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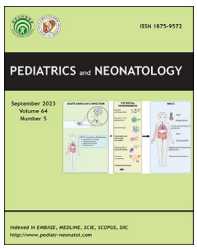

Original Article

Early neonatal hypoglycemia in term and late preterm small for gestational age newborns

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Key Words
hypoglycemia;
neonate;
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Background: Neonatal hypoglycemia is a common metabolic occurrence among small for gestational age (SGA) neonates. This study aims to determine the incidence of early neonatal hypoglycemia and confirms the potential risk factors among term and late preterm SGA neonates in a well-baby newborn nursery of a tertiary medical center in Southern Taiwan.
Methods: We performed a retrospective medical record review of term and late preterm SGA (birth weight <10 percentile) neonates, born between January 1, 2012 and December 31, 2020, in the well-baby newborn nursery, of a tertiary medical center in Southern Taiwan. Blood glucose monitoring was routinely performed at 0.5, 1, 2, and 4 h of life. Antenatal and postnatal risk factors were recorded. Mean blood glucose level, age of occurrence, symptomatic hypoglycemia, and need for intravenous glucose treatment of early hypoglycemia in SGA neonates were documented.
Results: 690 SGA neonates in the nursery met the criteria and were retrospectively enrolled in the study, 358 of whom (51.80%) were male and 332 (48.10%) female. Of 690 enrolled SGA neonates, 134(19.42%) SGA neonates developed hypoglycemia during a well-baby nursery stay. Among these neonates, 97% of early hypoglycemic episodes occur during the first 2 h of life. The lowest blood glucose level was 46.78 ± 11.13 mg/dL, recorded in the first hour of life. Among the hypoglycemic

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134 neonates, 26 (19.40%) neonates had to be transferred from the nursery to the neonatal ward and they required intravenous glucose treatment to achieve euglycemia. 14 (10.40%) neonates had symptomatic hypoglycemia. A multivariate logistic regression analysis revealed that cesarean delivery, small head circumference, small chest circumference, and low 1-min Apgar score were significant risk factors for early hypoglycemia in these neonates.

Conclusion: Periodic routine blood glucose level monitoring within the first 4 h of life in term and late preterm SGA neonates is required, especially those with cesarean delivery and low Apgar score.

1. Introduction

Hypoglycemia is a common metabolic disorder that occurs in the neonatal period. Numerous studies have shown that neonatal hypoglycemia can lead to brain injury and adverse neurodevelopmental outcomes.[1—3] During the perinatal period, the mother provides glucose to the fetus via facilitated diffusion across the placenta. After birth, placental glucose supply is interrupted, making the infants experience transient hypoglycemia with a rapid decline in blood glucose concentrations to a value as low as 20—25 mg/dL in the first 1—2 h.[4,5] Simultaneously, a change in endocrine is noted with a decrease in insulin level and an increase of catecholamine and glucagon for endogenous glucose production.[6,7] Small for gestation age (SGA) neonates are smaller than other newborns of the same gestational age, commonly defined as a birth weight below the 10th percentile for the gestational age. The SGA neonates are known to be at risk of developing hypoglycemia during the first hours of life. Therefore, SGA neonates' blood glucose screening and the prompt management of low blood glucose levels in the first hours of life are important to the level of care. In the last five decades, Cornblath et al.[8] discovered that low blood glucose levels in SGA and preterm infants were associated with seizures. In addition, numerous studies[1,9,10] have shown that neonatal hypoglycemia (glucose levels of less than 2.6 mmol/L) in preterm SGA newborns can lead to brain injury and persistent neurodevelopmental deficits until the age of 5.

Previous studies' definitions of hypoglycemia range from 1.7 to 2.6 mmol/L.[1,11,12] In 2011, the American Academy of Pediatrics (AAP) revised the neonatal hypoglycemia guidelines[5] and recommended routine monitoring of the blood glucose level among at-risk neonates: it suggested reaching a higher glucose level at 40 mg/dL (2.22 mmol/L) from birth to 4 h of age or 45 mg/dL (2.5 mmol/L) from 4 to 24 h of age, repeated oral feeding, or that IV glucose reach the target glucose of 45 mg/dL. Clinically, newborn infants experiencing neonatal hypoglycemia can present with non-specific symptoms or they can even be asymptomatic.[1,13] Therefore, various reports recommend routine blood glucose screening for all term newborns with a bodyweight below the 10th percentile.[14—16] However, limited information is available regarding early neonatal hypoglycemia among term and late preterm SGA neonates in Taiwan.

This study aims to determine the incidence and risk factors of early neonatal hypoglycemia in term and late preterm infants with SGA in a well-baby newborn nursery of a tertiary medical center in Southern Taiwan to design appropriate strategies for prevention. The study also compares the mean glucose value between the hypoglycemia and non-hypoglycemia groups, and it evaluates early neonatal hypoglycemia management.

