ORIGINAL ARTICLE

PREVALENCE AND RISK FACTORS OF NEONATAL HYPOGLYCAEMIA AT ST. PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE, ETHIOPIA

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ABSTRACT

Background: *Hypoglycaemia is a common metabolic abnormality in neonates that can cause preventable death. The overall incidence of neonatal hypoglycemia has been estimated to be 1 to 5 per 1,000 live births with a higher incidence in at-risk populations. There is limited data regarding neonatal hypoglycemia prevalence and risk factors in developing countries like Ethiopia. This study was aimed to assess the prevalence and risk factors of neonatal hypoglycemia in the neonatal intensive care unit at Saint Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia.*

Methodology*: A cross-sectional study was conducted from June 17 to August 3, 2018. Neonates, whose age was less than 48hrs and admitted to the neonatal intensive care unit were enrolled. Sociodemographic, maternal and neonatal factors were collected using a structured questionnaire. Blood glucose was measured using a glucometer with a test strip. Random blood glucose level < 47mg/dl was taken as a cut-off point to define hypoglycemia. The data were entered and analyzed using SPSS version 20.*

Result*: Neonatal hypoglycemia was detected in 25% (49/196) of the neonates. Birth weight, duration of labor, maternal age, and time of feeding initiation, hypothermia, and respiratory distress syndrome were associated with hypoglycemia. From these factors, maternal age, birth weight, and hypothermia were found to be independent predictors of the outcome.*

Conclusion: *Hypoglycaemia was prevalent in neonates admitted to the neonatal intensive care unit and was associated with low birth weight and hypothermia. These findings call for early detection of hypoglycemia, prevention of hypothermia, and early initiation of feeding to prevent neonatal morbidity and mortality.*

Keywords: *Hypoglycaemia, Prevalence, Neonates, Ethiopia*

BACKGROUND

Hypoglycemia is a common metabolic abnormality seen in neonates. It usually occurs shortly after delivery (1). In normal neonates, the random glucose level drops by 25–30 mg/dL and may lower down to 55–60 mg/dL in the first three hours of life. The glucose level

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then steadily rise over the first few days of life with the help of different adaptation mechanisms. Failure of this adaptation will result in hypoglycaemia (2,3).

The overall prevalence of neonatal hypoglycemia has been estimated to be 1 to 5 per 1,000 live births (4). In at-risk populations it can reach as high as 30% - 60% (3,5). But the lack of consistent hypoglycemia definition resulted in a different prevalence of neonatal hypoglycemia as it is shown in many studies (6-8).

Several risk factors have been identified for neonatal hypoglycemia including prematurity, small for gestational age (SGA), Post maturity, multiple gestations, maternal toxemia, perinatal asphyxia, hypothermia, sepsis, infant of diabetic mother (IDM), and delayed initiation of feeding (9). Neonates who are large for gestational age (LGA), polycythemic, or those who underwent exchange transfusion are also at risk of developing hypoglycemia (9,10). The main mechanisms by which these factors result in hypoglycemia include disruption of glycogenolysis or gluconeogenesis, decreased alternate fuel production, increased glucose demand, and failure to receive or absorb nutrients (4). Severe and prolonged hypoglycemia can result in serious neurodevelopmental abnormalities and can cause death. Therefore, timely identification of risk factors and interventions prevent neonates from unwanted complications of hypoglycemia (11-14).

Since Ethiopia has one of the highest neonatal mortality rates, decreasing preventable neonatal death is an essential public health concern (15). Therefore, early detection of neonates at risk for hypoglycemia can help to decrease neonatal death. There are few reports on prevalence and risk factors of neonatal hypoglycemia in developing countries (16-18). In the current study, we report the prevalence and risk factors of neonatal hypoglycemia which occurred in the first 48 hours, and its associated factors in a tertiary level teaching hospital in Ethiopia.

