ORIGINAL ARTICLE

Hypoglycemia Screening Before Discharge in Asymptomatic Newborns Identified as Being at Risk

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Objective: To assess the incidence and associated factors of hypoglycemia in asymptomatic at-risk infants at 48 to 60 hours of age, and to evaluate the reliability of point-of-care (POC) glucometers compared with standard plasma glucose methods.

Materials and Methods: A prospective cohort study was conducted between July 2023 and May 2024 at a tertiary care hospital. Asymptomatic neonates aged 48 to 60 hours, with gestational ages between 34 and 41 weeks, identified as being at risk for hypoglycemia were enrolled. Blood glucose levels were measured using both a glucometer and a standard plasma glucose testing.

Results: Among the 139 newborns included in the present study, the incidence of hypoglycemia was 10.8% when assessed using POC glucometers and 48.9% when measured with standard laboratory testing. Infants with discharged weights of 2,500 g or less were more than twice as likely to experience hypoglycemia (AOR 2.46, 95% CI 1.09 to 5.57). The mean glucose level obtained from POC glucometer measurements was 14.8 mg/dL higher than that obtained from laboratory measurement (95% CI 13.08 to 16.52).

Conclusion: There is a high incidence of hypoglycemia among asymptomatic neonates identified as being at risk before discharge. Asymptomatic neonates with risk factors for hypoglycemia and a discharge weight of 2,500 g or less should be screened for hypoglycemia at 48 to 60 hours of age.

Keywords: Neonatal hypoglycemia; Screening; Risk factors; Discharge

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Neonatal hypoglycemia is one of the most common metabolic disturbances and can adversely affect neurological development. It results from an imbalance between nutrient intake and glucose utilization, together with abnormalities in hormones involved in glucose homeostasis(1). Currently, the definition of neonatal hypoglycemia remains a subject of debate, and various screening and treatment guidelines have been proposed for newborns(2-4). In 2011, the American Academy of Pediatrics (AAP) issued guidelines for managing glucose levels in asymptomatic at-risk infants, including late-preterm infants, large for gestational age (LGA), small for gestational age (SGA), and infants of diabetic mothers (IDM). For IDM and LGA infants, screening is recommended before feeds during the first 12 hours after birth. For late-preterm and SGA infants, screening is recommended for 24 hours, with a target glucose level of 45 mg/dL or greater. Screening can be discontinued if pre-feed glucose levels were normal for three consecutive measurements and the infant remains asymptomatic(5). The Canadian Pediatric Society (CPS) similarly recommends screening for hypoglycemia in at-risk infants, including those with maternal diabetes, birth asphyxia, prematurity, SGA, and LGA. Initial screening is suggested at two hours of age, with continued monitoring every three to six hours if glucose levels were 47 mg/dL or greater for two consecutive measurements(6).

Although most cases of hypoglycemia occur within the first 24 hours, some infants experience their first hypoglycemic episode later. Harris et al.(7) reported that one-third of at-risk infants developed hypoglycemia after three normal initial blood tests, with 6% experiencing their first episode after 24 hours. Similarly, Karbalivand et al.(8) reported a 10% incidence of hypoglycemia in asymptomatic infants aged 24 to 48 hours. Current guidelines focus on glucose screening and management within the first 24 hours after birth, with no specific recommendations for screening at 24 to 48 hours or for pre-discharge

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assessment[9]. In the present study, the authors aimed to examine the incidence and associated factors of hypoglycemia in asymptomatic at-risk infants at 48 to 60 hours of age, and to assess the reliability of point-of-care (POC) glucometers compared with standard plasma glucose methods.

Materials and Methods

The present study was a prospective cohort study conducted between July 2023 and May 2024 at Panyananthaphikkhu Chonprathan Medical Center (PCMC), a tertiary care hospital and neonatal center of excellence in an urban area. Ethical approval was obtained from the Human Research Ethics Committee of PCMC, Srinakharinwirot University (Certificate of Approval No. 13.2/2566), on July 6, 2023. The present study adhered to the principles of the Declaration of Helsinki, and written informed consent was obtained from parents of all participating neonates before enrollment.

