with increasing length of PICU stay (χ^2 , p=0.045) (Table-1).

Only 4 (3.5%) of the population had hypoglycemia. Of those having hypoglycemia, three were discharged and one had expired. The mean length of PICU stay in children with hypoglycemia was 102.50 hours (4.27days) and in those without hypoglycemia was 81.03 hours (3.3 days). Hypoglycemia was not associated with significant mortality (Pearson Chi-Square =0.196 and p value 0.66) or increase in length of stay (p= 0.351). The mean value of glucose variability by standard deviation was 20.81±23.26 and that by coefficient of variance was 0.18±0.14. The values among those expired were 24.15±32.27 and 0.19±0.18 respectively. There was no significant association with mortality. However it was significantly increased the length of stay of the patient (χ^2 - p value for standard deviation = 0.005, and for coefficient of variance= 0.032) (Table-2).

Increased glucose variability was associated with increased morbidity in terms of length of IPCU stay (χ^2 , p=0.005, p=0.038; standard deviation and coefficient of variance respectively) (Table-2); however was not associated with increased mortality. Binary logistic regression showed a strong correlation between glucose variability by coefficient of variation and length of stay (p=0.020).

Insulin infusion was used in children with hyperglycemia i.e. single venous blood glucose >200 mg/dl. A total of 12 patients required insulin infusion of which 8 (66.7%) expired. Fischer's exact test was applied showed significant (p = 0.025) association with mortality questioning the role of tight glycaemic control (Table-3).

DISCUSSION

The study showed hyperglycemia and glucose variability in critically ill children in PICU are associated with increased morbidity in form of increase in length of stay in PICU. Even so, tight glycaemic control with insulin infusion was significantly associated with significant mortality.

In acutely ill children, during stress hyperglycemia, there is catabolism associated with peripheral insulin resistance and gluconeogenesis because of counter-regulatory hormone like cortisol and the inflammatory cytokines.^{7,8}

In the present study, higher incidence of hyperglycemia was noticed in the first 30 hours of admission in those who expired (mean glucose at 30 hours being 178.25 ± 52.83) though the prevalence of hyperglycemia was less as compared to other studies as it has been estimated 49–72% of children having blood glucose level >150 mg/dl, and about 20–35% having glucose level >200mg/dl.⁹ Srinivasan et al. observed 86% of

patients with > 128mg/dl of peak blood glucose level. Faustino et al showed the prevalence to be being 16.7% to 75.0%.¹⁰ Wintergrest et al. showed hyperglycemia to be 86.7%, 61.0%, and 35.2% for children with glucose levels of >110, >150, and >200 mg/dl, respectively.¹ Thus suggesting that hyperglycemia is commonly observed in Pediatric critically ill patients.

There was no association between hyperglycemia and mortality, but it was associated with increased morbidity (length of PICU stay). Hyperglycemia due to stress was believed to be favourable but now it has been shown to be contributing to poor outcome in the form of increased length of stay. The study confirms significant relation between maximal glucose and duration of hospital stay.¹¹ Other studies have shown hyperglycemia is also associated with organ dysfunction^{2,12,13} and rate of infection¹⁴ besides mortality.^{10,13,15-17} Srinivasan et al showed that mortality rate was higher with hyperglycemia in infants.¹⁰ Wintergrest et al. found an association of hyperglycemia with length of stay as in our study but also increased mortality rate.¹ Faustino et al showed increased mortality of patients with hyperglycemia.¹⁶ Our study fails to establish association between mortality and hyperglycemia. Klein et al. too did find hyperglycemia to be associated with length of stay, or mortality.¹⁸ We do learn that hyperglycemia is no more just a bystander, does influence the morbidity of critically ill.

Critically ill children are prone for hypoglycemia due to reduced glucose production or exogenous insulin. In our study the prevalence of hypoglycemia was found to be similar to Faustino et al. and less when compared to Wintergrest et al. who showed in 18.6% of patients.^{1,19} Hypoglycemia in our study was observed to have no statistical association with mortality or increased length of PICU stay. Whereas Wintergrest et al. and Faustino et al. showed significant association of increase in mortality rates with hypoglycemia.^{1,19} Even in adult ICU Van den Berghe et al. showed higher mortality rates patients with hypoglycemia.¹⁷ A multivariate analysis revealed hypoglycemia to increase 1.87 days of length of stay of critically ill children.²⁰ Hypoglycemia which results in dangerous neuroglycopenia causing damage to developing brain and cognition in future.^{1,13,19-22} This suggests that hypoglycemia is associated with morbidity and mortality that calls for our attention for more work in this area.

