Original Research Article

Incidence of glucose level abnormalities in neonatal sepsis and its association with mortality

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ABSTRACT

Background: Plasma glucose abnormalities were previously noted in neonatal sepsis, but data in neonates is limited and the association with mortality is not established. The aim of the study was to determine the incidence of plasma glucose abnormalities among newborns with sepsis and their association with mortality.
Methods: This was a prospective observational study including 50 neonates with suspected, probable and proven sepsis. Plasma glucose level was measured within 2 hours of admission and the patients were monitored till discharge or death. The patients were divided into hyperglycaemic, hypoglycaemic and normoglycemic subgroups as per the serum glucose levels.
Results: Majority (56%) were noted to have normoglycemia, followed by hypoglycaemia in 32% and 12% had hyperglycaemic. Mortality in the hypoglycemic, hyperglycemic, and normoglycemic subgroups were 50.0, 33.3, and 7.2% respectively. Mortality was high in hyperglycemic patients compared to normoglycemic patients but the difference was not statistically significant between two groups, whereas the mortality was high in hypoglycemic patients compared to normoglycemic patients and the difference was statistically significant between two groups. A significant association was noted between hypoglycemia in neonatal sepsis with mortality.
Conclusions: Altered glycemic status is common in neonatal sepsis. Mortality is higher among septic neonates with hypoglycemia. We conclude that majority of septic neonates had high mortality rate when plasma glucose levels were either >145 mg/dl or <45 mg/dl. This signifies the importance of plasma glucose estimation in cases of neonatal sepsis to improve mortality outcome.

Keywords: Hypoglycemia, Hyperglycemia, Mortality, Neonatal sepsis, Plasma glucose

INTRODUCTION

Sepsis is the second major cause of mortality among neonates, killing more than one million neonates annually.[1] Neonatal sepsis, pneumonia and meningitis together result in a quarter of all newborn deaths.[2] Globally, of the three million annual neonatal sepsis cases (2202/1,00,000 live births), India has the highest incidence of clinical sepsis (17,000/ 1,00,000 live births).[3] The case fatality rate of sepsis among neonates ranges between 25% to 65% in India.[4,5] These rates are likely to be underestimated, and more accurate data is expected from the 'Global maternal and neonatal sepsis initiative.[6,7] Despite advances in maternal and neonatal care, infection remains a frequent and important cause of neonatal and infant mortality and morbidity.[8] A high or low blood glucose level may have a significant effect on the outcomes in patients of culture proven and probable neonatal sepsis.

The operational threshold for hypoglycemia is defined as "that concentration of plasma or whole blood glucose at

which clinicians should consider intervention, based on the evidence currently available in literature. This threshold is currently believed to be a blood glucose value of less than 40 mg/dl (plasma glucose less than 45 mg/dl).[9] Sepsis has been known to be the cause of 9.6% cases of neonatal hypoglycemia.[11] A neonate having sepsis develops reluctance to feed contributing to hypoglycemia. Similarly increased metabolic demand and hypothermia accused by sepsis can bring down the glucose levels.[12]

Hyperglycemia is defined as a plasma glucose level more than 145 mg/dl.[10] In neonatal sepsis, several neuroendocrine and inflammatory mediators are released which causes hyperglycemia. There is an increased production of stress hormones like glucagon, growth hormone, catecholamines, and glucocorticoids. These hormonal changes along with an increase in pro-inflammatory cytokines, i.e., interleukin 1,6 (IL-1, IL-6), and tumor necrosis factor (TNF)- alpha, are important factors leading to hyperglycemia.[14] The present study was aimed at determining the incidence of plasma glucose abnormalities among newborns with sepsis and their association with mortality.

METHODS

This hospital based prospective observational cross-sectional study was conducted in Neonatal intensive care unit (NICU) of a tertiary care hospital over a period of 2 years, from August 2018 to September 2020. A total of 50 neonates with suspected sepsis under the age of 28 days were included in our study.

Inclusion criteria were all newborn admitted to NICU with positive septic screen or clinically suspected sepsis. Positive sepsis screening criteria includes total leukocyte count (TLC) <5000/cu mm or >15,000/cu mm, C reactive protein (CRP) >1 mg/dL and platelets <150000 cu mm.

