



Original Research Article

Study of altered blood glucose levels in term neonate with sepsis

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ABSTRACT

Introduction: Neonatal hypoglycemia is common metabolic disorder. Hyperglycemia can also occur in other conditions like exogenous parenteral glucose administration, preterm, ELBW babies, stressed premature infants (requiring mechanical ventilation), hypoxia or neonatal diabetes mellitus. The major clinical problems associated with hyperglycemia are hyper osmolality and osmotic diuresis leading to alteration in cerebral auto regulation. Aim & objective: To study the effect of hyperglycemia in term neonate with sepsis and compare it with hypoglycemia.

Materials and Methods: It is a hospital based prospective observational study. The study was carried out in the special care neonatal unit and pediatric indoor of Department of Pediatrics, SCB Medical College, Cuttack and SVP Postgraduate Institute of Pediatrics, Cuttack during the period from September 2018 to August 2020.

Observation: The number of cases of neonatal sepsis with normoglycemia hypoglycemia and hyperglycemia were, 90(44%), 67(32%), 52(24%) cases respectively. The total number of cases with proven sepsis (n=47) hyperglycemia accounts for 40.4% of cases followed by hypoglycemia 18 cases (38.3%) and normoglycemia seen in 10 cases (21.2%).

Conclusion: Both hypoglycemia and hyperglycemia were associated with increased mortality rates at all thresholds but hyperglycemia was independently associated with increased odds of death in patients with neonatal sepsis compared to hypoglycemia.

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1. Introduction

Neonatal infections currently cause about 1.6 million deaths annually in developing countries.¹ In India neonatal sepsis is responsible for up to 750,000 deaths every year.² Sepsis still remains the major cause of neonatal mortality and morbidity despite the development of newer more potent antimicrobial agents.³ The incidence of Neonatal Septicemia in the hospital setting has varied from 0.1 to 4.5%.⁴ The NNPD (National Neonatal Perinatal

Database) Network conducted the largest hospital based study enrolling 1,45,623 intramural neonatal at 18 centers over a period of 2 years. The incidence of Neonatal Septicemia was 3.0%, the early onset sepsis being 67% and late onset sepsis being 31.6%. The Neonatal Septicemia accounted for 18.6% of the total neonatal deaths. The network also published data on extramural entries (n = 11026) during the same time period. Neonatal Septicemia was the most common morbidity seen in 39.7% of neonates as well as the most common primary cause of death in 39% of extramural neonates.⁵ A high or low blood glucose

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levels may have a significant effect on the outcomes in a patient of neonatal sepsis. Sepsis has been known to be cause of 9.6% cases of neonatal hypoglycemia (Najati et al 2010).⁶ Severe and prolonged neonatal hypoglycemia is associated with risk of long term neuro developmental sequelae. Persistent hypoglycemia leads to irreversible cellular dysfunction, organ failure and eventually death. Neonatal hypoglycemia (blood glucose <40mg/dl or plasma glucose <45mg/dl) is common metabolic disorder seen in neonate.⁷ Many different groups are at risk of developing low blood glucose levels: Preterm, IUGR (Intra Uterine growth Retardation), infant of diabetic mother, Beckwith Weidman syndrome rhesus hemolytic disease, moderate to severe perinatal HIE (Hypoxic Ischemic Encephalopathy), maternal beta blocker medication and septicemia.⁸

Hyperglycemia is defined as a whole blood glucose levels higher than 125 mg/dl or plasma values higher than 145mg/dl (Cloherty).⁷ In neonatal sepsis due to depressed insulin release, cytokines or endotoxin result in decreased glucose utilization stress hormones such as cortisol and catecholamine are elevated in sepsis. Hyperglycemia can also occur in other conditions like exogenous parenteral glucose administration, preterm, ELBW (Extremely Low Birth Weight) babies, stressed premature infants (requiring mechanical ventilation), hypoxia or neonatal diabetes mellitus. The major clinical problems associated with hyperglycemia are hyper osmolality and osmotic diuresis leading to alteration in cerebral auto regulation. Hyperosmolar state cause movement of water from intercellular to extracellular compartment, the resultant contraction of intracellular volume leads to intracranial hemorrhage.

A high or low blood glucose level may have a significant effect on the outcomes in patients of neonatal sepsis. During the past few years many studies have been conducted to ascertain importance and consequence of hyperglycemia and hypoglycemia in both pediatric and adult patients. Several studies have shown that hyperglycemia is associated with adverse outcome in pediatric age group.

