

Original article

Hypoglycemia in preterm babies *Incidence and risk factors*

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ABSTRACT Hypoglycemia is one of the most common problems in neonates, especially in preterm babies. Although in the majority of cases the outcome is good, symptomatic or asymptomatic hypoglycemia may give significant complications that may cause death or developmental delay later in life. We conducted a cross sectional study from September 5, 1999 through May 8, 2000 to identify factors associated with hypoglycemia in preterm babies treated at the Division of Perinatology, Cipto Mangunkusumo Hospital, Jakarta. There were 112 babies included in the study, with the mean gestational age of 33.3 (range 22 to 37, SD 4.2) weeks, and mean birth weight of 1801 (range 850 to 2440, SD 420) grams. Twenty-seven of the 112 infants showed hypoglycemia. Univariate analysis disclosed that birth weight, degree of perinatal asphyxia, small for gestational age (SGA), presence of respiratory distress syndrome, mothers with preeclampsia or eclampsia, and mothers who had intravenous infusion of glucose during labor were significantly associated with hypoglycemia in preterm babies. Gestational age, meconium staining, or infant of diabetic mother were not significantly associated with neonatal hypoglycemia. On logistic regression analysis to control confounders we found that only the degree of perinatal asphyxia and small for gestational age were associated with hypoglycemia in those preterm babies. [Paediatr Indones 2001; 41:82-87]

Keywords: hypoglycemia, preterm babies, risk factors

HYPOLYCEMIA IS ONE OF THE MOST COMMON PROBLEMS encountered in neonatal period, especially in preterm babies.^{1,2} While most hypoglycemic babies do not show any clinical manifestations, it may give severe or even fatal outcome in some cases. It is estimated that in Indonesia, not less than 190,000 newborn babies suffered from a certain degree of hypoglycemia annually. There have been many approaches to define abnormal low blood glucose concentration which included clinical definition, statistical definition, neurodevelopmental definition, and neurophysiological definition.³⁻⁵ Most authorities believe that neonatal hypogly-

cemia is defined as blood glucose level is less than 30 mg/dL (less than 1.6 mmol/L).^{6,7}

Studies show that neonatal hypoglycemia (with or without symptoms) can cause problems in neonatal period or in later life. A substantial proportion of neonates with hypoglycemia die as the result of the disease with or without accompanying disease, while some of the survivors show delayed development later in life.⁸⁻¹⁰ Identification of risk factors associated with hypoglycemia is important for early detection and proper management of the problem. There have been few studies on neonatal hypoglycemia published in Indonesian literature.

We conducted this study to determine the incidence of hypoglycemia in preterm babies at the Division of Perinatology, Cipto Mangun-kusumo Hospital, and to identify risk factors associated with neonatal hypoglycemia.

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TABLE 1. CHARACTERISTICS OF STUDY SUBJECTS

Characteristics		n	%
Neonates			
	Sex		
	Male	60	53.6
	Female	52	46.4
Mode of delivery	Spontaneous	61	54.5
	Cesarean section	43	38.4
	Vacuum Extraction	2	1.8
	Forcipal Extraction	6	5.3
Gestational age (weeks)	< 30	9	8.0
	30-33	37	33.0
	34-37	66	59.0
Birth weight (grams)	500- 999	7	6.3
	1000-1499	17	15.2
	1500-1999	36	32.1
	>2000	52	46.4
Nutritional Status	SGA	19	17.0
	AGA	93	83.0
RDS	Yes	29	25.9
	No	83	74.1
Perinatal asphyxia	No	75	67.0
	Yes : mild-moderate	27	24.1
	severe	10	8.9
Meconium Staining	Yes	0	0.0
	No	112	100.0
Mothers			
Gestational diabetic	Yes	0	0.0
	No	112	100.0
Preeclampsia/eclampsia	Yes	29	25.9
	No	83	74.1
IV dextrose infusion during labor	Yes	29	25.9
	No	83	74.1

Methods

This cross sectional study was done in Cipto Mangunkusumo Hospital, Jakarta, from September 5, 1999 until May 8, 2000. All preterm babies born in the study period were included in the study. We excluded babies whose mothers did not have record of their last menstrual cycle, or babies who had received glucose (either in the form of infusion or given orally), breast milk, milk formula, or sweetened water. Babies whose mothers had been given glucose infusion in the rate of >25 grams per hour during labor, or those who were

diagnosed as having sepsis, congenital anomalies, or multiple births were also excluded.

