

Maternal and Neonatal Risk Factors for Hypoglycemia in Preterm Infants

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Abstract: Hypoglycemia is a common morbidity in preterm infants. It might cause transient and permanent disturbances in brain structural and have impact on neurological development. The criteria for identifying preterm infants who are at risk of hypoglycemia remain unclear. This study was conducted to determine incidence of hypoglycemia in preterm infants and associated with maternal and neonatal risk factors. A cross-sectional study on 50 consecutive preterm infants on hospitals in Medan, Indonesia from June to August 2018. Maternal and neonatal risk factors were recorded. Blood glucose levels were obtained from venous blood sample and were checked serial from the time of delivery within the first hour of life until discharged from hospital or 72 hours of age. Univariate and bivariate (Chi square and Fisher exact test) analysis were performed with 95% CI and P value <0.05 were considered statistically significant. Out of 50 preterm infants, there were 13 infants experienced hypoglycemia (26%). Preterm infants with birth weight ≤ 2500 gr and 32-<35 weeks of gestational age were significantly increased the risk of developing hypoglycemia ($p=0.010$, $PR=4.69$; $p=0.021$, $PR= 3.11$, respectively). There were significant associations between birth weight ≤ 2500 gr and gestational age 32-<35 weeks with hypoglycemia.

1 INTRODUCTION

Prematurity is one of the highest causes of perinatal death in addition to low birth weight (LBW) infants, asphyxia or respiratory disorders. Neonatal mortality rates in Asia due to prematurity amounted to 413,000 or 30% of total neonatal deaths in 2000-2003. Caring premature infants is still a challenge. The biggest challenge is how to reduce the risk of morbidity which will reduce neurological disorders and long-term growth and development disorders so that these preterm infants can grow optimally (Howson, 2012).

One of the most common morbidity in premature infants is hypoglycemia. The immaturity of the glucose formation system, inadequate energy storage, and hyperinsulinism conditions can affect the occurrence of hypoglycemia, even severe and recurrent hypoglycemia in preterm infants (Zanardo, 1999).

Symptoms of hypoglycemia in neonates include jitteriness, convulsions, hypotonia, coma, refusal to feed, cyanosis, high pitched cry, hypothermia and even asymptomatic in most cases. Therefore detection of hypoglycemia must always be confirmed

biochemically (Dhananjaya, 2011). Hypoglycemia conditions have an effect on transient and permanent disturbances in the brain structural and have an impact on neurological development. (Goode, 2016). Research on risk factors for hypoglycemia in premature infants is still limited and shows controversial results. The purpose of this study is to determine incidence of hypoglycemia in preterm infants and associated maternal and neonate risk factors for hypoglycemia.

2 METHODS

This was a cross sectional study. We examined 50 moderate to late preterm labor infants with 32-36 weeks of gestational age through normal vaginal delivery and section caesarean. Patients were obtained consecutively. Minimum sample size calculated using one population sample formula. Stillbirth infants and severe congenital abnormalities were excluded. This study conducted from June to August 2018 in five hospitals, Adam Malik General Hospital, Universitas Sumatera Utara Hospital, Stella

Maris Mother and Child Hospital, Sarah Hospital, and Bunda Thamrin Hospital. All hospitals are located in Medan, Indonesia.

Maternal characteristics such as maternal age, weight, gravidity and parity, and delivery methods were recorded as maternal risk factors. Neonate characteristics such as gender, birthweight, gestational age, one-minute Apgar score, five-minute Apgar score were recorded as neonate risk factors. Blood glucose levels were obtained from venous blood sample and were checked serial from the time of delivery within the first hour of life until discharged from hospital or 72 hours of age. Blood glucose levels of 40 mg/dL or lower were considered as hypoglycemia. All patients gave informed consent. This study was approved by the Institutional Review Board of Universitas Sumatera Utara. Statistical data composed of univariate and bivariate were analyzed using SPSS version 22 (SPSS Inc., Chicago) with 95% confidence interval. The analysis was carried out using chi square and fisher exact test. P value <0.05 were considered statistically significant.

3 RESULT

3.1 Baseline Maternal Characteristics of Subjects

Mean of maternal age were 30.9 years with mean of body weight were 69.3 kgs. A total of 96% gave birth through cesarean delivery where 58% having medical indications. There were 54% of premature infantshadLBW.About66% were 35–37 weeks of gestational age. (Table1).