Patients with infants of diabetic mother and congenital anomalies were excluded. Those cases who received intravenous glucose or antibiotics before admission were also excluded from this study.

A detailed history and thorough physical examination was done in each patient on admission. Plasma glucose level and mortality of neonates having hypoglycemia and hyperglycemia were analysed. Glucose level was measured within 2 hours of admission using Accu-Chek device (Roche Diabetes Care Inc., Basel, Switzerland), which measures the glucose level from a drop of blood from a heel prick and automatically gives the reading of plasma glucose.Venous blood was collected before administering intravenous fluids, dextrose or antibiotics. Complete blood counts, CRP levels, blood glucose and blood culture were sent to laboratory within half hour of collection. Lumbar puncture was done in neonates with signs of meningitis and cerebrospinal fluid was sent for cell type and count, protein, glucose levels and culture.

CRP levels >1 mg/dl considered as positive and less than 1 mg/dl considered as negative.

Glucose levels were divided into three groups i.e. <45 mg/dl, 45-145 mg/dl, and >145 mg/dl. All the patients were treated accordingly and followed up. The outcome and relevant data from history, physical examination and investigations were recorded in predesigned questionnaire.

Statistical analysis

Data were processed manually and analysed with the help of Statistical package for social sciences (SPSS) version 16.0. Quantitative data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage and comparison carried by Chi-square (χ^2) test. A probability $p<0.05$ was considered statistically significant.

RESULTS

Of 50 neonates admitted with clinical sepsis, 29 (58%) were males and 21 (42%) were females with male to female ratio of 1.4:1. Maternal risk factors for sepsis were present in 18 (36.0%) and absent in 32 (64.0%) children. Low birth weight was noted in 37 (74 %) neonates and 13 (26%) had normal weight. 35 (70%) were preterm and 15 (30%) were term babies (Table 1).

Table 1: Demographic data of neonatal sepsis (n=50).

Category	Distribution	Frequency	%
Gender	Male	29	58
	Female	21	42
Mode of delivery	NVD	12	24
	LSCS	38	76
Maternal risk factor for sepsis*	Present	18	36
	Absent	32	64
Maturity of baby	Preterm	35	70
	Term	15	30
Low birth weight (<2500 grms)	Yes	37	74
	No	13	26

*Maternal risk factors included in our study were urinary tract infection (UTI) during pregnancy, PROM more than 18 hours, chorioamnionitis, meconium stained liquor, eclampsia.

Blood culture positive was positive in 9 (18%) patients; of which 2 (22.2%) were normoglycemic, 4 (44.4%) were hypoglycemic and 3 (33.3%) were hyperglycaemic. CRP was positive in 22 newborns of which majority (59.3%) of CRP positive patients were hypoglycemic, 26.3% were normoglycemic and only 15.2% had hyperglycaemia.

Table 2: Association of hypoglycemia and hyperglycemia with mortality.

Glycemic status	Total Number (n)	Mortality n %		Odds ratio (C I)	P value
Normoglycemic	28	02	7.2	13 (2.2809-74.0943)	0.003
Hypoglycemic	16	08	50.0		
Normoglycemic	28	02	7.2	6.5 (0.7026-60.1359)	0.267
Hyperglycemic	06	02	33.3		

Table 3: Risk factors for hypoglycemia.

Risk factor	Normoglycemic	Hypoglycemic	Odds ratio (C I)	P value
Gender				
Male	17	08	0.647 (0.187-2.234)	0.708
Female	11	08		
GA				
<37 weeks	17	14	4.529 (0.857-23.928)	0.126
≥37 weeks	11	02		
LBW				
Yes	17	15	9.705 (1.117-84.303)	0.004
No	11	01		
Maternal risk factor				
Present	06	10	5 (1.328-18.814)	0.032
Absent	21	07		
CRP				
Positive	09	14	14.777 (2.752-79.334)	0.001
Negative	19	02		
Blood culture				
Positive	02	04	4.333 (0.695-27.014)	0.228
Negative	26	12		

GA: Gestation age, LBW: Low birth weight, CRP: C-reactive protein

Table 4: Risk factors for hyperglycemic.