Despite improved pediatric and obstetric care, there continues to be a significantly high neonatal mortality rate in Odisha. During the last decade several national and state sponsored programs like JSSK (Janani Shishu Surakshya Karyakrama), IMNCI (Integrated Management of Newborn and Childhood Illnesses), FIMNCI (Facility based Integrated Management of Newborn and Childhood Illnesses) have been implemented, with improvement in hospital delivery practices as well as better transport facility and opening of SNCU (Special Newborn Care Unit) in peripheral hospitals. Therefore it is necessary to reevaluate the contributors to neonatal mortality. Given the above background and limited literatures in our country and no literature in the state of Odisha regarding the effect of altered blood glucose on morbidity and mortality pattern

in term neonates with sepsis the present study was carried out at newborn care center of S.C.B. Medical college and SVPPGIP, Cuttack with an aim to determine glycemic status in neonatal sepsis and to evaluate the association of hypoglycemia and hyperglycemia with mortality in patients of neonatal sepsis.

2. Aim & Objective

To study the alteration in glycemic status in term newborns with sepsis and its effect on morbidity and mortality pattern in proven and probable sepsis.

3. Materials and Methods

It is hospital based prospective observational study carried out in the special care neonatal unit and pediatric indoor of Department of Pediatrics, SCB Medical College, Cuttack and SVP Postgraduate Institute of Pediatrics, Cuttack during the period from September 2018 to August 2020 (Institutional ethical committee letter no-817/09-01-2019). Study includes clinically suspected, screen positive and proven cases of term neonatal sepsis within the range of 1 to 28 days.

The study groups were divided into Cases of screen positive and proven sepsis with normoglycemia, hypoglycemia (asymptomatic, symptomatic, persistent and refractory cases) & hyperglycemia.

3.1. Case definitions

3.1.1. Probable sepsis/clinical sepsis (Culture negative)

Clinical syndrome with systemic signs and symptoms of infection with no growth of organism from blood cultures. The presence of any one of the following is enough for assigning probable diagnosis of infection.

1. Existence of predisposing factors: maternal fever, foul smelling liquor, PROM > 24hrs or gastric polymorph > 5/ HPF.
2. Positive sepsis screen (two of 5 parameters: TLC < 5000/ mm³, Band cell to total polymorph ratio of >0.2, ANC < 1500/ mm³, CRP > 6mg/l & micro ESR > 15mm in 1st hour).
3. Radiological evidence of Pneumonia.

3.1.2. Culture positive/proven sepsis

Clinical picture suggestive of septicemia, pneumonia or meningitis along with either of the following.

1. Isolation of pathogen from blood/urine ICSF/abscess.
2. Pathological evidence of sepsis.

3.1.3. Hypoglycemia

Blood glucose value of less than 40 mg/dl (plasma glucose less than 45 mg/dl).

3.1.4. Hyperglycemia

Whole blood glucose level higher than 125 mg/dL or plasma glucose values higher than 145 mg/dL.

3.2. Inclusion criteria

1. All cases of the proven sepsis in term neonate.
2. Term neonate with hypoglycemia in screen positive cases of sepsis.
3. Term neonate with hyperglycemia in screen positive cases of sepsis.
4. All term neonate with clinical sepsis with clinical features fever more than 37.5 degrees, poor feeding, lethargy, high pitched cry/seizure, jaundice, abdominal distension, vomiting, jaundice, fast breathing >60/min, bleeding, umbilical discharge, low body temperature less than 35.5 degree Celsius.

3.3. Exclusion criteria

1. At risk neonates for hypoglycemia
 - (a) LBW less than 2.5kg.
 - (b) Preterm babies less than 37 weeks.
 - (c) SGA (Small for gestational age) and LGA (Large for gestational age).
 - (d) Infants of the diabetic mothers,
 - (e) Infant with Rh hemolytic disease,
 - (f) Infants born to mother receiving beta blocker medication birth asphyxia.
2. Neonates with congenital malformation.
3. Neonates who received intravenous dextrose therapy before screening of the blood glucose levels.
4. Any baby who couldn't be followed up till improvement or death.