2. Materials and methods

This is a hospital-based retrospective study. We performed a retrospective medical record review of term and late preterm SGA neonates, born between January 1, 2012 and December 31, 2020, in the well-baby newborn nursery of Chi Mei Medical Center, Tainan, Taiwan. To determine the incidence of early neonatal hypoglycemia which was defined as a blood glucose concentration of less than 40 mg/dL (2.22 mmol/L) according to the AAP recommendation (Committee on Fetus and Newborns in 2011 for monitoring newborns at risk of hypoglycemia).[5] The investigation was conducted following approval from the Institutional Ethics Committee (ethics committee approval number:11,008—013).

Our well-baby nursery admits newborns with a gestational age of more than 35 weeks who are healthy-appearing after birth. In our well-baby nursery, all newborns undergo 4 h of observation and fasting after admission to the well-baby nursery. According to our well-baby newborn nursery policy, it is routine to check glucose levels in the first 4 h in at-risk infants. Therefore, we routinely screen all SGA infants' blood glucose levels in the first 30 min and then at 1 h, 2 h, and 4 h of age to monitor neonatal hypoglycemia within the first 4 h of birth according to the AAP recommendation in the well-baby nursery.

Inclusion criteria were term or late preterm SGA neonates admitted to the well-baby nursery room, whose birth weight was less than the 10th percentile for gestational age according to the Lubchenco Growth Curve.[12,17,18] We also included term infants with a low birth weight ≦ of 2500 gm. Late preterm was defined as gestational age between 34 weeks and 0 days and 36 weeks and 6 days gestational age. Term gestation was defined as gestational age between 37 weeks and 41 weeks and 6 days of gestation.

Exclusion criteria were infants with chromosomal anomalies, major congenital malformations, congenital infection, perinatal asphyxia, endocrine deficits, and those missing newborn blood glucose testing before the age of 4 h. The data extracted included maternal and neonatal demographics, presence of risk factors for neonatal hypoglycemia, and blood glucose values within 4 h of birth.

2.1. Blood glucose testing

The heel pricks capillary blood sample was collected. Blood glucose concentrations were measured using the "Fora MD Control, POCT S10 (TD-4258)" (TaiDoc Technology Corporation, TAIWAN) (ForaCare Inc., UNITED STATES).

The reagent strips method was used to detect and screen capillary blood glucose. The glucometer was set to convert whole blood glucose concentrations to plasma equivalents and it was calibrated monthly. All glucose test strip values of less than 40 mg/dL were confirmed by a plasma glucose concentration analyzer (TBA-c16000, TOSHIBA Medical System Corporation, Japan) from capillary blood also obtained from a heel prick.

Capillary blood glucose was screened at 0.5, 1, 2 and 4 h of age, respectively, before feeding. Management of hypoglycemic newborns was based on the 2011 AAP guidelines.[5] Hypoglycemia was defined as blood glucose values less than 40 mg/dL (birth to 4 h of age) or 45 mg/dL (4—24 h of age). Tremors, jitteriness, irritability, seizures, lethargy, apathy, limpness, poor feeding, vomiting, apnea, and weak or high-pitched cry were considered clinical symptoms and signs of hypoglycemia. Neonates were considered asymptomatic if hypoglycemia was not associated with clinical symptoms and signs. Neonates found to be hypoglycemic were clinically examined and fed according to standard protocol.

If the first capillary blood glucose level was less than 25 mg/dL, feeding was immediately administered, and glucose was measured 30 min later. If the glucose concentration stayed $<$25 mg/dL intravenous glucose, below 40 mg/dL, repeated feeding was administered. Thereafter, neonates with clinical symptoms and those with 2 glucose measurements less than 40 mg/dL were transferred from the nursery to the neonatal ward to receive intravenous glucose. All neonates remained in the nursery room until their 3 glucose measurements were $>$40 mg/dL.

Thereafter, neonates with clinical symptoms and those with 2 glucose measurements $\leqq$ 25 mg/dL or those with more than 3 glucose measurements $\leqq$ 25—40 mg/dL were transferred from the nursery to the neonatal ward to receive intravenous glucose. An episode of hypoglycemia was defined as one or more consecutive blood glucose concentrations $<$40 gm/dL.

Mean blood glucose value, age of occurrence, symptomatic hypoglycemia, and need for intravenous glucose treatment of early hypoglycemia in SGA neonates were documented. The logistic regression model was used to estimate the association between the potential risk factors and neonates with hypoglycemia or non-hypoglycemia groups.