Risk factor	Normoglycemic	Hyperglycemic	Odds ratio (CI)	P value
Gender				
Male	17	04	1.294(0.201-8.306)	1
Female	11	02		
GA				
<37 weeks	17	04	1.294(0.201-8.306)	1
≥37 weeks	11	02		
LBW				
Yes	17	05	3.235(0.331-31.538)	0.560
No	11	01		
Maternal risk factor				
Present	06	02	1.75(0.255-11.992)	0.961
Absent	21	04		
CRP				
Positive	09	04	2.814(0.517-15.317)	0.431
Negative	19	03		
Blood C/S				
Positive	02	03	8.666(1.176-63.868)	0.079
Negative	26	03		

GA: Gestation age, LBW: Low birth weight, CRP: C-reactive protein

Mortality was high in hypoglycaemics (50.0%) in comparison with normoglycemic newborns (7.2%) and the difference was statistically significant (p=0.003) between two groups. Mortality was also high in hyperglycaemic neonates (33.3%) in comparison with normoglycemic patient (7.2%); however, it didn't reach statistical significance (p=0.267) (Table 2).

On multivariate logistic regression low birth weight (odds ratio (OR)-9.705; p=0.004), maternal risk factors for sepsis (OR-5, p=0.032) and CRP positivity (OR-14.777; p=0.001) were independent predictors for hypoglycemia in babies admitted to NICU. Preterm babies had 4-fold increased risk for hypoglycemia compared to term babies, babies with positive blood culture also had 4-fold increased risk for hypoglycaemia however both did not show any significant association for hypoglycemia (Table 3).

On multivariate logistic regression analysis babies with low birth weight had 3-fold increased risk for hyperglycemia compared to babies with normal birth weight (OR 3.235). Babies with positive CRP were 3 times more prone to hyperglycemia compared to babies with negative (OR 2.814), while having positive blood culture was associated with 8 folds increase of having hyperglycemia (OR 8.666). However, none of the factors were statistically significant (Table 4).

DISCUSSION

This observational study was done to determine the glycemic status in neonatal sepsis and to evaluate the association of hypoglycemia and hyperglycemia with mortality in sepsis.

In our study we observed that majority (56.0%) of the patients were normoglycemic (45-145 mg/dl) followed by 32.0% hypoglycemic (<45 mg/dl) and 12.0% hyperglycaemic (>145 mg/dl). Ahmad et al study showed the glucose levels were below 40 mg/dl in 9.9%, between 40 mg/dl to 100 mg/dl in 64.1%, between 101 mg/dl to 200 mg/dl in 18.9% and above 200 mg/dl in 6.9% patients.[12] In another study Begum et al. observed hyperglycemia in 4.62% of their study patients.[13]

Several studies have shown that hyperglycemia is associated with adverse outcomes in the paediatric age group. Different reasons for this association have been proposed example- enhanced apoptosis, increased production of cytokine, hyper coagulation, acute dyslipidaemia, endothelial dysfunction etc. A study by Wintergerst et al has shown that hyperglycemia, hypoglycemia and glucose variability were associated with increased mortality rates and increased length of stay in PICU.[14] We observed that mortality was high in hyperglycemic patient (33.3%) when compared with normoglycemic patient (7.2%) but was not statistically significant (p=0.267). Lugt et al found that 27 out of 66 infants with hyperglycemia (41.0%) died.[15] Similar finding also observed by Ahmad et al which are not comparable with the present study. In our study mortality was high in hypoglycaemic patient (50%) compared with normoglycemic patient (7.2%) and the difference was statistically significant (p=0.003).[12] Ahmad et al found 32% mortality in hypoglycaemic patient which was consistent with the finding of present study, but statistical significance was not present in their study.[12]

Newborns with sepsis and probable sepsis, with high glucose levels or with hypoglycemia, are at increased risk of death, and should be treated as high risk patients. They should be detected early and should receive early treatment, before hyperglycemia and hypoglycemia set in. Studies are needed to ascertain whether or not more stringent control of glucose levels in patients of neonatal sepsis can improve outcomes. However, small-scale study does not reflect the whole population and definite conclusion is yet to be drawn.