3.4. Methods

Detailed history including antenatal, natal, postnatal history was taken in all the patients. In baby presenting within 3 days of birth i.e. early onset sepsis, risk factors like multiple per vaginal examination, chorioamnionitis, rupture of membranes (>18 hours), need for resuscitation, preterm prolonged rupture of membrane, unexplained asphyxia are noted. In those presenting after 3 days i.e. late onset sepsis (community acquired), history regarding bottle feeding, poor hygiene, poor cord care, overcrowding are noted. Those babies who had, history regarding prolonged hospitalization, prematurity, LBW, previous antibiotic use, invasive procedures presence of foreign bodies (Endotracheal tube, catheter), contaminated parenteral fluids and fomites, lack of enough disposables, overcrowding and understaffing were recorded. Clinical examination with special reference to early and subtle manifestation of sepsis was performed in all cases.

Glucose levels of all studied neonates were checked and recorded within one hour of admission through glucometer using glucose oxidation strips by trained nursing staffs who were briefed about the standard procedure. Blood samples of all patients were collected and complete blood counts, CRP (C Reactive Protein) levels and blood culture and urine sample and were sent for routine examination and culture. Lumbar puncture & cerebrospinal fluid analysis was done for those patients who showed signs and symptoms of meningitis. Radiological investigations were done as applicable.

3.5. Procedure

All neonates after admission were screened for blood glucose levels at 2, 12, 24, 48 and 72 hours. The blood glucose was screened by glucometer and confirmed in laboratory by glucose oxidase method. Other relevant investigations to diagnose comorbidities due to sepsis were also done. Statistical data was mentioned regarding the number of admission and morbidities which were associated with term neonates with sepsis and altered blood glucose.

3.6. Statistical analysis

Attempts were made to find the correlation of changes with these factors by statistical analysis. All data were analyzed by using the software SPSS (21), Medcalc.

4. Observation

Out of that total number (n=2970) of neonatal sepsis cases was 850 (28.53%). Basing upon the exclusion criteria and inclusion criteria 209 newborns were subjected to the present study.

Males outnumbered females in a ratio 1.3:1, P value 0.071 not statistically significant. Table 1

Out of all the hypoglycemic patients admitted, 42 (62.68%) cases were early onset sepsis and only 25 (37.22%) cases were late onset sepsis. Similarly out of 52 cases with hyperglycemia, 33 (63.46%) were early onset sepsis cases and the rest 19 (36.53%) cases were late onset sepsis. The age of presentation and altered blood glucose were statistically insignificant as suggested by chi square test with p value 0.134. Table 2

More number of unresolved deaths was associated with hyperglycemia (85%) than in hypoglycemia (64.7%). The p value for hyperglycemia being 0.092 and that in hypoglycemia being 0.088 both are statistically insignificant. Table 3

Out of the total number of cases with probable sepsis (162) normoglycemia seen in 80 cases (49.8%), hypoglycemia in 49 cases (30.2%), hyperglycemia in 33 cases (20.3%). Table 4

And out of the total number of cases with proven sepsis (n=47) hyperglycemia accounts for 40.4% of cases followed

Table 1: Sex of baby with relation to altered blood glucose.

Sex of the baby	Altered blood glucose			Total
	Hypo	Normo	Hyper	
Male	31(26.5%)	58(49.6%)	28(23.9%)	117
Female	36(39.1%)	32(34.8%)	24(26.1%)	92
Total	67	90	52	209

Table 2: Relationship between glucose level and onset of sepsis

Glucose level	Early onset sepsis		Late onset sepsis		Total
	0-3 days	4-7 days	>7 days		
Hypoglycemia	42(62.68%)	10(14.92%)	15(22.38%)		67
Normoglycemia	53(58.8%)	8(8.88%)	29(32.22%)		90
Hyperglycemia	33(63.46%)	6(11.5%)	13(25.0%)		52
Total	128	28	57		209

Table 3: Duration of resolution of altered blood glucose

Glucose level	N=number of patients	Unresolved deaths	Resolved deaths(due to other factors)	Minimum duration of resolution	Maximum duration of resolution	Mean duration of resolution
Hyperglycemia	52	24(85%)	4(15%)	1	8	3.4 days
Normoglycemia	90	Nil	Nil	Nil	Nil	Nil
Hypoglycemia	67	11(64.7%)	6(35.29%)	1 day	10 days	3.9 days

Table 4: Altered blood glucose in proven and probable sepsis

Parameter	Hypoglycemia	Normoglycemia	Hyperglycemia	Total
Probable sepsis	49(30.2%)	80(49.38%)	33(20.3%)	162
Proven sepsis	18(38.3%)	10(21.2%)	19(40.4%)	47

by hypoglycemia 18 cases (38.3%) and normoglycemia seen in 10 cases (21.2%).

