Association of Hyperglycaemia with Outcome in Critically Ill Children in Central India - A Prospective Study

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ABSTRACT

BACKGROUND

Hyperglycaemia is a common occurrence in children with critical illness. Several studies relate hyperglycaemia occurring during intensive care unit (ICU) admission to be associated with increased mortality. We wanted to evaluate the incidence of hyperglycaemia and its association with mortality among critically ill children.

METHODS

A prospective observational study was conducted among critically ill children admitted to the Paediatric Intensive Care Unit (PICU) of a tertiary care centre, Raipur, Chhattisgarh in central India, from 1st May 2016 to 31st October 2016. All patients aged 1 month to 14 years who were admitted in PICU during this study period (N = 113) were included. Children who were known cases of diabetes mellitus, hepatic failure or renal failure requiring dialysis and children who left against medical advice (LAMA) or died within 24 hours of admission were excluded (N = 13). Thus 100 children were included in the study.

RESULTS

In the study population, incidence of hyperglycaemia was 60 %; overall 37 (37 %) died and the mortality rate was significantly higher (46.6 % vs. 19.4 %) in children with hyperglycaemia than in children without hyperglycaemia. Non-survivors had higher mean blood glucose levels at 48 hours (218.35 ± 87.42 mg / dL) than survivors (141.12 ± 55.26 mg / dL) ($P < .001$). Peak blood glucose (218.35 ± 87.42 mg / dL vs. 141.12 ± 55.26 mg / dL), need for mechanical ventilation (54.5 % vs. 27.3 %), need for inotropes (76.4 % vs. 23.5 %) and Paediatric Risk of Mortality Score (PRISM) III (16.25 ± 5.46 vs. 9.06 ± 4.35) were significantly higher in non-survivors than in survivors. On regression analysis, blood sugar at 24 hours and duration of stay were found to be significant.

CONCLUSIONS

In this study, in the PICU, the mortality rate was significantly higher in children with hyperglycaemia than in children without hyperglycaemia. Non-survivors had significantly higher mean blood glucose levels at 48 hours than survivors. Peak blood glucose, need for mechanical ventilation, need for inotropes and PRISM III scores were significantly higher in non-survivors than in survivors.

KEYWORDS

Hyperglycaemia, Critically Ill, PICU, Outcome, Mortality

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BACKGROUND

Critical patients admitted in intensive care units undergo many endocrinal and metabolic changes, including alteration in the glucose homeostasis.[1] Hyperglycaemia is a common occurrence in children with critical illness, even in those who had previously normal glycaemic status.[2–5] There are several studies which relates hyperglycaemia occurring during ICU admission to be associated with increased mortality, duration of stay and infection rates in heterogeneous critically ill patient.[2,3,6–9]

In acute phase, stress hyperglycaemia develops which is thought to be adaptive response mediated by neuroendocrine hormones (i.e., epinephrine, norepinephrine, cortisol, glucagon, and growth hormone) causing relative insulin deficiency, insulin resistance, beta cell dysfunction leading to impaired metabolism of glucose[1,10,11] and often iatrogenic factors like intravenous dextrose, medication also contribute to the hyperglycaemia.

Even though the stress hyperglycaemia is considered likely harmful by the clinicians, they fear the iatrogenic hypoglycaemia when treated with insulin. Blood glucose levels in most children spontaneously normalise within 48 hours, at normal glucose intake and without insulin treatment.[1]

Stress hyperglycaemia is common in paediatric intensive care unit , with patient experiencing blood sugar level of > 110 mg / dl in 80 %, > 150 mg / dl in 60 % and > 200 in 30 % of admitted critically ill children.[12–15] Prevalence of hyperglycaemia among critically ill, non-diabetic children ranges from 16.7 % to 75 %.[2,6,16] Higher glucose variability was associated with a significantly higher hospital length of stay and mortality.[5,17] Peak blood glucose concentration in critically ill children can often range as high as 172 ± 78 mg / dl to 283 ± 115 mg / dl. Peak blood glucose concentration in non-survivors were higher than survivors.[2,6,15] Table 1 shows some of the key studies done to check for the association of stress hyperglycaemia and mortality in critically ill children.