CONCLUSION

Alteration of glycemic status occurs in septic newborns. Mortality is high among the septic newborns with hypoglycemia. Neonatal hypoglycemia and hyperglycemia were a significant factor in the overall mortality in neonatal sepsis.

REFERENCES

1. Abubakar I, Tillmann T, Banerjee A. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117-71.
2. Chan GJ, Lee AC, Baqui AH, Tan J, Black RE. Risk of early-onset neonatal infection with maternal infection or colonization: a global systematic review and meta-analysis. PLoS Med. 2013;10(8):e1001502.
3. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med. 2018;6(3):223-30.
4. Bangi V, Devi S. Neonatal sepsis: A risk approach. J Dr NTR University Health Sci. 2014;3(4):254-8.
5. Kartik R. Evaluation of screening of neonatal sepsis. Int J Contemp Pediatrics. 2006;5(2):580-3.
6. Gordon SM, Srinivasan L, Harris MC. Neonatal meningitis: overcoming challenges in diagnosis, prognosis, and treatment with omics. Front Pediatr. 2017;5:139.
7. World Health Organization (WHO) Executive Board (EB140.R5). Improving the prevention, diagnosis

and clinical management of sepsis. 2017. http://apps.who.int/gb/ebwha/pdf_files/EB140/B140 _R5-en.pdf?ua=1. Accessed on 20 September, 2020.

8. Stoll BJ, Shane AL. Infection of the neonatal infant. In: Behrman RE; Kliegman RM, Stanton BF, III JWSG, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. Philadelphia: Elseveir Saunders. 2015;909-25.

9. Jain A, Aggarwal R, Jeeva Sankar M, Agarwal R, Deorari AK, et al. Hypoglycemiain the newborn. Indian J Pediatr. 2010;77:1137-42.

10. Wilker RE. Hypoglycemia and Hyperglycemia. In: Cloherty JP, Eichenwald EC, Stark AR, editors. Manual of Neonatal Care. 6th edition. Philadelphia: Lippincott Williams and Wilkins. 2008;540-49.

11. Najati N, Sabotakin L. Prevelance and underlying etiologies of neonatal hypoglycemia. Pak J Biol Sci. 2010;13:753-6.

12. Ahmad S, Khalid R. Blood Glucose Levels in Neonatal Sepsis and Probable Sepsis and its Association with Mortality. J Coll Bangladesh J Child Health. 2016;40:24.

13. Branco RG, Tasker RC, Garcia PCR, Piva JP, Xavier LD. Glycemic Control and Insulin Therapy in Sepsis and Critical Illness. J Pediatr. 2007;83:128-36.

14. Begum S, Baki MA, Kundu GK, Islam I, Kumar M, et al. Bacteriological Promle of Neonatal Sepsis in a Tertiary Hospital in Bangladesh. J Bangladesh Coll Phys Surg. 2012;30:66-70.

15. Wintergerst KA, Buckingham B, Gandrud L, Wong BJ, Kache S, et al. Association of hypoglycaemia, hyperglycemia, and glucose variability with morbidity and death in pediatric intensive care unit. Pediatrics. 2006;118:173-9.

16. Kao LS, Morris BH, Lally KP, Stewart CD, Huseby V. Hyperglycemia and morbidity and mortality in extremely low birth weight infants. J Perinatol. 2006;26:730-6.

17. Tam EW, Haeusslein LA, Bonifacio SL, Glass HC, Rogers EE, et al. Hypoglycemiais associated with increased risk for brain injury and adverse neuro developmental outcome in neonates at risk for encephalopathy. J Pediatr. 2012;161:88-93.

18. Ssekitoleko R, Jacob ST, Banura P, Pinkerton R, Meya DB, et al. Hypoglycemia at admission is associated with in hospital mortality in Ugandan patients with severe sepsis. Crit Care Med. 2011;39:2271-6.

19. Hoseth E, Joergensen A, Ebbesen F, Moeller M. Blood Glucose Levels in a Population of Healthy, Breast Fed, term Infants of Appropriate Size for Gestational Age. Arch Dis Child Fetal Neonatal Ed. 2000;83:117-19.