Table 1: Basic maternal characteristicsofsubjects.

Characteristics	n = 50
Maternal age, years, mean \pm SD	30.9 \pm 5.23
>31 years	21 (42%)
\leq 31 years	29 (58%)
Maternal weight, kg, mean \pm SD	69.3 \pm 10.87
>69 kg	25 (50%)
\leq 69 kg	25 (50%)
Maternal parity, times, median (min-max)	1 (0 – 2)
>1	8 (16%)
	42 (84%)

0 – 1	
Delivery, n (%)	
Vaginal delivery	2 (4%)
<i>Sectio caesarean</i>	48 (96%)
Indication of preterm labor, n (%)	
Medical indication	29 (58%)
Spontaneous	21 (42%)
Gender, n (%)	
Male	25 (50%)
Female	25 (50%)
Birthweight, gram, mean \pm SD	2,503.5 \pm
\leq 2500	542.21
>2500	27 (54%)
	23 (46%)
Gestational age, weeks, n (%)	
32 – <35 weeks	17 (34%)
35 – <37 weeks	33 (66%)
One-minute Apgar score, n (%)	
\leq 3	1 (2%)
4-6	9 (18%)
\geq 7	40 (80%)
Five-minute Apgar score, n (%)	
\leq 3	0 (0%)
4-6	1 (2%)
\geq 7	49 (98%)

n = total numberofsubjects

3.2 Association between Maternal and Neonate Characteristics with Hypoglycemia in Preterm Infants

Out of 50 preterm infants, there were 13 infants who had hypoglycemia (26%). Table 2 showed association between maternal characteristics and hypoglycemia in preterm infants. There were significant association between birth weight and prematurity with hypoglycemia. Infants with a birth weight \leq 2500 gr were increasedrisk of 4.69 times experiencing hypoglycemia compared to birth weight > 2500 gr (p=0.010). Infants with 32- <35 weeks of gestational age had 3.11 times higher risk to had hypoglycemia than 35-<37 weeks (p=0.021). There were no significant association between maternal age, weight, gravidity, parity, indication of preterm labor, gender, 1-minute and 5-minute Apgar score with hypoglycemia in preterm infants.

Table 2: Association Between Maternal and Neonatal Characteristics with Hypoglycemia in Preterm Infants

Variable	Hypoglycemia		Total n (%)	P	PR (95% CI)
	Yes n (%)	No n (%)			
Maternal age					
>31 years	8 (38.1)	13 (61.9)	21 (100)	0.097	2.21 (0.84-5.81)
≤31 years	5 (17.2)	24 (82.8)	29 (100)		
Maternal weight					
>69 kg	6 (24)	19 (76)	25 (100)	0.747	0.86 (0.34-2.19)
≤69 kg	7 (28)	18 (72)	25 (100)		
Maternal gravidity					
>2	2 (15.4)	11 (84.6)	13 (100)	0.469	0.52 (0.13-2.03)
1 – 2	11 (29.7)	26 (70.3)	37 (100)		
Maternal parity					
>1	0 (0%)	8 (100)	8 (100)	0.093	1.45 (1.18-1.77)
0 – 1	13 (31)	29 (69)	42 (100)		
Indication of preterm labor					
Medical	9 (31)	20 (69)	29 (100)	0.340	1.63 (0.58 – 4.59)
Spontaneous	4 (19)	17 (81)	21 (100)		
Gender					
Male	6 (24)	19 (76)	25 (100)	0.747	0.86 (0.34-2.19)
Female	7 (28)	18 (72)	25 (100)		
Birthweight					
≤2,500 gr	11 (40.7%)	16 (59.3)	27 (100)	0.010*	4.69 (1.16-19)
>2,500 gr	2 (8.7%)	21 (91.3)	23 (100)		
Gestational age					
32 – <35 weeks	8 (47.1)	9 (52.9)	17 (100)	0.021*	3.11 (1.2-8.05)
35 – <37 weeks	5 (15.2)	28 (84.8)	33 (100)		
One-minute Apgar score					
<7	4 (40)	6 (60)	10 (100)	0.420	1.78 (0.69-4.61)
≥7	9 (22.5)	31 (77.5)	40 (100)		
Five-minute Apgar score					
<7	0 (0)	1 (100)	1 (100)	1,000	1.36 (1.15-1.61)
≥7	13 (26.5)	36 (73.5)	49 (100)		