METHODOLOGY

A hospital-based cross-sectional study was conducted from June 17, 2018, to August 2, 2018, in the neonatal intensive care unit (NICU) of Saint Paul's Hospital Millennium Medical College (SPHMMC). SPHMMC is one of the largest teaching hospitals in Addis Ababa, Ethiopia, which gives NICU service for babies delivered at SPHMMC and referred from other health facilities. Around 300 neonates are admitted to the unit each month.

Inclusion Criteria

All neonates admitted to the SPHMMC NICU during the study period whose age was less than 48hrs at admission with mothers who gave consent were included.

Procedure

Sample size calculation

The sample size was calculated using a formula for estimation of single population proportion taking the magnitude of neonatal hypoglycemia in SPHMMC to be p=15% margin of error 5% and using 95% confidence level. As a result, the sample size of 196 was calculated. This was based on the previous prevalence of neonatal hypoglycemia of 14.9 % in Tikur Anbessa Hospital in Addis Ababa, Ethiopia (unpublished data).

Data collection

Socio-demographic and clinical data were collected using a semi-structured, pre-tested questionnaire and a chart review. The questionnaire included questions on maternal and neonatal risk factors for neonatal hypoglycemia. The data was collected by general practitioners and health officers working in the NICU. Blood glucose was measured by Accu -Chek glucometer with a test strip. The procedure was done by general practitioners, residents, and health officers working in the NICU. The pre-warmed heel of a neonate was cleaned with an alcohol swab and after drying, skin puncture was done on the posterior-lateral aspect by a lancet. The first drop of blood was discarded then the second drop of blood was applied to the test strip and blood glucose was noted. The first blood glucose measurement was performed in the first 3 hours of life. Subsequent measurements were at 3-24 hours and 24-48 hours. The temperature of the neonates was also recorded with each blood glucose determination. Neonates who were found to be hypoglycaemic and hypothermic were managed as per the NICU protocol immediately.

Operational definition

1. Neonatal hypoglycemia: random blood sugar (RBS) level < 47mg/dl for any gestational age or postnatal age (4)
2. Mild hypothermia: axillary temperature 36.0° C- 36.5°C (19)
3. Moderate hypothermia: axillary temperature 32.0-36.0° C (19)
4. Severe hypothermia: axillary temperature less than 32.0° C (19)
5. Polycythaemia: venous hematocrit more than 65% or venous hemoglobin> 22gm/dl (20)
6. Transient neonatal hypoglycemia: Hypoglycemia occurs in the first 48 hours of neonatal age (21).

Data processing and analysis

The coded data were entered and analyzed using SPSS version 20. Data were summarized in proportions and frequency tables for descriptive analysis. Binary logistic regression was used to identify crude odds ratio and confidence interval (CI). Variables with P less than 0.05 in the bivariate analysis were considered statistically significant. Variables of P value less than 0.25 were included in

the multivariable analysis to determine independent predictors that were associated with outcome variables.

RESULTS

During the study period, a total of 196 neonates were enrolled in the study. According to their birth weight, 32.7% were low birth weight, 12.2% were very low birth weight (VLBW), 52.5% had normal birth weight and 2% were macrosomic. The characteristics of the neonates are shown in (**Table 1**).

Table 1. Description of demographic characteristics of neonates

Variables	Frequency	Percent
Neonatal age		
<3hrs	170	86.7
3-24hr	26	12.8
Gestational age		
Preterm	70	35.7
Term	121	61.7
Post term	5	2.6
Sex		
Male	111	56.6
Female	85	43.4
Weight for GA		
LGA	2	1
AGA	158	80.6
SGA	36	18.3

GA= Gestational age, LGA= large for gestational age, AGA= appropriate for gestational age, SGA= small for gestational age

Prevalence of Neonatal Hypoglycemia

Of the neonates enrolled, 25% (49/196) had hypoglycemia in the first 48 hours of their age.