2.2. Statistical analysis

The data are summarized as the mean $\pm$ standard deviation (SD) for normally distributed continuous variables, and median with interquartile range (IQR) when the distribution was skewed. Categorical variables, such as sex, mode of delivery, low birth weight, and preterm were presented by percentage frequency. Then, we compared neonates with hypoglycemia and those without hypoglycemia using Fisher's exact test for categorical variables and Student's test for continuous variables. In addition, the distribution of blood glucose levels in different hours of life was presented by box plots. The logistic regression was used to perform the associated risk factors of hypoglycemia with the odds ratios (ORs) and 95% confidence intervals (CIs). All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Inc., Cary, NC, USA). A p-value $<$0.05 was considered statistically significant.

3. Results

3.1. The clinical characteristics of the SGA infants

During the study period, 772 newborns were identified as SGA (birth weight less than the 10th percentile for gestational age). Our analysis excluded 46 newborns due to missing blood glucose data. Also excluded were 36 newborns who required IV dextrose infusions at birth for reasons other than hypoglycemia. Of the remaining 690 newborns who met our inclusion criteria and were enrolled in the study, 358 (51.88%) were male and 332 (48.11%) female.

Of the 690 SGA neonates screened, 134 (19.42%) had experienced at least one episode of hypoglycemia, 65 of whom (48.50%) were male and 69 (51.49%) female. Table 1 presents the sociodemographic characteristics of SGA neonates with and without episodes of hypoglycemia.

The mean gestational age, mean birth bodyweight, mean head circumference, chest circumference, body height, and Apgar score at 1 min were all significantly lower in the hypoglycemia group than in the non-hypoglycemia group ($p < 0.0001$). As shown in Table 1, hypoglycemia was found mostly in 93 (69.40%) of neonates born with low body weight. In addition, hypoglycemia was found mostly in neonates born at lower gestation age, and those less than 37 weeks numbered 51 (38%) neonates. Hypoglycemia was found mostly in infants born via cesarean delivery, consisting of 91 (67.91%, $p < 0.0001$) and a low Apgar score at 1 min ($p = 0.0010$). No sex ($p = 0.3881$) or Apgar score at 5 min ($p = 0.0720$) differences were noted between hypoglycemia and non-hypoglycemia groups.

3.2. Incidence of hypoglycemia at different hours of life and incidence of hypoglycemia needing IV glucose treatment

The 134 infants screened experienced at least one episode of hypoglycemia; 65 of them (48.50%) were male and 69 (51.49%) female. 109 infants (81.34%) had only one episode of hypoglycemia, 21 infants (15.67%) had two, and 4 infants

Table 1 Clinical characteristics of hypoglycemia and non-hypoglycemia groups.

	Hypoglycemia (n = 134, 19.42%)	Non-hypoglycemia (n = 556, 80.58%)	P-Value
Sex, n (%)			0.3881
Male	65 (48.51)	293 (52.70)	
Female	69 (51.49)	263 (47.30)	
Mode of delivery, n (%)			<0.0001
Vaginal delivery	43 (32.09)	335 (60.25)	
Cesarean section	91 (67.91)	221 (39.75)	
Birth weight (gm), Mean ± SD	2315.80 ± 274.50	2537.90 ± 229.00	<0.0001
Gestational age (weeks), Mean ± SD	37.44 ± 1.41	38.57 ± 1.32	<0.0001
Low birth weight, n (%)	93 (69.40)	204 (36.69)	<0.0001
Late preterm, n (%)	51 (38.06)	64 (11.51)	<0.0001
Head circumference, Mean ± SD	32.01 ± 1.31	32.67 ± 1.08	<0.0001
Chest circumference, Mean ± SD	29.31 ± 1.80	30.47 ± 1.48	<0.0001
Body height, Mean ± SD	46.89 ± 2.35	47.88 ± 2.45	<0.0001
Apgar score (1 min), Mean ± SD	7.81 ± 0.58	7.98 ± 0.18	0.0010
Apgar score (5 min), Mean ± SD	8.96 ± 0.27	9.00 ± 0.09	0.0720
Blood glucose level (mg/dL, Mean ± SD)			
0.5 h, Mean ± SD	50.13 ± 12.34	69.47 ± 13.54	<0.0001
1 h, Mean ± SD	44.97 ± 12.86	67.44 ± 14.16	<0.0001
2 h, Mean ± SD	64.26 ± 18.68	73.96 ± 13.73	<0.0001
4 h, Mean ± SD	79.06 ± 22.75	78.81 ± 14.05	0.9024
Severe hypoglycemia (<25 mg/dL), n (%)	5 (3.73)	—	

a. Categorical variables analysis by Fisher's exact test, continuous variables analysis by Independent sample t test.
b. Values are presented as mean ± standard deviation or number (%).
c. Low birth weight defined as birth weight <2500 gm, late preterm: a preterm infant born between 34 weeks 0 days, to 36 weeks and 6 days of gestation.

(2.24%) had three episodes (Table 1). The overall incidence of hypoglycemia among the SGA neonates in this study was 19.42% (n = 134).