Study	Definition of Hyperglycaemia (Blood Glucose Levels)	Mortality Associated with Hyperglycaemia (OR / RR)
Srinivasan[6]	≥ 150 mg / dl	OR 3.4
Yung[4]	> 126 mg / dl	OR 3.1
Faustino[2]	≥ 150 mg / dl	RR 2.5
Hirshberg[5]	≥ 150 mg / dl	OR 11.1
Wintergerst[17]	> 150 mg / dl	RR 4.8
Yates[3]	≥ 126 mg / dl	OR 1.5
Branco[18]	> 178 mg / dl	RR 2.6
Patki[16]	> 126 mg / dl	OR 1.7

Table 1. Key Studies of Association of Stress Hyperglycaemia and Mortality in Critically Ill Children

RR = Relative Risk; OR = Odds Ratio; CI Confidence Interval

It is unclear whether hyperglycaemia is a marker of critical illness in children or an etiological factor contributing to worse outcome. Hence, to confirm the above this study was undertaken with objective of-

1. To find out the incidence of hyperglycaemia among critically ill children.
2. To find out the outcome in terms of survivors and non-survivors and compare it with various parameters after admission in paediatric intensive care unit.

METHODS

This was a prospective observational study conducted in paediatric intensive care unit at a tertiary care centre, Raipur, Chhattisgarh over a study period of 6 months from 1st May 2016 to 31st October 2016. Sample size was calculated using the formula:

$$n = \frac{z^2 pq}{d^2}$$

Considering the level of confidence (z) = 95 %, precision (d) as 10 %, and prevalence[2,6,16] as 50 %. Sample size was calculated as 97 cases.

All patients from the age group of 1 month to 14 years who were admitted in PICU during this study period (N = 113) were included in the study. Children who were known case of diabetes mellitus, hepatic failure, renal failure requiring dialysis, left against medical advice and death within 24 hours of admission were excluded (N = 13). By these exclusion criteria 100 patients were included in the study.

All patients were studied from day of admission and followed up till death or discharge. A detailed history, thorough examination, all relevant investigations were done. The treatment history of the children with details of mechanical ventilation, vasoactive infusions, steroids, and medications diluted with dextrose solutions were noted. Severity of illness was measured by PRISM III. The patients were followed throughout their hospital stay and their outcome in terms of mortality and duration of PICU stay were recorded.

For this study, we defined normoglycemia as a blood glucose level of 61 - 110 mg / dL, hypoglycaemia < 60 mg / dL, and hyperglycaemia as a blood glucose level of > 126 mg / dL. This was based on criteria for the diagnosis of diabetes mellitus as determined by the World Health Organization.[19] Blood glucose levels between 110 and 126 mg / dL were considered to represent a state of abnormal glucose tolerance. A blood glucose level between 150 - 200 mg / dL was considered as moderate hyperglycaemia and levels above 200 mg / dL was considered as severe hyperglycaemia. Initial blood glucose level was measured on admission and thereafter every 6 hourly in all children. Patients who had abnormal blood glucose values had more frequent measurements of glucose. The highest blood glucose level in the first 48 hours was defined as the peak glucose level. No patient in this study had undergone insulin infusion for glucose control.

The first sample for glucose estimation sent to laboratory was random serum glucose value. The remaining blood glucose values were obtained bedside with the help of glucometer (Accu-Check-Brand Roche). These were capillary whole blood glucose values.

The study determined the proportion of enrolled children in the PICU who developed hyperglycaemia, hypoglycaemia, impaired glucose tolerance in their stay and studied its association with mortality and duration of stay in the PICU.

The research ethical clearance approval letter was obtained from the institutional ethics committee at Pt. JNM Medical College, Raipur, Chhattisgarh, India.

Statistical Analysis

The data were entered in Microsoft Excel and analysed by IBM SPSS Statistics 25. Data was tabulated in the form of frequency tables; test of significance was done for categorical data by chi-square test, for metric data Student t-test and for non-normal data Mann-Whitney U Test was used. The association of the study was considered significant if P-value was less than 0.05.

RESULTS

Total study population consisted of 100 children with median age of 3 years. Sixty (60 %) had hyperglycaemia, 40 (40 %) had non-hyperglycaemia. Out of 60 hyperglycaemics, 3 had blood glucose levels in between 126 - 150 mg / dL, 22 had blood glucose levels in between 151 - 200 mg / dL, 35 had blood glucose levels of > 200 mg / dL; out of 40 non-hyperglycaemics, 20 patients had normoglycemia, 4 patients had hypoglycaemia and 16 had abnormal glucose tolerance. 2 patients developed hyperglycaemia during their PICU stay.