Blood glucose level was first measured before the age of 2 hours. Those who had blood glucose level of less than 30 mg/dl were recorded. Then, we identified all factors presumed to be associated with hypoglycemia (independent variables), i.e., gestational age, birth weight, small for gestational age (SGA), degree of perinatal asphyxia, meconium staining, respiratory distress syndrome (RDS), preeclampsia or eclampsia, mothers with gestational diabetes, and glucose infusion to mother during labor.

TABLE 2. CORRELATION OF EACH INDEPENDENT VARIABLE AND HYPOGLYCEMIA (UNIVARIATE ANALYSIS)

Characteristics	Hypoglycemia		Hypothesis testing	
	Yes (n=27)	No (n= 85)		
Birth weight mean (grams) SD	1627,41 (391,83)	1856,24 (415,23)	p=0.001	
Gestational age (wk)	< 30	2	7	p=0.619
	30-33	17	20	OR=0.68 (0.08; 4.56); p=0,2
	34-37	8	58	OR=1.06 (0.13; 6.66); p=0.00
Perinatal Asphyxia	No	12	63	p=0.004
	Mild-moderate	9	18	OR=2.6 (0.85; 8.09); p=0.05
	Severe	6	4	OR=7.88 (1.62; 40.52); p=0.001
Nutritional status	AGA	17	76	p=0.001
	SGA	10	9	OR=4.97 (1.56; 16.03), p=0.00
RDS	Yes	11	18	OR=2.56 (0.92; 7.14); p=0.043
	No	16	67	
Meconium	Yes	0	0	
Pre-eclampsia/eclampsia	No	16	67	OR=2.56 (0.92; 7.14); p=0.043
	Yes	11	18	
Diabetic mother	Yes	0	0	
IV glucose during labor	Yes	11	18	OR=2.56(0.92-7.14); p=0.043
	No	16	67	

Independent t test was used to determine association between numerical variables in groups with and without hypoglycemia. For nominal data we used χ^2 test to determine the association. In addition, odds ratio (OR) was calculated with its 95% confidence interval. To control confounding among independent variables, multivariate analysis (logistic regression) model was applied; p value of <0.05 was considered significant. All analyses were carried out by using SPSS for Windows v. 10.

Results

There were 112 preterm babies eligible for the study born during the study period. Most of them were male (53.6%), and were delivered spontaneously (54.5%).

Only few cases had perinatal asphyxia (33.0%), SGA (17.0%), and RDS (25.9%). The range for gestational age was 22-37 weeks (mean 33.3 weeks), and for birth weight were 850-2440 grams (mean 1801.1 grams). There were only 29 mothers who suffered from pre-eclampsia or eclampsia, or had received dextrose infusion during labor. Other infant and maternal characteristics are depicted in Table 1.

Twenty-seven out of 112 infants showed blood glucose level of less than 30 mg/dl, giving the incidence of 24.1%. Results of univariate analyses disclosed that birth weight, perinatal asphyxia, nutritional status, RDS, mothers with preeclampsia/eclampsia, and mothers with dextrose infusion during labor were associated with hypoglycemia, while gestational age was not (Table 2).

TABLE 3. RESULTS OF UNIVARIATE ANALYSIS AND LOGISTIC REGRESSION AMONG FACTORS ASSOCIATED WITH HYPOGLYCEMIA IN PRETERM BABY

Variable	Univariate Analysis		Logistic regression	
	Odds ratio	p	Odds ratio	p
Birth weight		0.002		0,9949
Perinatal asphyxia	0.001	0,1764		0,0307
SGA	0,15	0,000	- 0,2763	0,0023
RDS	3,13	0,031		0,7411
Glucose infusion	2,56	0,043		0,7666
Preeclampsia/eclampsia	2,56	0,043		0,9602

Logistic regression analysis with hypoglycemia as dependent variable showed that perinatal asphyxia and SGA were associated with hypoglycemia in preterm neonates, while other variables were not (Table 3).

Discussion

Differences in defining the definition of hypoglycemia, population under consideration, timing to decide hypoglycemia, nutritional status, and how to manage the preterm baby, can cause the different incidence hypoglycemia in many studies.¹¹

In this study we found 27 preterm babies (24.1%) suffered from hypoglycemia. Similar result was reported by Lubchencho et al⁶ who found 20.3% of babies had hypoglycemia. The definition of hypoglycemia used in this study was blood glucose concentration of less than 30 mg/dL (< 1.6 mmol/L).^{6,7,12} With the same definition Retayasa¹³ found the incidence of hypoglycemia in low birth weight (LBW) infants of 20.8%.