From the evaluation of the time when hypoglycemia was discovered, hypoglycemia incidence was maximum at 1 h of life (52.99%, 71 neonates). This is followed by an incidence of 34.33% (46 neonates) at 0.5 h of life, 9.70% (13 neonates) at 2 h of life, and 2.99% (4 neonates) at 4 h of life (Fig. 1). In these neonates, 97% of early hypoglycemic episodes occur during the first 2 h of life.

Among the 134 hypoglycemic neonates, 26 (19.40%) were to be transferred from the nursery to the neonatal ward as they required intravenous glucose infusion to achieve euglycemia (Fig. 1). Of these 26 neonates, 14 neonates were symptomatic for hypoglycemia, and in the remaining 12 persistent hypoglycemia was due to unsuccessful repeated feeding. We reported no baby with a seizure attack. The most commonly observed symptoms were jitteriness, lethargy, tachypnea, and apnea.

Table 2 shows the sociodemographic characteristics of hypoglycemic neonates with and without IV glucose infusion. Among the hypoglycemia with IV glucose infusion group (9 males, 17 females), a total of 18(69.23%, p = 1.000) were born via cesarean delivery. The hypoglycemic-with-IV-glucose-infusion neonates demonstrated more severe intrauterine growth retardation than those neonates without IV glucose infusion, as reflected by lower birth body weight (2194.50 ± 246.20 gm vs. 2345.10 ± 274.00 gm, p = 0.0115), lower chest circumference (28.38 ± 2.01 vs. 29.53 ± 1.68, p = 0.0032), and lower body height (45.62 ± 2.67 vs. 47.20 ± 2.16, p = 0.0017), respectively. No significant differences were noted in sex, gestational age, the proportion of cesarean delivery, and the proportion of late preterm or Apgar score 1 and 5 min between the hypoglycemic newborns with and without IV glucose infusion groups.

3.3. The blood glucose level

3A. Mean blood glucose level in SGA between hypoglycemia and non-hypoglycemia group:

Among the hypoglycemia neonates, the mean blood glucose level at 0.5 h after birth was 50.13 ± 12.34 mg/dL, at 1 h it was 44.97 ± 12.86 mg/dL, at 2 h 62.26 ± 18.68 mg/dL and at 4 h it was 79.06 ± 22.75 mg/dL (Table 1). The lowest blood glucose level was 44.97 ± 12.86 mg/dL recorded in the first hour of life. Five infants have blood glucose levels less than 25 mg/dL (Table 1) (Fig. 2).

The hypoglycemic neonates had lower mean blood glucose level than the non-hypoglycemic neonates at 0.5 h (50.13 ± 12.34 vs. 69.47 ± 13.54 mg/dL, p < 0.0001), 1 h (44.97 ± 12.86 vs. 67.44 ± 14.16 mg/dL, p < 0.0001) and 2 h (64.26 ± 18.68 vs. 73.96 ± 13.73 mg/dL, p < 0.0001) (Table 1) (Fig. 2) after birth. At 4 h, the mean blood glucose level in hypoglycemic neonates is very close to that of the non-hypoglycemic neonates (79.06 ± 22.75 mg/dL vs 78.81 ± 14.05 mg/dL, p = 0.9024) (Table 1) (Fig. 2).

3B. Mean blood glucose level in SGA hypoglycemia with/without IV glucose infusion group:

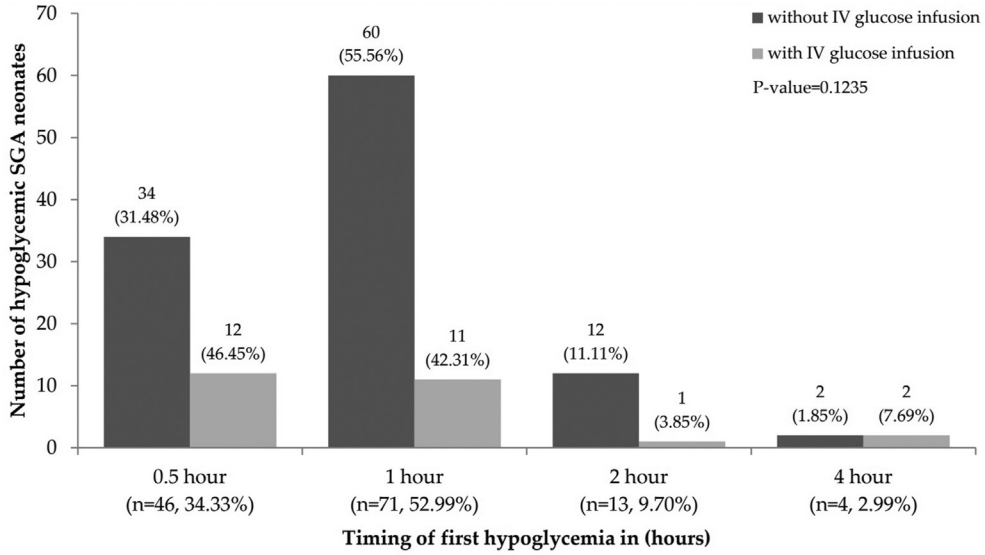

Figure 1 Timing of the first episode of hypoglycemia. Black bar represents hypoglycemic SGA neonates without IV glucose infusion. Grey bar represents hypoglycemic SGA neonates with IV glucose infusion.