Out of the total number of death in probable sepsis with hyperglycemia was observed in 15(45.5%) cases, hypoglycemia was observed in 13(26.5%) cases and normoglycemia was observed in 4(5%) cases. Table 5

There is a significant association between hyperglycemia and mortality among patients with proven sepsis as indicated by a p value of <0.001, whereas there is no significant association between hypoglycemia and mortality in cases with proven sepsis.

Among the cases admitted as either probable or proven sepsis hypoglycemic cases were observed to have a 7.3 times higher mortality than the normoglycemic patients, whereas the hyperglycemic cases were observed to have 25 times higher mortality as compared to normoglycemic cases. Significant association is present between mortality and hyperglycemia as well as hypoglycemia, as indicated by p value <0.001. Table 6

Among the ventilated cases hyperglycemic cases were observed to have a 10.625 times higher rate of ventilation as compared to normoglycemic cases, whereas hypoglycemic cases were observed to have a 2.305 times higher rates of ventilation as compared to normoglycemic cases. Significance of association between ventilation and altered

blood glucose levels is denoted by p value <0.001. Table 7

5. Discussion

Basing on the inclusion and exclusion criteria the number of cases of neonatal sepsis with normoglycemia hypoglycemia and hyperglycemia were, 90(44%), 67(32%), 52(24%) cases respectively (n=209). The male infants 117(56%) outnumbered the female infants 92(44%). Somu et al 1976⁹; Seiget et al 1978;¹⁰ khatua et al 1986¹¹ and Anita Sharma et al 1993¹² made similar observations in their studies wherein they found a male predominance between the range of 55% to 82%. It was observed that hyperglycemia 28(23.9%) cases more marked in males and hypoglycemia 36(39.1%) cases were more marked among females. Although no significant gender variability was found in patients with altered blood glucose as suggested by chi square test with p value of 0.071.

In our study neonates with early onset sepsis and late onset sepsis were 128(61.2%) cases and 81(38.8%) cases respectively. NNPD 2002⁵ reports have shown similar occurrences of early onset and late onset sepsis as 67% and 33% respectively. The median age of presentation in the current study was 3 days, the mean age of presentation was 5.76 days and 61.2% of admissions were in the first 3 days of life (presenting as early onset sepsis). Mohammad Saiful

Table 5: Outcome in patients with altered blood glucose levels with probable sepsis (A) V/S proven sepsis (B).

Risk factors	Death		Discharge		p Value	
	A	B	A	B	A	B
Hyperglycemia	15(45.5%)	13(76.4%)	18(54.5%)	6(20%)	<0.001	P<0.001
Normoglycemia	4(5%)	0	76(95%)	10(33.33%)		
Hypoglycemia	13(26.5%)	4(23%)	36(73.5%)	14(46.6%)	<0.001	0.107

Table 6: Altered blood glucose and outcome

Risk factors	Death n=49	Discharge n=160	p Value	Odds ratio	CI(95%)
Hyperglycemia n=52	28(53.8%)	24(46.2%)	P<0.001	25.08	(8.01 to 78.52)
Normoglycemia n=90	4(4.4%)	86(95.6%)			
Hypoglycemia n=67	17(25.4%)	50(74.6%)	P<0.001	7.3	(2.3 to 22.94)

Table 7: Altered blood glucose and ventilation

Parameter	Ventilated	Not Ventilated	p Value	Odds Ratio	CI
Hypoglycemia	8(24%)	59(33%)	<0.001	2.305	(0.719-7.395)
Normoglycemia	5(15%)	85(48%)			
Hyperglycemia	20(61%)	32(18%)	<0.001	10.625	(3.6-30.69)
Total	33	176	-	-	-

Islam et al,¹³ Njhia et al 2011¹⁴ made similar observations in their study. The relation between age of presentation and altered blood glucose is not statistically significant as suggested by chi square test with p value 0.134.

