Prevalence and Risk factors of Hypoglycaemia in Neonates at St. Paul's Hospital Millennium Medical College Neonatal Intensive Care Unit, Ethiopia: A Cross Sectional Study

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Abstract

Background Hypoglycaemia is a common metabolic abnormality seen in neonates that can cause preventable death. Its overall incidence has been estimated to be 1 to 5 per 1,000 live births, with higher incidence in at-risk populations. There is limited data regarding its prevalence and risk factors in developing countries like Ethiopia. Therefore, this study was aimed to determine the prevalence and risk factors of neonatal hypoglycaemia in neonatal intensive care unit (NICU) at Saint Paul's Hospital Millennium Medical College (SPHMMC), Addis Ababa, Ethiopia. **Methodology** A cross sectional study was conducted from June 17 to August 3, 2018 at SPHMMC, NICU. Neonates whose age was less than 48hrs and admitted to NICU were enrolled. Sociodemographic, maternal and neonatal factors were collected using structured questionnaire. Blood glucose was measured using glucometer with a test strip. Random blood glucose level < 47mg/dl was taken as a cut-off point to define hypoglycaemia. The data was entered and analysed using SPSS version 20. **Results** Neonatal hypoglycaemia was detected in 25% (49/196) of the neonates. Birth weight, duration of labor, maternal age, time of feeding initiation, hypothermia and respiratory distress syndrome were associated with hypoglycaemia. 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 NICU of SPHMMC and was associated with low birth weight and hypothermia. These findings calls for early detection of hypoglycaemia, prevention of hypothermia and early initiation of feeding to prevent neonatal morbidity and mortality.

Background

Hypoglycaemia 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 levels 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 hypoglycaemia 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]. But the lack of consistent hypoglycaemia definition resulted in different prevalence of neonatal hypoglycaemia as it is shown in many studies [5-7].

Several risk factors have been identified for neonatal hypoglycaemia including prematurity, SGA, Post maturity, multiple gestation, maternal toxemia, perinatal asphyxia, hypothermia, sepsis, IDM and delayed initiation of feeding [8]. Neonates who are LGA, polycythemic or those who underwent exchange transfusion are also at risk of developing hypoglycaemia [8, 9]. The main mechanisms by which these factors result in hypoglycaemia 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 [10- 13].

Reports on prevalence and risk factors of neonatal hypoglycaemia in developing countries in general [14-17] and in Ethiopia in particular are limited [18]. Since Ethiopia has one of the highest neonatal mortality rates, decreasing preventable neonatal death is an essential public health concern [19]. Therefore, early detection of neonates at risk for hypoglycemia can help to decrease neonatal death. In this study we report the prevalence and risk factors of neonatal hypoglycemia in a tertiary level teaching hospital in Ethiopia.

Methodology

This 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 in born and out born babies. Around 300 neonates are admitted to the unit each month.

Inclusion and Exclusion Criteria

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

Neonates admitted after 48 hours of age to the NICU of SPHMMC and neonates whose mothers were not voluntary for enrolment were excluded from the study.

Procedure

Sample size calculation

The sample size was calculated using a formula for estimation of single population proportion taking magnitude of neonatal hypoglycaemia 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 previous prevalence of neonatal hypoglycaemia of 14.89 % in Tikur Anbessa Hospital in Addis Ababa, Ethiopia [18].

Data collection

Socio-demographic and clinical data were collected using a semi-structured, pre-tested questionnaire and the chart review. The questionnaire included questions on maternal and neonatal risk factors for neonatal hypoglycaemia. Blood glucose was measured by Accu-Chek glucometer with a test strip. Temperature of the neonates was also recorded. Neonates who were found to be hypoglycaemic and hypothermic were managed as per the NICU protocol.

Operational definition

1. Neonatal hypoglycaemia: RBS level < 47mg/dl for any gestational age or postnatal age [4]
2. Mild hypothermia: axillary temperature 36.0° C- 36.5°C [20]
3. Moderate hypothermia: axillary temperature 32.0-36.0° C [20]
4. Severe hypothermia: axillary temperature less than 32.0° C. [20]
5. Polycythemia: venous hematocrit more than 65% or venous hemoglobin > 22gm/dl [21]
6. In born those who are born in the hospital and out born those who are born elsewhere.