Table 2 Clinical characteristics of hypoglycemic SGA neonates with and without Intravenous glucose infusion.

	Hypoglycemic SGA		P-Value
	with IV glucose (n = 26, 19.40%)	without IV glucose (n = 108, 80.60%)	
Sex, n (%)			0.1306
Male	9 (34.62)	56 (51.85)	
Female	17 (65.38)	52 (48.15)	
Mode of delivery, n (%)			1.0000
Vaginal delivery	8 (30.77)	35 (32.41)	
Cesarean section	18 (69.23)	73 (67.59)	
Birth weight (gm), Mean ± SD	2194.50 ± 246.20	2345.10 ± 274.00	0.0115
Gestational age (weeks), Mean ± SD	37.14 ± 1.45	37.51 ± 1.40	0.2345
Low birth weight, n (%)	22 (84.62)	71 (65.74)	0.0952
Late preterm, n (%)	13 (50.00)	38 (35.19)	0.1820
Head circumference (cm), Mean ± SD	31.60 ± 1.16	32.11 ± 1.33	0.0749
Chest circumference (cm), Mean ± SD	28.38 ± 2.01	29.53 ± 1.68	0.0032
Body height (cm), Mean ± SD	45.62 ± 2.67	47.20 ± 2.16	0.0017
Apgar score (1 min), Mean ± SD	7.50 ± 0.91	7.88 ± 0.45	0.0470
Apgar score (5 min), Mean ± SD	8.92 ± 0.27	8.96 ± 0.27	0.5017
Blood glucose level (mg/dL, Mean ± SD)			
0.5 h, Mean ± SD	45.96 ± 17.62	51.13 ± 10.56	0.1619
1 h, Mean ± SD	37.46 ± 16.64	46.78 ± 11.13	0.0109
2 h, Mean ± SD	59.50 ± 23.35	65.41 ± 17.31	0.2343
4 h, Mean ± SD	67.23 ± 29.19	81.97 ± 20.05	0.0211
Severe hypoglycemia (<25 mg/dL), n (%)	4 (15.38)	1 (0.93)	0.0050

a. Categorical variables analysis by fisher's exact test, continuous variables analysis by Independent sample t-test.
b. Values are presented as mean ± standard deviation or number (%).
c. SGA: small for gestational age.
d. Low birth weight defined birth weight <2500 gm, Late preterm: a preterm infant born between 34 weeks 0 days, to 36 weeks and 6 days of gestation.

Among the hypoglycemic SGA neonates with IV glucose infusion group, the mean blood glucose level at 0.5 h was 45.96 ± 17.62 mg/dL, at 1 h it was 37.46 ± 16.64 mg/dL, at 2 h it was 59.50 ± 23.35 mg/dL and at 4 h it was 67.23 ± 29.19 mg/dL (Table 2) (Supplementary Fig. 1). The lowest blood glucose level appeared in the first hour of life (37.46 ± 16.64 mg/dL, p = 0.0109). Four neonates had blood sugar less than 25 mg/dL.