Out of 47 proven sepsis (culture positive) patients; hyperglycemia was observed in 19(40.4%) cases followed by hypoglycemia and normoglycemia in 18(38.3%) cases and 10(21.2%) cases respectively. In probable sepsis group (n=162) hyperglycemia was observed in 33(20.3%) cases, hypoglycemia was observed in 49(30.2%) cases and normoglycemia was observed in 80(49.35%) cases. Mohammad Saiful Islam et al¹³ in their study found occurrence of normoglycemia in 57.2% of cases, followed by hyperglycemia in 23.8% and hypoglycemia in 19% cases.

Out of the total number of cases with proven sepsis (n=47) gram negative organism growth was seen in 33(70.21%) cases. Growth was seen in 39.3% cases in hypoglycemic groups, and in 42.4% cases in hyperglycemic group and 18.2% cases in normoglycemic group. Louaib D et al¹⁵ found in their study that culture positive patients with gram negative sepsis were predominantly hyperglycemic 38% of cases.

Out of the total number of deaths in cases with probable sepsis n=32, hyperglycemia was observed in 15(45.5%) cases, hypoglycemia in 13(26.5%) cases and normoglycemia was observed in 4(5%) cases. Out of the total number of deaths in proven sepsis n=17 cases, hypoglycemia was observed in 4(23%) cases and hyperglycemia in 13 (76.4%) cases. There is a significant association between hyperglycemia and mortality among patients with proven sepsis as indicated by a p value of <0.001, whereas there is no significant association between

hypoglycemia and mortality in cases with proven sepsis.

Out of the total number of deaths (n=49), hyperglycemia was observed in 28(53.8%) cases followed by hypoglycemia 17(25.4%) cases and normoglycemia in 4(4.4%) cases. The total number of cases admitted as either probable sepsis or proven sepsis hypoglycemic cases were observed to have a 7.3 times higher mortality rates than the normoglycemic patients, whereas the hyperglycemic cases were observed to have 25 times higher mortality rates as compared to normoglycemic cases. Significant association is present between mortality and hyperglycemia as well as hypoglycemia, as indicated by p value <0.001. Similar results were reflected in the study done by Wintergest et al 2006,¹⁶ Ahmad and Khalid et al 2012,¹⁷ Mohammad saiful Islam et al,¹³ Lugt et al,¹⁸ Hall et al¹⁹ and Bhutia et al.²⁰

In the current study we found that out of the total 33 ventilated patients' hypoglycemia was observed in 8(24%) cases, normoglycemia in 5 (15%) cases and hyperglycemia in 20(61%) cases. Out of the total number of ventilated cases hyperglycemic cases were observed to have a 10.625 times higher rate of ventilation as compared to normoglycemic cases, whereas hypoglycemic cases were observed to have a 2.305 times higher rates of ventilation as compared to normoglycemic cases. Significance association between ventilation and altered blood glucose levels is denoted by p value <0.001. Although no such study is available to compare altered blood glucose and requirement of positive pressure ventilation however studies in adult. Edriss H et al 2017²¹ observed increased duration of mechanical ventilation in populations having increased blood glucose levels. So a long term prospective study is needed to establish the findings.

6. Summary

In this present series 209 neonates with suspected (clinical sepsis) were studied out of which 47(22.5%) were proved to have sepsis with positive blood culture. There was significant association between hyperglycemia and mortality in patients with proven sepsis as indicated by a p value of <0.001. Out of the total number of deaths (n=49), hyperglycemia was observed in 28(53.8%) followed by hypoglycemia 17(25.4%) and normoglycemia 4(4.4%). Among the ventilated cases hyperglycemic cases were observed to have a 10.625 times higher rate of ventilation as compared to normoglycemic cases, whereas hypoglycemic cases were observed to have a 2.305 times higher rates of ventilation as compared to normoglycemic cases. There was a significant association (p value <0.001) between ventilation and altered blood glucose levels.

7. Conclusion

Altered blood glucose was a common occurrence in sepsis and has a significant impact on outcome. Supportive measures in form of ventilation were related to glycemic levels. Hyperglycemia prolonged the duration of ventilation in comparison to hypoglycemia. During the study we found that both hypoglycemia and hyperglycemia were associated with increased mortality rates at all thresholds but hyperglycemia was independently associated with increased odds of death in patients with neonatal sepsis compared to hypoglycemia.

8. What this Study Add

Hyperglycemia was independently associated with increased odds of death in patients with neonatal sepsis, must be treated as well for decreasing neonatal mortality.

9. Contributions of Authors

All authors were involved in research design, data analysis, and manuscript preparation and editing.

10. Source of Funding

None.

11. Conflict of Interest

None.

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