Sl. No.	Parameter			Non-survivors (n = 37)	Survivor (n= 63)	P Value (χ^2 test)
1	Age group	< 1 year	Hyperglycaemia	8	14	1.0*
			Non-hyperglycaemia	4	7	
		1 - 5 years	Hyperglycaemia	11	6	0.007
			Non-hyperglycaemia	2	11	
		6 - 10 years	Hyperglycaemia	1	7	1.0*
			Non-hyperglycaemia	2	6	
		> 10 years	Hyperglycaemia	8	5	0.067*
			Non-hyperglycaemia	1	7	
2	Gender	Males	Hyperglycaemia	10	19	0.738
			Non-hyperglycaemia	4	12	
		Females	Hyperglycaemia	18	13	0.006
			Non-hyperglycaemia	5	19	
3	Management	Primarily ventilation only	Hyperglycaemia	2	4	0.567*
			Non-hyperglycaemia	3	2	
		Inotropes only	Hyperglycaemia	9	4	0.250*
			Non-hyperglycaemia	1	3	
		Inotropes + ventilation	Hyperglycaemia	14	0	1.0*
			Non-hyperglycaemia	5	0	
4	Outcome		Hyperglycaemia	28	32	0.014
			Non-hyperglycaemia	9	31	

Table 2. Distribution of Study Subjects According to the Glycaemic Levels, Management, and Outcome

*Fisher Exact Test Statistics

Incidence of hyperglycaemia was 66.7 % (22 / 33) in the age group of 1 month - 12 months, 56.7 % (17 / 30) in age group of 1 year to 5 years, 50 % (8 / 16) in age group of 6 year to 10 years and 61.9 % (13 / 21) in above 10 years age group. Hyperglycaemia was almost similar in all the disease categories without significant preference to a particular system. Incidence of hyperglycaemia in children with cardiac disease was 60 %, in neurological cases 67.3 %, in infective cases 57.1 %, and in miscellaneous cases 47.4 %.

Incidence and timing of hyperglycaemia: At 48 hrs. after PICU admission, hyperglycaemia was present in 62 % of patients, whereas only 20 % were normoglycemic. 14 % had values that represented abnormal glucose tolerance, while 4 % had peak levels in hypoglycaemic range. Non-survivors had higher mean blood glucose levels at 48 hrs. (218.35 + - 87.42 mg / dL) than survivors (141.12 + - 55.26 mg / dL) (P < .001).

The requirement of mechanical ventilation (10 % vs. 7.5 %) among hyperglycaemic children was not significantly (P = 0.37) higher than that of non-hyperglycaemic, also the need for inotropic support was not significantly associated (P = 0.11) between hyperglycaemics and non-hyperglycaemics. The subgroup of patients who were managed with both mechanical ventilation and vasoactive infusions was 19 % and had a mortality of 100 %.

Out of the total 100 children studied, 37 (37 %) expired and mortality was significantly higher (46.6 % vs. 19.4 %) in hyperglycaemic children than non-hyperglycaemics [P-value = 0.014, Odds ratio = 3.01 (95 % CI = 1.22 - 7.40)]. Mortality was 3 (14 %) in normoglycemic, 2 (50 %) in hypoglycaemic and 4 (26 %) in patient with abnormal glucose tolerance. The mortality rate in moderate hyperglycaemia (151 - 200 mg / dl) was 15 %. While with severe hyperglycaemia (> 200 mg / dl) it was 63 %.

Sl. No.	Parameter		Non-survivors (n = 37)	Survivor (n = 63)	P Value (t-test)
1	Mean blood glucose at 24 hrs.	Hyperglycaemia	298.82 ± 81.03	198.72 ± 41.98	< 0.001
		Non-hyperglycaemia	95 ± 28.87	101.52 ± 19.16	0.53
2	Mean blood glucose at 48 hrs.	Hyperglycaemia	250.24 ± 69.70	181.5 ± 53.72	< 0.001
		Non-hyperglycaemia	102.75 ± 19.74	102.51 ± 16.28	0.975
3	Peak RBS (mean)	Hyperglycaemia	304.31 ± 79.41	207.33 ± 54.02	< 0.001
		Non-hyperglycaemia	104.38 ± 20.54	107.43 ± 13.89	0.700
4	Median duration of hospital stay	Hyperglycaemia	6	10	0.001#
		Non-hyperglycaemia	3	9	0.024#

Table 3. Association of Outcome with Glycaemic Levels, Peak RBS Levels, Duration of Stay

Mann-Whitney U Test

Peak blood glucose (218.35 + - 87.42 mg / dL vs. 141.12 + - 55.26 mg / dL), requirement of mechanical ventilation (54.5 % vs. 27.3 %), requirement of inotropes (76.4 % vs. 23.5 %) and PRISM III score (16.25 ± 5.46 vs. 9.06 ± 4.35) were significantly higher in non-survivors than in survivors.