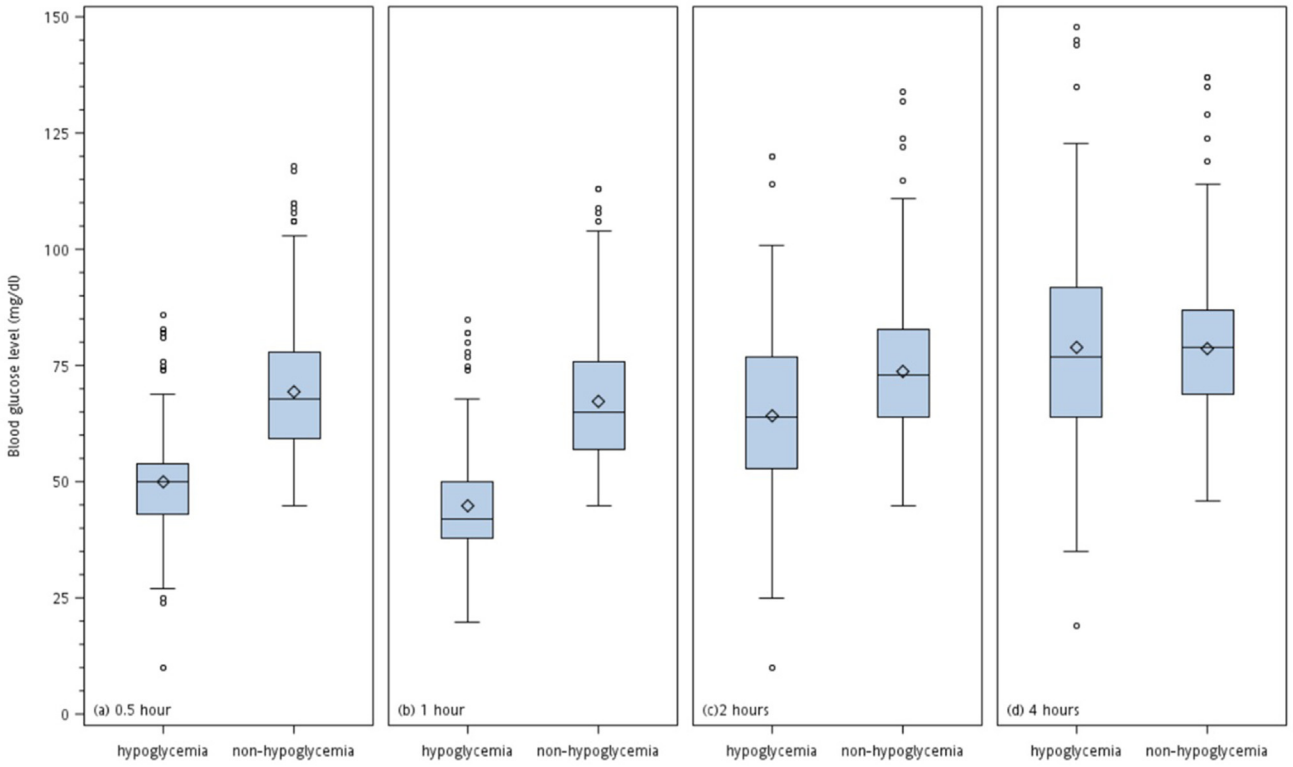

Figure 2 Box plot of blood glucose levels over first 4 h in SGA neonates of hypoglycemia versus non-hypoglycemia group. (a) 0.5 h (b) 1 h (c) 2 h (d) 4 h. Bars express interquartile range.

Most hypoglycemic SGA neonates requiring IV glucose infusion were found within 0.5 h of life (46.45%, 12 neonates), followed by 42.31% (11 neonates) at 1 h of life, 3.85% (1 neonate) at 2 h of life, and 7.69% (2 neonates) at 4 h of life (Fig. 1).

The hypoglycemic SGA neonates in IV glucose infusion group had lower mean blood glucose level than those without IV glucose infusion at 1 h of age (37.46 ± 16.64 vs. 46.78 ± 11.13 mg/dL, p = 0.0109) and 4 h of age (67.23 ± 29.19 vs. 81.97 ± 20.05 mg/dL, p = 0.0211) (Table 2) (Supplementary Fig. 1). There was no significant difference between babies 0.5 h of age (45.96 ± 17.62 vs. 51.13 ± 10.56 mg/dL, p = 0.1619) and 2 h of age (59.50 ± 23.35 vs. 65.41 ± 17.31 mg/dL, p = 0.2343) (Table 2) (Supplementary Fig. 1).

3.4. Risk factors of early hypoglycemia

Table 3 presents the results of potential risk factors of SGA with hypoglycemia. The outcomes of the univariate logistic regression analysis revealed low birth weight newborns (OR 3.91; 95% CI, 2.61–5.87; p < 0.0001), preterm (OR 4.72; 95% CI, 3.06–7.30, p < 0.0001), head circumference (OR 0.61; 95% CI, 0.51–0.72, p < 0.0001), chest circumference (OR 0.60; 95% CI, 0.52–0.68, p < 0.0001), body height (OR 0.86; 95% CI, 0.80–0.93, p = 0.0002), 1-min Apgar score (OR 0.25; 95% CI, 0.14–0.45, p < 0.0001), 5-min Apgar score (OR 0.18; 95% CI, 0.06–0.59, p = 0.0044) and cesarean delivery (OR 3.21; 95% CI, 2.15–4.79, p < 0.0001) were the potential risk factors associated with hypoglycemic SGA neonates, except for the sex item (OR 1.18; 95% CI,

Table 3 Logistic regression of risk factor for neonatal hypoglycemia among SGA neonates.