Description of obstetric characteristics of the mothers

The majority of mothers (84.2%) were in the age range of 20-35 years. Fifty percent of the neonates were delivered from primiparous mothers. The duration of labour was >24hrs in 9.2% while rupture of membrane (ROM) lasted >18hrs in 14.3%. The mode of delivery by spontaneous vaginal delivery (SVD) was 49%, instrumental delivery was 8.7%, and caesarean section (CS) in 41.8%. The description of maternal characteristics is shown in (**Table 2**)

Table 2. Description of Clinical characteristics of the Mothers

Variables	Frequency	Percent
Maternal age		
<20yr	8	4.1
20-35yr	165	84.2
>35yr	23	11.7
Maternal DM		
Yes	2	1.0
No	194	99.0
HIV		
Yes	8	4.1
No	188	95.9
Drugs		
Neither	133	67.9
Antibiotics	19	9.7
Steroid	30	15.3
Both	14	7.1
PIH		
Yes	39	19.9
No	157	80.1

DM= diabetes mellitus, PIH= pregnancy induced hypertension

Feeding was initiated at <3hr of age in 11.2%, at 3-24hrs in 62.2%, at 24-48hrs in 33(16.8%), and in 9.7% feeding was not started in the first 48hrs of life. Exclusive breastfeeding was started in 80.6% and mixed feeding in 9.7%. Description of the Neonatal characteristics is shown on (Table 3).

Table 3. Description of Clinical characteristics of the neonates

Variables	Frequency	Percent (%)
Sepsis		
Suspected	73	37.2
Culture positive	13	6.6
No sepsis	110	56.1
polycythemia		
Yes	12	6.1
No	184	93.9
PNA		
Yes	27	13.8
No	169	86.2
MAS		
Yes	35	17.9
No	161	82.1
RDS		
Yes	35	17.9
No	161	82.1
Temperature		
Hypothermic*	85	43.4
No or mild hypothermia	111	56.6

PNA=perinatal asphyxia, MAS= meconium aspiration syndrome, RDS= respiratory distress syndrome
Hypothermic= Moderate and severe hypothermia

From the socio-demographic variables, birth weight was the only independent variable with statistically significant association to the outcome with low birth weight (LBW) neonates having a 2.14 times more risk to develop hypoglycemia (COR 2.14; 95%CI 1.03-4.47) while very low birth weight (VLBW) neonates have a 3.9 times increased risk (COR 3.99; 95% CI 1.54-10.33).

Prematurity and small for gestational age were not found to have statistically significant associations (COR 0.52 95% CI 0.031-8.71 and COR 1.41; 95CI 0.63-3.13), respectively.

From the maternal and obstetric factors, duration of labor and maternal age were found to be significantly associated with outcome. Neonates born after more than 24hr duration of labor were 9.3% less likely to develop hypoglycemia (COR 0.093; 95%CI 0.011-0.793) and maternal age 20- 35yr was associated with a 33.7% reduction in the risk of neonatal hypoglycemia (COR 0.337; 95%CI 0.136-0.835).

Parity, mode of delivery, HIV status of the mother, pregnancy-induced hypertension was not found to have statistically significant associations with the outcome (Primipara COR 1.05; 95% CI 0.553-2.016, CS delivery COR 1.583; 95% CI 0.814-3.078, HIV COR 1.852; 95% CI 8.051).

From the neonatal factors, three variables were found to have a statistically significant association with neonatal hypoglycemia. These were initiation of feeding in the first three hours of life, the presence of moderate to severe hypothermia, and respiratory distress syndrome.

The diagnosis of respiratory distress syndrome was associated with a 2.4 times elevated risk in neonatal hypoglycemia at the same time the presence of moderate to severe hypothermia were associated with 2.1 times increased in risk (COR 2.400; 95%CI 1.108-5.199 and COR 2.105; 95%CI 1.093-4.057, respectively). Moreover, initiation of feeding in the first three hours of life was associated with a 6.5% decrement in the risk of hypoglycemia (COR 0.065; 95%CI 0.007-0.593).