PRISM III Score in Hyperglycaemia	Non-Survivors	Survivors	Total	P Value (χ^2 test)
01 - 10	4	21	25	< 0.001
11 - 20	17	10	27	
21 - 30	7	1	8	
Total	**28**	**32**	**60**	

Table 4. Association of PRISM III Scoring with Outcome

	β	Wald	Sig.	Odds	95 % C.I. for Odds	
					Lower	Upper
Blood glucose at 24 hours	0.015	18.245	0.000	1.015	1.008	1.022
Duration of stay	- 0.200	10.828	0.001	0.819	0.727	0.922

Table 5. Odds (95 % Confidence Intervals) of Variables in Logistic Regression Model Associated with Mortality

In logistic regression using the backward stepwise method for the variables – blood glucose at 24 hours, blood glucose at 48 hours, peak blood glucose, duration of stay, age and sex; the blood glucose at 24 hours and duration of the stay were only found significant with odds of 1.015 [95 % CI (1.008 - 1.022)] and 0.819 [95 % CI (0.727 - 0.922)] respectively, associated with mortality. (Table 5)

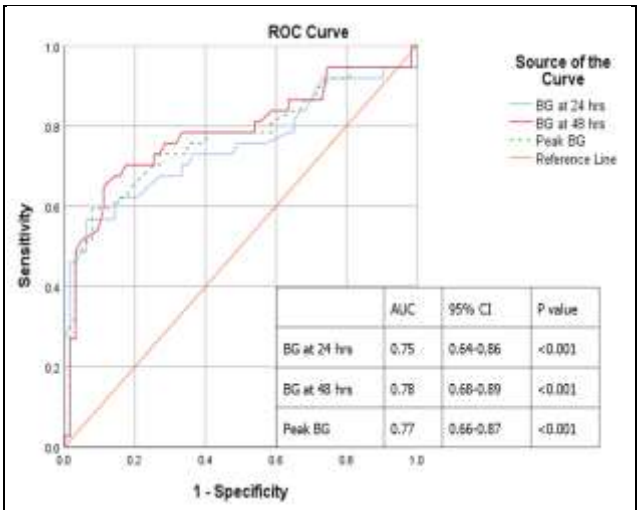

Figure 1. ROC of Blood Glucose Level at 24 Hrs., Blood Glucose Level at 48 Hrs., Peak Blood Glucose Level, and Mortality

AUC= Area Under the Curve, ROC = Receiver Operating Characteristic, BG = Blood Glucose, CI = Confidence Interval

Figure 1 shows receiver operating characteristic (ROC) curves; compared with blood glucose at 24 hours [AUROC = 0.751 (95 % CI = 0.64 - 0.86)] and peak blood glucose [AUROC = 0.767 (95 % CI = 0.66 - 0.87], blood glucose at 48 hours [AUROC = 0.783 (95 % CI = 0.68 - 0.89] had greater AUROC values for the development of adverse outcome (mortality). The cut off value was then determined to be blood glucose level of 206 mg / dl with a sensitivity of 62 % and specificity of 84 %, for the development of adverse outcome.

DISCUSSION

We found hyperglycaemia to be surprisingly frequent, more than half of study population had hyperglycaemia. The incidence of hyperglycaemia in this study had similar findings with studies like Srinivasan et al. (2004); Wintergerst et al. (2006); Allen et al. (2008); Yung et al. (2008); and Patki and Chougule (2014).

Hyperglycaemia though common is underappreciated in critically ill children receiving mechanical ventilation and vasoactive infusions. Hyperglycaemia, in initial 48 hrs. of PICU admission was associated with a significant increase in mortality risk in such critically ill patients. Incidence of hyperglycaemia in ventilated children and those who required ionotropic support was very high in our study which is also consistent with Srinivasan et al. (2004); Branco and Tasker, (2007); Day et al. (2008);[20] Allen et al. (2008); Yung et al. (2008); and Patki and Chougule (2014), though not statistically significant. This could be due to systemic and pulmonary effects of hyperglycaemia.[18]

The admission blood glucose values, and duration of the stay were significantly higher in non survivors than survivors which is similar to study by Ruiz Magro et al. (1999);[21] and Patki and Chougule, (2014). The median duration of stay was longer in hyperglycaemics than non-hyperglycaemics.

Association between peak blood glucose level during the first 48 hours with mortality has been documented by Srinivasan et al. (2004); Yates et al. (2006); Branco and Tasker, (2007); and Patki and Chougule, (2014). Our study was inconsistent with theirs. PRISM III score in hyperglycaemic patients was significantly higher in non-survivors than in survivors.

CONCLUSIONS

In this study, in the PICU, the mortality rate was significantly higher in children with hyperglycaemia than in children without hyperglycaemia. Non-survivors had significantly higher mean blood glucose levels at 48 hours than survivors. Peak blood glucose, need for mechanical ventilation, need for inotropes and PRISM III scores were significantly higher in non-survivors than in survivors.

Limitations

The limitations of the study include non-examination of the effects of medications, vasoactive drugs, and nutrition in the analysis. The method of blood glucose collection was not standardised, the frequency of blood glucose measurements was not fixed, frequent measurements were taken from patients who had abnormal blood glucose levels, and patients who had normal values did not undergo frequent measurements.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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