	hypoglycemia vs. non-hypoglycemia			
	Univariate OR (95%CI)	P-value	Multivariable OR (95%CI)	P-value
sex (ref = male)	1.18 (0.81–1.73)	0.3838	1.03 (0.68–1.57)	0.8805
Cesarean delivery	3.21 (2.15–4.79)[a]	<0.0001	2.11 (1.32–3.37)[a]	0.0018
Low birth weight	3.91 (2.61–5.87)[a]	<0.0001	1.36 (0.76–2.44)	0.3052
Late preterm	4.72 (3.06–7.30)[a]	<0.0001	1.43 (0.81–2.53)	0.2143
Head circumference	0.61 (0.51–0.72)[a]	<0.0001	0.76 (0.62–0.94)[a]	0.0119
Chest circumference	0.60 (0.52–0.68)[a]	<0.0001	0.81 (0.66–0.99)[a]	0.0380
Body height	0.86 (0.80–0.93)[a]	0.0002	1.03 (0.93–1.14)	0.5751
Apgar score (1 min)	0.25 (0.14–0.45)[a]	<0.0001	0.44 (0.23–0.84)[a]	0.0130
Apgar score (5 min)	0.18 (0.06–0.59)[a]	0.0044	0.73 (0.20–2.67)	0.6292

[a] p < 0.05, OR, odds ratio; CI, confidence interval.

0.81—1.73, p = 0.3838). According to the multivariable logistic regression in Table 3, babies by cesarean delivery presented 2.11-fold risk of (95% CI, 1.32—3.37; p = 0.0018) compared with babies by vaginal delivery. However, 1-min Apgar score (OR 0.44; 95% CI, 0.23—0.84; p = 0.0130), head circumference (OR 0.76; 95% CI, 0.62—0.94; p = 0.0119), and chest circumference (OR 0.81; 95% CI, 0.66—0.99; p = 0.0380) remained significant risk factors as those variables increase by one unit for early hypoglycemia in SGA neonates.

4. Discussion

Neonatal hypoglycemia is one of the most frequently encountered metabolic problems in neonatal medicine. The overall incidence is estimated at 1.3 to 4.4 cases per 1000 full-term births.[19,20] However, the incidence might be much higher among high-risk populations. SGA neonates are more prone to developing hypoglycemia because of less hepatic glycogen and fat stores, inefficient production of glucose through the gluconeogenesis pathway, higher energy requirement, increased insulin sensitivity, and lack of counter-regulatory hormone response.[21—25] The reported incidence of SGA neonates with hypoglycemia ranges from 15 to 36%.[12,26,27]

The incidence of hypoglycemia in Term SGA varies based on the rate reported by existing studies. Holtrop et al.[15] reported that the frequency of hypoglycemia in Term SGA neonates was 14.7%. However, Bhat et al.[26] stated that the incidence of hypoglycemia was 23.92% in full-term SGA babies. Mejri et al.[16] reported that the incidence of hypoglycemia in full-term SGA was 26% of all SGA neonates screened. However, Lubchenco et al.[12] stated that the incidence of hypoglycemia in full-term SGA neonates was 25%. Variation in incidence among reports could be associated with different hypoglycemia screening methods, screening frequencies, feeding practices, degrees of neonatal sickness, or different study populations. In the present study, the incidence of early hypoglycemia among term and late preterm SGA neonates was 19.42%, which was within incidence levels previously reported by other studies.[12,15,16,26]

From the outcomes of blood glucose levels shortly measured after birth (0.5, 1, 2, and 4 h of life) in SGA neonates, their mean lowest blood glucose level appears in the first hour after birth. This was consistent with results presented by Srinivasan et al. on blood glucose levels in term neonates, by Bhat MA[26] on blood glucose levels in SGA neonates, and by Yoon JY[25] on blood glucose levels in preterm infants. The mean lowest blood glucose level was 44.97 ± 12.86 mg/dL in hypoglycemic SGA neonates and 67.44 ± 14.16 mg/dL in non-hypoglycemic SGA neonates (p < 0.0001) (Table 1). Our data revealed that blood glucose values declined as early as 0.5 h after birth, reaching their lowest level at 1 h of age. The blood glucose values increased with hours of life. However, at 4 h the mean blood glucose level in hypoglycemia SGA is close to that of non-hypoglycemia SGA (79.06 ± 22.75 mg/dL vs. 78.81 ± 14.05 mg/dL, p = 0.9024) (Table 1, Fig. 2).

We found most hypoglycemic SGA neonates were noted in the 1st hour of life. This finding was consistent with previous reports.[4,25] We observed that (52.99%, 71 neonates) half of hypoglycemia was detected at 1 h of life, 34.33% (46 neonates) was detected at 0.5 h of life, 9.70% (13 neonates) at 2 h of life and 2.99% (4 neonates) at 4 h of life. The majority (97%) of hypoglycemic episodes occur in the first 2 h of life, and five infants were identified whose blood glucose level was less than 25 mg/dL. From these findings, it is critical to check blood glucose levels immediately after birth and to start administering feeding as early as possible (0.5 h of life). In addition, periodic routine blood glucose monitoring is crucial for term and late preterm SGA neonates within the first 4 h of life, especially during 4 h-fasting observation after delivery at the newborn nursery.