The presence of perinatal asphyxia, polycythemia, and sepsis was not found to have a statistically significant association with the outcome (COR 0.646; 95%CI 0.231-1.809, COR 1.544; 95%CI 0.444-5.371 and COR 0.838; 95%CI .215-3.259).

After controlling for confounders, only maternal age, birth weight, and the presence of moderate to severe hypothermia were seen to have a significant association with neonatal hypoglycemia. VLBW neonates have a 4 fold increase in risk while neonates with moderate to severe hypothermia were 2.06 times more likely to develop neonatal hypoglycemia (AOR 4.011; 95% CI 1.425-11.292 and AOR 2.064; 95% CI 1.001-4.256) as shown in (Table 4).

Table 4. Multivariate analysis of Neonatal factors

Variable	Category	COR	AOR
Neonatal age	<3hrs	2.844(0.815-9.925)	
	3-24hrs		
Birth weight	LBW	2.146(1.031-4.470)*	
	VLBW	3.996(1.545-10.336)*	4.011(1.425-11.292)*
RDS	Yes	2.400(1.108-5.199)*	
	No		
MAS	Yes	0.568(0.220-1.462)	
	No		
Sepsis	Suspected	0.848(0.426-1.688)	
	Culture positive	0.838(0.215-3.259)	
	No		
Temperature	Moderate/Severe Hypothermia	2.105(1.093-4.057)*	2.064(1.001-4.256)*
	No/mild hypothermia		

*p-value <0.05, **RDS= respiratory distress syndrome, MAS= meconium aspiration syndrome**

Neonates born to mothers in the age range 20 -35yrs have a 32.3% decrement in hypoglycemia keeping all other factors constant. (AOR 0.323; 95% CI 0.121-0.862) as shown in (Table 5).

Table 5. multivariate analysis of Maternal factors

Variable	Category	COR	AOR
Maternal age	<20yrs	2.167(0.415-11.302)	
	20-35yrs	0.337(0.136-0.835)*	**0.323 (0.121-0.862)***
	>35yr		
DOL	<24hr	0.514 (0.227-1.160)	
	>24hr	0.093(0.011-0.793)*	
MOD	SVD		
	Instrumental	0.213(0.027-1.698)	
	CS	1.583(0.814-3.078)	
PIH	yes	4.151(0.918-1.952)	
	No		

*p-value <0.05, **DOL= duration of labor, MOD=mode of delivery, PIH= pregnancy induced hypertension**

Discussion

There is an ongoing controversy about the definition of neonatal hypoglycemia (4,6-8). In this study, a blood glucose level less than 47mg/dl was considered hypoglycemia for any postnatal or gestational age. In the current study, we found the prevalence of hypoglycemia in 25% of the neonates admitted to NICU. The prevalence of neonatal hypoglycemia in our study was slightly lower than the study done in Nigeria which was 28%. In their study, every newborn baby delivered in that hospital during the study period including those who were asymptomatic babies and did not have risk factors were included(16).

A higher prevalence of neonatal hypoglycemia was seen in the current study compared to previous studies done in Israel and Iran which were 12.1% and 15%, respectively (9,17). In their studies, they took the prevalence of hypoglycemia in neonates in the first three hours of age that explains the lower prevalence in their study compared to our study. In addition, in the Iran study, they took also a lower cut off point (35 mg/dl) to consider hypoglycemia compared to the current study.

Several risk factors have been identified for neonatal hypoglycemia (4,9,10). In this study, we found birth weight less than 2500gm to be the most significant variable associated with neonatal hypoglycemia. LBW neonates had a twofold increased risk and VLBW neonates had a fourfold increase in the risk of hypoglycemia. Similar results were seen in a study conducted in south India (18). Babies with LBW and VLBW have limited reserve of glycogen and fat, which predispose them to develop neonatal hypoglycemia (22) .