The delicate balance of maintaining the glucose levels in physiological state may tip off in critically ill patients leading to variability of blood glucose levels. Blood glucose variability in our study was associated with significant increase in length of stay and not with increased mortality. Wintergrest et al. also showed a strong association of glucose variability index with median length of stay and mortality rate.¹ Bagshaw et al. found that glucose variability was independently associated with increased the risk of mortality among ICU patients.²³ Egi et al. observed that blood glucose variability in adults was independently associated with hospital mortality in intensive care unit.²⁴ Variability may not only be an important marker of poor outcome⁴ but pose as an increased risk for acquiring nosocomial infection as shown by Hirshberg et al.^{14,25} The fluctuation of blood glucose levels leads to adverse effects on hydration and nutrition of critically ill as well as cell damage and apoptosis due to oxidative stress especially so when blood glucose levels rise swiftly.^{1,6,24,26,27} The mechanism of oxidative stress is thought to be upsurge of superoxide and

peroxynitrite (reactive oxygen species) which causes damage to the minute blood vessels.^{1,6,28} Thus control of this variability seems warranted. The association between glucose variability and mortality not being seen could be due lack of comparison to a control group and could also be due to various other confounding factors.

In the present study showed tight glycaemic control (TGC) may be associated with increased mortality. But Van den Berghe showed in adult ICU that TGC reduced mortality as well as bacteraemia. In a randomised control study in PICU by Vlasselaers et al. in which TGC was done by intensive insulin therapy led to in a shorter stay in the PICU.²⁹ Randomised control trial in PICU by Jeschke et al and Agus et al. showed decrease in rate of infection in those who received insulin therapy as TGC.³⁰⁻³² Also a recent meta-analysis showed no reduction in 30-day mortality with TGC using intensive insulin therapy but did show reduction in nosocomial infection.⁹

Insulin therapy with its strong anti-inflammatory effects is thought to counter the deleterious effects of hyperglycemia by safeguarding the physiology and anatomy of the mitochondria.³³ Therefore, despite the scarcity of beneficial effects in outcome studies, insulin therapy should not be disregarded in children in keeping with its potential benefits. The insulin therapy in TGC to achieve normoglycemia has been demonstrated to improve morbidity and mortality in children³³, but also resulted in hypoglycaemia.³ Van den Berghe et al TGC did not show any improvement in mortality rates except for a subgroup who blood where in ICU for more than three days.¹⁷ Thus an indication that tight glucose control is not as simple as anticipated. The risk of severe hypoglycemia is a potential problem of insulin therapy. Also that segregation of blood sugar levels among treatment subgroups may probably be an explanation for inconsistent results. A multi-center randomised control trial Heart and Lung Failure - Pediatric INSulin Titration (HALF-PINT) is underway in which insulin therapy is being studied in critically ill children in PICU with hyperglycemia [registered at ClinicalTrials.gov NCT01565941].

Limitations of our study included small sample size as larger studies are needed to study role of insulin in TGC in not only acute as well as chronic stages of critical illness. The causal relation between length of stay and mortality with glucose parameters cannot be linked as these as statistical associations. The blood glucose measurement done more frequently may have led to detection of glucose variability among critically ill children.

CONCLUSION

This study throws light on the most common metabolic abnormality encountered in PICU and its effect on the mortality and morbidity of children admitted in PICU. Our study also confirms to the existing evidence that hyperglycemia prolongs the length of PICU stay. It is also evident that glucose variability increases the PICU stay and hence morbidity. Hence we suggest a closer watch on blood glucose variability. Though our study did show increase in mortality in children in whom insulin infusion was started; more data and large randomised control trials are required to evaluate the effect of tight glycaemic control on critically ill children.

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