Data processing and analysis

The coded data was entered and analyzed using SPSS version 20. Data was summarized in proportions and frequency tables for descriptive analysis. Binary logistic regression was used to identify crude odds ratio and CI. Variables of P less than 0.05 in the bivariate analysis were considered statistically significant. Variables of P value less than 0.25 were used in multivariable analysis to determine independent predictors that were associated with outcome variables.

Results

During the study period, a total of 196 neonates were enrolled into the study. According to their birth weight 32.7% were low birth weight, 12.24% were VLBW, 52.5% had normal birth weight and 2% were macrosomic. The characteristics of the neonates are shown in Table 1.

Table 1description of demographic characteristics of neonates in SPHMMC, July 2018

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

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

Majority of mothers (84.2%) were with age range of 20–35 years. Fifty percent of the neonates were delivered from primiparous mothers. The duration of labor was > 24hrs in 9.2% while ROM lasted > 18hrs in 14.3%. The mode of delivery by SVD was 49%, instrumental delivery was 8.7% and CS in 41.8%. The description of maternal characteristics is shown in Table 2.

Table 2
Description of maternal characteristics,
SPHMMC, July 2018

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

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 breast feeding 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 neonatal characteristics, SPHMMC, July
2018

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

From the socio-demographic variables, birth weight was the only independent variable with statistically significant association to the outcome with LBW neonates having a 2.14 times more risk to develop hypoglycemia (COR 2.14; 95%CI 1.03–4.47) while 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 20–35 year 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 were 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 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 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 were not found to have 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 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. Neonates born to mothers in the age range 20-35yrs have 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 4
multivariate analysis of Neonatal factors, SPHMMC, July 2018

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	Yes	2.105(1.093–4.057)*	2.064(1.001–4.256)*
	No/mild hypothermia		

*p-value < 0.05

Table 5
multivariate analysis of Maternal factors, SPHMMC, July 2018

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			

Discussion

Hypoglycaemia is a common metabolic abnormality in neonates which is usually seen shortly after delivery [1]. During their transition from intrauterine to extra-uterine life, their plasma glucose concentrations usually decline in the first few hours of life. Failure of adaption mechanisms that will rise their glucose to the normal level due to different risk factors will result in hypoglycaemia [2]. There is an ongoing controversy about the definition of hypoglycaemia regarding blood glucose measurements [4–7]. In this study, a blood glucose level less than 47 mg/dl was considered hypoglycaemia for any postnatal or gestational age.

As there are few reports on neonatal hypoglycaemia in developing countries like Ethiopia [14–18], we evaluated transient neonatal hypoglycaemia which is seen in the first 48 hours [22] and its association with maternal, obstetric and neonatal factors in a tertiary care hospital setting from a developing country. In this study we found prevalence of hypoglycaemia in 25% of the neonates. Our finding is slightly lower than the study done in Nigeria in 2008 which was 28% [14] but it was similar with the report from Kenyatta National hospital which showed around 23.2% prevalence [15]. Unlike our finding, the study done on high risk neonates with SGA, IDM, preterm and other factors by Deborah L et al showed a prevalence of 51% which is higher than the current study [23].

Our study showed higher prevalence compared to a previous study done in Ethiopia at Tikur Anbessa hospital [18] and Tehran hospital [16] which was 14.89% and 15%, respectively. In these two studies they took a lower cut of point to consider hypoglycaemia (40 mg/dl and 35 mg/dl, respectively). In addition in

the Tehran hospital study, the neonates were of age less than 3 hours, which can explain the difference from the current study [16]. Another study by Ruben et al [24] showed a 12% prevalence of hypoglycaemia in neonates in the first three hours of age. This can explain the lower prevalence compared to the current study which was done in the first 48 hours of age.

Several risk factors have been identified for neonatal hypoglycaemia including prematurity, SGA, postmaturity, multiple gestation, maternal toxaemia, perinatal asphyxia, hypothermia, sepsis, IDM, neonates who underwent exchange transfusion and delayed initiation of feeding. Neonates who are LGA, polycythemic are also at risk of developing hypoglycaemia [4, 8, 9].

In this study we found birth weight less than 2500 gm to be the most significant variable associated with neonatal hypoglycaemia. LBW neonates had a twofold increased risk and VLBW neonates had a fourfold increase in the risk of hypoglycaemia. Similar results were seen in a study conducted in south India and they found low birth weight to be an independent predictor of the risk of hypoglycaemia [17]. In contrast to our findings, a report from Nepal did not find low birth weight to be significantly associated with hypoglycaemia after adjusting for confounders [25].