*p<0.05

4 DISCUSSION

Hypoglycemia is common in neonates. The lowest blood glucose level in 2 hours of life which is generally due to physiological rather than pathological factors (Sperling, 2012; Mitanchez, 2007; Aggarwal, 2010). Previous studies reported prevalence of hypoglycemia varied in neonates, approximately 15.1-29.1% (Lodhi, 2006; Dashti, 2007; Osiet, 2003; Dalgic, 2002). The prevalence of hypoglycemia is significantly higher in preterm infants. Singh. showed the prevalence of hypoglycemia in preterm infants and term infants were 19.05% vs 14.42%

(Singh, 2014).

This recent study found the prevalence of hypoglycemia in preterm infants was 26%. This prevalence difference is due to differences in the definition of hypoglycemia, inclusion criteria, sample size, and detection method of hypoglycemia. There were significant association between LBW and prematurity with hypoglycemia. Infants with a birth weight ≤2500 gr were significantly increased risk of 4.69 times experiencing hypoglycemia compared to birth weight > 2500 gr. Infants with 32 – <35 weeks of gestational age were significantly increased risk of 3.11 times experiencing hypoglycemia compared to 35 – <37 weeks of gestational age. This result is in line with previous studies (Singh, 2014; Rasmussen, 2007).

In the first week of life, premature infants are at risk of developing glucose homeostasis. Premature and LBW infants are prone to hypoglycemia because their small reserves and immature metabolic pathways. After birth, the transplacental glucose supply is interrupted, while vital organs require continuous glucose supply to meet nutritional needs. Simultaneously glycogenic hormones (e.g. glucagon, catecholamines, glucocorticoids) increase, partially suppressing insulin secretion. In preterm and LBW infants prone to hypoglycemia because of these adaptive changes and premature metabolic pathways. Premature infants become prone to hypoglycemia due to the limited glycogen and fat stores, lack of ability to generate glucose through the gluconeogenesis pathway, have a high metabolic demand due to relatively higher brain size, and have a poorly developed counter-regulatory mechanisms to prevent hypoglycemia

(Ramzan, 2017; Bromiker, 2017; Sharma, 2017). The American Academy of Pediatrics (AAP) recommends hypoglycemia screening in high-risk populations including premature infants (Adamkin, 2011).

Neonatal patients with hypoglycemia are mostly asymptomatic. Hypoglycemic neonates were asymptomatic due to increased utilization of alternative substrates, such as lactate, in combination with intracerebral storage of glycogen. All neonates with hypoglycemia should receive careful surveillance including glucose monitoring and therapy because of possible adverse long-term effects (Dashti, 2007; Jain, 2008).

This study shows that there were no significant association between maternal age, weight, gravidity, parity, indication of preterm labor, gender, 1-minute and 5-minute Apgar score with hypoglycemia in preterm infants. Neonates from diabetic mothers, including type 1 diabetes, type 2, and gestational diabetes, have a high risk of developing hypoglycemia due to the relative fetal hyperinsulinism resulting in a feedback mechanism for the balance of high glucose levels induced by maternal diabetes (Stanescu, 2014). There was only 1 diabetic mother in this study where her infant had hypoglycemia. The limitation of this study is that infant of diabetic mother was not analyzed as a risk factor for hypoglycemia in preterm infants because there was only 1 case of diabetic mother in this study and breastfeeding in the delivery room could not be anticipated even though the amount are expected to be almost negligible (Dollberg, 2001). Jain, A., Aggarwal, R., Jeevasanker, M., Agarwal, R., Deorari, A., Paul, V., 2008. Hypoglycemia in the newborn. *Indian J Pediatr.* 75:63-7. Lodhi, M., Shah, N., Shabir, G., 2006. Risk factors associated with neonatal hypoglycemia. *Prof Med J.*

5 CONCLUSIONS

Infants with birth weight ≤ 2500 g and 32-35 week of gestation a large were significantly increased risk to had hypoglycemia.

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