134 infants screened had at least one episode of hypoglycemia. 109 infants (81.34%) with hypoglycemia had only one episode; 21 infants (15.67%) had two; and 4 infants (2.24%) had three episodes (Table 1). Our result showed that oral feeding corrected hypoglycemia among most hypoglycemic SGA neonates (108/134). Among the 134 hypoglycemic SGA neonates, 26 (19.40%) neonates were transferred from the newborn nursery to the neonatal ward as they required intravenous glucose infusion to achieve euglycemia (Fig. 1). Of these, 14 neonates presented with clinical symptoms of hypoglycemia. In the remaining 12 neonates, repeated feeding regimen was unsuccessful.

A total of 19.40% (26/134) of the hypoglycemic SGA neonates received IV glucose to correct hypoglycemia. They were usually associated with more severe growth-retardation (lower birth weight, lower chest circumference, and lower body height) which resulted in more severe hypoglycemia than those in the without IV glucose infusion group.[26,28]

In 5 neonates with severe hypoglycemia (blood glucose ≦ 25 mg/dL), 4 neonates required an IV glucose infusion to correct hypoglycemia. Previously published literature[29] reported that severe, prolonged hypoglycemia caused irreversible brain damage and death in an untreated case. Therefore, it is important to distinguish such extremely low blood glucose among healthy babies in the nursery room. In addition, serial blood glucose levels should be routinely measured for early detection of hypoglycemia in SGA neonates. Screening for early hypoglycemia in SGA neonates will aid in its early detection, early treatment, and prevention of its long-term sequelae.

Symptomatic hypoglycemia had been associated with adverse neurologic outcomes.[30] In this study, we observed that 10.40% (14/134) of hypoglycemic SGA neonates were symptomatic. The incidence was lower than those of the previous reports,[1,19,26,31] which could be due to periodic early monitoring and aggressive treatment in these hypoglycemic neonates. In our study, no baby suffered seizure, the most common symptoms/signs observed being jitteriness, lethargy, tachypnea and apnea.

From previous reports, preterm birth and low birth weight were found to be strong risk factors for neonatal hypoglycemia.[7,32,33] Univariate logistic regression analysis revealed low birth weight, late preterm, head circumference, chest circumference, body height, cesarean delivery and 1-min Apgar score were associated with hypoglycemia. However, according to multivariable logistic regression analysis, only cesarean delivery, head circumference, chest

circumference, and 1-min Apgar score remained significant risk factors for early hypoglycemia in SGA neonates (Table 3).

In our study, small head circumference and small chest circumference were associated with early hypoglycemia in SGA neonates. These findings indicate the more severe the growth retardation, the greater is the susceptibility of these neonates to developing hypoglycemia. Similar results were reported by Karan et al. and Mishra et al.[26,34] In addition, Pal DK et al.[34] showed that small head circumference was associated with moderate hypoglycemia (less than 2.0 mmol/L) among term infants with low birth weight. SGA neonates with cesarean delivery were also more prone to developing hypoglycemia compared to those with vaginal delivery (Table 1). We revealed that cesarean delivery presented a 2.11-fold risk of (95% CI, 1.32—3.37; $p = 0.0018$) compared with vaginal delivery. Our results indicate that vaginal delivery may protect SGA neonates against hypoglycemia. This finding suggested that stress at birth induced the release of endogenous catecholamines and steroids during vaginal delivery.[14,15,35,36] These endogenous catecholamines and steroids potentially initiated gluconeogenesis in infants during labor. Low 1-min Apgar score of SGA neonate was associated with increased hypoglycemic incidence and the need for IV glucose infusion (Tables 1 and 2). These were consistent with previous findings that neonates with perinatal asphyxia were prone to hypoglycemia.[25,37]

There were some limitations in our study. We recorded the blood glucose level at 0.5, 1, 2, and 4 h of life. Therefore, the results from this study can only represent incidence and risk factors for early hypoglycemia in SGA newborns within 4 h of birth. SGA infants may develop hypoglycemia after 4 h of age. According to the AAP guideline, late preterm infants and infants who are small for gestational age should be fed every 2—3 h and screened before each feeding for at least the first 24 h. To identify the true incidence of hypoglycemia in the well-baby nursery in SGA infants, the time of blood glucose check should be increased. Further studies are needed to increase the frequency and timing of routine blood glucose testing until 48 h or 72 h of age to determine the incidence and risk factors of hypoglycemia among term and late preterm SGA admitted to the well-baby newborn nursery.

5. Conclusion

Early hypoglycemia is a common occurrence among term and late preterm SGA neonates. This study demonstrated that the incidence of early hypoglycemia among SGA neonates was 19.42% using universal screening in a well-baby nursery room. Periodic routine blood glucose level monitoring within the first 4 h of life in term and late preterm SGA neonates is required, especially for those with cesarean delivery and low Apgar score. Thus, screening for early hypoglycemia in SGA neonates will improve early detection, provide early treatment, and prevent long-term sequelae.

Declaration of competing interest

The author declares that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2022.09.021.