Univariate and multivariate analyses done in this study allowed us to determine the real association between the hypothesized risk factors and the development of hypoglycemia in the preterm babies. Multivariate analysis can effectively control potential confounders that may lead to spurious association in univariate analysis.

Nutritional status and perinatal asphyxia has been known among the risk factors of hypoglycemia in preterm baby. In this study, significant association of the two risk factors and hypoglycemia was established both in univariate and in multivariate analysis. The incidence of hypoglycemia was higher in preterm babies with small for gestational age (SGA) than in those babies with appropriate for gestational age (AGA), i.e., 53% (10/19) babies vs. 18% (17/93) in AGA babies. This is similar to that of Lubchencho et al⁶ who found hypoglycemia in 67% preterm neonates with SGA and 15% preterm neonates with AGA, and also to that of Retayasa¹³ (52.4% of SGA neonates and 23.6 % of AGA neonates). Higher incidence of hypoglycemia in SGA babies can be explained by the fact that SGA infants has high brain to body mass ratio, reduced fat stores, failure of counter-regulation (including delayed maturation of gluconeogenesis) and hyperinsulinism.^{4,12,14-17}

The incidence rate of hypoglycemia also associated with the degree of perinatal asphyxia. We found that the more serious the asphyxia, the more likely hypoglycemia would occur. There were only 16% (12/75) of preterm neonates without asphyxia suffered from hypoglycemia, that rose to 33% (9/27) in those with mild-moderate asphyxia and up to 60% (6/10) in those with severe asphyxia. It is generally believed that the

development of hypoglycemia in preterm neonates with asphyxia is associated with catecholeminic release that induces depletion of secondary glycogen and hyperinsulinism.^{12,14,16-18} This can also explain why hypoglycemia is more likely to occur in severe asphyxia, since the depletion of secondary glycogen is higher as the result of hypoxia.

It is a bit surprising that birth weight or gestational age were not significantly associated with the development of hypoglycemia. However infants with low birth weight which were correlation with gestational age (SGA), is an important risk factor for hypoglycemia in neonates.

Table 2 (univariate analysis) shows that babies born to mothers with preeclampsia or eclampsia tended to suffer from hypoglycemia. However on multivariate analysis the association between maternal preeclampsia/eclampsia was not associated with hypoglycemia in preterm babies. This means that spurious association between maternal preeclampsia/eclampsia and infant's hypoglycemia was caused by confounding factor, i.e., mothers with eclampsia-preeclampsia had higher incidence of SGA babies which was truly associated with hypoglycemia.

Similar finding was also observed on the association of maternal intravenous glucose infusion with hypoglycemia in preterm babies. In this study out of 27 neonates with hypoglycemia; 11 neonates (40.7%) were born to mothers that received intravenous infusion of glucose during labor. The rate intravenous infusion of glucose 3-4 grams per hour for maximal of 8 hours. It means that the mother received D5 maximal 640 ml during labor. Table 2 show significant association between maternal intravenous glucose infusion with the incidence of hypoglycemia in preterm babies, but no association was found on logistic regression analysis (Table 3). This must be caused by confounding factors. It is possible that the indication of giving intravenous glucose infusion that was associated with conditions that led to hypoglycemia in the newborn, a phenomenon known as 'confounding by indication'.

This finding differs from previous studies,^{10,19} what found significant association between maternal glucose infusion and hypoglycemia in the neonates. But if we thought more careful, the hypoglycemia can rise if the mother had glucose bolus infusion. Like the studies before, one study⁴ found that intravenous infusion

of >10 grams glucose per hour (D5 200 ml per hour) can make hypoglycemia for the neonates. Another study²⁰ found that hypoglycemia in the neonates can develop baby when <25 grams glucose per hour which had infusion. But the hypoglycemia more apparent if the mothers were infused with > 25 grams glucose per hour (D5 500 ml per hour). Grylackj et al²¹ found that intravenous infusion < 25 grams per hour (D5 500 ml per hour) in 2 hours before delivery cause an effect like NaCl 0,9% infusion. An increase in maternal glucose concentration as a result of exogenous glucose infusion can cause an increase in fetal glucose concentration as well, which in turn causes an increase in fetal insulin levels. Then the high fetal insulin can depress endogenous glucose production and increasing the utilization of glucose. This situation finally can cause hypoglycemia in the neonates.¹⁴

In conclusion we have shown that a quarter of preterm babies has hypoglycemia (blood glucose level of less than 30 mg/dL), and perinatal asphyxia and small for gestational age are independent risk factors for the development of hypoglycemia in such babies. Further studies are recommended to determine the long-term outcome of preterm babies who had hypoglycemia in the first few hours of life.

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