Another factor that was found to be significantly associated with hypoglycemia after multivariate analysis was hypothermia. The association between hypothermia and hypoglycemia is widely described in different studies (10, 23, 24). The glucose requirement increases in neonates who have hypothermia which will increase the risk of hypoglycemia (9, 10). In our study, neonates with moderate to severe hypothermia had a considerable increase in the risk of hypoglycemia. Comparable results were also seen in previous studies done by Sasidharan et al they examined the risk factors for neonatal hypoglycemia in 605 neonates. In their series, a significant proportion of hypoglycaemic neonates were hypothermic at the time of sampling. They also found hypothermia to be significantly associated with hypoglycemia after adjusting for confounders (18). In the current study neonates diagnosed to have RDS were also at an increased risk to develop hypoglycemia this finding was also seen in other studies, as there is increased work of breathing in RDS which will result in increased consumption of glucose (23, 24)

Our study found neonates born to mothers in the age range of 20-35yrs were less likely to

develop hypoglycemia. In contrary to our finding, a matched case-control study was conducted in Allentown on the term, non-diabetic pregnancies and they found maternal age was not significantly associated with neonatal hypoglycemia (25). The association of maternal age seen in our study could be due to a significant portion (84.2%) of the participant's mothers falling in this age range.

The results of our study did not show a statistically significant difference in some factors that prior studies have identified as predictors of risk, such as maternal DM, gestational age, small for gestational age, polycythemia, perinatal asphyxia, and pregnancy-induced hypertension (23-27). This is in contrast to our investigation, in which none of these factors seem to influence the odds of hypoglycemia. This could be attributed to the small number of neonates with those risk factors in our study. There is also no statistically significant difference observed in the mode of delivery in the current study.

Encouraging early and frequent breast feeding is a safe strategy to prevent hypoglycemia in neonates (28). It was also evident in our study, early feeding initiation was found to be protective in 6.8% of the neonates.

In summary, our study found the prevalence of neonatal hypoglycemia to be 25% in the first 48hrs of life. Low birth weight and the presence of moderate to severe hypothermia contribute considerably to the risk of hypoglycemia. We found these two factors to be the strongest predictors of hypoglycemia in these neonates. Neonates diagnosed to have RDS are also at an increased risk to develop hypoglycemia. Moreover, initiation of feeding in the first 3hrs of life is found to be a protective factor.

Finally, we recommend prevention of hypothermia, monitoring the blood glucose in high -risk babies with RDS and those with LBW, and early initiation of feeding are crucial steps to prevent neonatal hypoglycemia. Early detection of hypoglycemia in the first 48 hours and timely management of neonatal hypoglycemia are important factors to prevent the long-term neurologic complications seen in neonates with neonatal hypoglycemia.

Abbreviations

AGA: appropriate for gestational age; **AOR**: Adjusted odds ratio; **C/S**: caesarean section; **COR:** Crude odds ratio; **CI:** Confidence interval; **DOL**: Duration of labour; **HCT:** haematocrit; **HGB**: haemoglobin **HIV**: human immunodeficiency virus**; IDM:** infant of diabetic mother; **LGA:** large for gestational age LBW: low birth weight; **NICU:** Neonatal intensive care unit; **NBW:** Normal birth weight; **MAS**: Meconium aspiration syndrome; **PIH:** pregnancy induced hypertension; **PNA:** perinatal asphyxia; **ROM**: Rupture of membrane; **RDS**: Respiratory distress syndrome; **SPHMMC**: Saint Paul's hospital millennium medical college; **SGA:** small for gestational age;

SVD: spontaneous vaginal delivery; **VLBW:** very low birth weight;

Declarations

Ethics approval and consent to participate: Consent from the care givers were taken and the research got IRB approval from SPHMMC IRB.

Consent to publish: Not applicable

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Authors' Contributions: IN: conceptualized and designed the study and data collection tools, performed data collection, and drafted the initial manuscript. BF: Guided the study design, provided critical feedback in the development of the study, advised the data collection, revised, approved, and submitted the final manuscript.

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