Another factor which was found to be significantly associated with hypoglycaemia after multivariate analysis was hypothermia. The association between hypothermia and hypoglycaemia is widely described in different studies [26–28]. Hypothermia increases the risk of hypoglycaemia by increasing their glucose requirement [8, 9]. In our study, neonates with moderate to severe hypothermia had a considerable increase in the risk of hypoglycaemia. Comparable results were also seen in previous studies done by Sasidharan et al in 2002 who 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 hypoglycaemia after adjusting for confounders [17]. On the contrary, a cross sectional study conducted in Nepal on 578 neonates aged 0-48hrs, did not identify hypothermia as a significant risk factor for hypoglycaemia [25].

Our study found neonates born to mothers in the age range of 20-35yrs were less likely to develop hypoglycaemia. In contrary to our finding, a matched case control study was conducted in Allentown on term, non-diabetic pregnancies and they found maternal age was not significantly associated with neonatal hypoglycaemia [29]. 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, mode of delivery, gestational age, small for gestational age, polycythemia, perinatal asphyxia and pregnancy induced hypertension [26, 27, 28, 30, 31]. Evaluating the association of maternal DM and neonatal hypoglycaemia was not feasible in our study since there were only two neonates born to diabetic mothers from the participants. Unlike our study, Ruben et al and colleagues conducted a cross sectional study on 4000 neonates to determine the true incidence of early neonatal hypoglycaemia and to confirm potential risk factors. They found gestational age to have the strongest association with hypoglycaemia [24]. Another study done in south

India showed prematurity, maternal pre-eclampsia and eclampsia and birth asphyxia independently predicted the risk of neonatal hypoglycaemia [17]. This is in contrast to our investigation, in which none of these factors seem to influence the odds of hypoglycaemia. In a study from Nepal they found an independent association between polycythemia and hypoglycaemia [25]. This result was not replicated in our study. This could be attributed to the very small number of patients with polycythemia included in our study.

We did not find parity of the mother and prolonged rupture of membranes to be significantly associated with hypoglycaemia. Comparable results were seen in a prospective study from south India. Their data did not show significant difference in the incidence of hypoglycaemia between infants born to primipara and multipara mothers. Prolonged rupture of membrane also did not influence the risk of hypoglycaemia in their study [17].

Mode of delivery and small for gestational age were also not found to be significant predictors of neonatal hypoglycaemia in our study. Similar result was also seen in a cross sectional study conducted at a tertiary medical centre in Israel in 2014. They found small for gestational age was not associated with hypoglycaemia in the neonates [24].

In our study early feeding initiation was found to be protective in 6.8% of the neonates. However, delayed feeding initiation and whether the neonates were started on breast milk or mixed feeding was not associated with neonatal hypoglycaemia. Similar result was reported from Nepal [25] where they found no correlation between feeding delay and the risk of hypoglycaemia. On the contrary, in the study conducted in Kerala they found delay in initiation of feeding for more than 2hrs postnatal to be an independent predictor of the risk of neonatal hypoglycaemia [17].

In summary, our study found the prevalence of neonatal hypoglycaemia to be 25% in the first 48hrs of life as reported in other studies showing its burden. Low birth weight and the presence of moderate to severe hypothermia contribute considerably to the risk of hypoglycaemia. We found these two factors to be the strongest predictors of hypoglycaemia in these neonates. Neonates diagnosed to have RDS are also at an increased risk to develop hypoglycaemia. Moreover, initiation of feeding in the first 3hrs of life has been found to be a protective factor. Neonates delivered after prolonged duration of labor beyond 24hrs and those born to mothers in the age range of 20–35 year were also less likely to develop hypoglycaemia. These findings call for the need for early detection of hypoglycaemia and timely interventions such as early initiation of feeding and prevention of hypothermia. Therefore, looking for predisposing factors, taking timely preventive measures and early treatment of hypoglycemia is crucial to save neonates from acute complications, long term neurological abnormalities and mortality.

Abbreviations

AGA: appropriate for gestational age; AOR: Adjusted odds ratio; **C/S: caesarean section**; COR: Crude odds ratio; CI: Confidence interval; DOL: Duration of labor; **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

Availability of data and materials: We have lost the raw data (Computer infected by virus)

Competing interests: The authors declare that they have no competing interests

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Authors' Contributions: BF, Generation of idea, designing the study, guidance during data collection and analysis and manuscript writing and IN: proposal writing, Data collection and analysis and draft manuscript. Both authors read the manuscript.

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