Patients

Eligible participants were asymptomatic neonates aged 48 to 60 hours, with a gestational age between 34 and 41 weeks. Inclusion criteria required that neonates roomed in with their mothers, were able to feed orally, had not received intravenous fluids, and were identified as being at risk for hypoglycemia. Risk factors for neonatal hypoglycemia included LGA, SGA, IDM type 1, type 2, or gestational diabetes, and late-preterm infants of gestational age 34 weeks 0 days to 36 weeks 6 days. LGA and SGA were defined according to the Fenton growth chart as birth weight above the 90th percentile and below the 10th percentile, respectively. Infants with sepsis, polycythemia, persistent hypoglycemia, defined by the Pediatric Endocrine Society (PES) as severe hypoglycemia requiring intravenous dextrose at a glucose infusion rate greater than 10 mg/kg/minute, or inability to consistently maintain pre-prandial plasma glucose greater than 50 mg/dL up to 48 hours of age and greater than 60 mg/dL thereafter[10], or congenital syndromes were excluded. Demographic, obstetric, and neonatal data were collected from medical records. Blood glucose levels were monitored using a POC glucometer within the first 24 hours of life. If hypoglycemia was detected, immediate treatment was administered according to institutional protocol. For asymptomatic neonates with risk factors for hypoglycemia, mothers were encouraged to establish skin-to-skin contact and initiate breastfeeding as soon as possible after birth. Neonates were fed on demand, with intervals not exceeding three hours. Supplemental formula was provided if maternal breast milk was insufficient. All at-risk, asymptomatic neonates received their first feed within the first hour after birth. Blood glucose levels were measured using a glucometer before feeding at 1, 3, 6, 12, and 24 hours of age. Pre-discharge evaluations included the type of feeding, discharge weight, and neonatal readiness for hospital discharge. At 48 to 60 hours of age, blood samples for POC glucometer testing and standard plasma glucose analysis were collected before feeding, along with routine thyroid-stimulating hormone (TSH) screening. POC glucometer testing was performed immediately at the bedside, while plasma glucose samples were sent to the laboratory within 15 minutes of collection.

Glucose measurement and quality control

At the authors' institute, both plasma glucose and bedside glucometer blood glucose levels were measured from venous blood samples. Plasma glucose samples were collected in fluoride-containing tubes and transported to the central clinical biochemistry laboratory within 15 minutes of collection. Analysis was performed using the BioMajesty JCA-BM6010/C (Nihon Kohden, Japan), which employed the enzymatic ultraviolet (UV) hexokinase method. Bedside POC glucose testing was performed by nurses trained in venipuncture and standardized device operation, using the Accu-Chek Instant glucometer (Roche Diabetes Care, Germany), which utilizes the glucose oxidase-peroxidase method. The Accu-Chek Instant glucometer underwent daily internal quality control with manufacturer-provided solutions before patient testing. The BioMajesty JCA-BM6010/C was maintained and operated according to the manufacturer's recommendations, including routine calibration and internal and external quality control at prescribed intervals.

Target plasma glucose concentration at 48 to 60 hours

In accordance with the PES recommendations, the authors used a target plasma glucose concentration of greater than 60 mg/dL, a level above the threshold for neurogenic symptoms and close to the target for older infants and children, to ensure safe discharge[10].

Sample size calculation

The sample size calculation for the present study, estimating a proportion, was based on a previously published study reporting a neonatal hypoglycemia incidence of 0.1[8]. To achieve 80% power at a 0.05 significance level and 5% margin of error, a minimum of 139 neonates was required.

Statistical analysis

Statistical analyses were conducted using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). The chi-square test was used to compare categorical variables, while the independent samples t-test was used to compare continuous data between two independent groups. The authors used Bland-Altman plot to evaluate agreement between POC glucometers and the standard plasma glucose method. Multivariate analysis was performed using a binary logistic regression model, and results were presented as adjusted odds ratios. Statistical significance was defined as a two-sided p-value less than 0.05.

Results

During the study period, 147 neonates were identified as eligible based on predefined risk criteria for neonatal hypoglycemia. However, eight neonates were excluded because of incomplete data. One hundred thirty-nine newborns at risk of hypoglycemia were included. Of these, 76 (54.7%) were male. The mean gestational age was 37.75±1.24 weeks, and the mean birth weight was 3,000.74±555.29 g. Most newborns (87.8%) had one risk factor for hypoglycemia, while 12.2% had two. The most common risk factor was maternal diabetes at 55.4%, followed by SGA at 26.5%, and late preterm birth at 17.6%. Among mothers with diabetes, gestational diabetes was the most common type. The mean blood glucose level measured at one hour of life using a glucometer was 63.64±18.99 mg/dL. Notably, 7.2% of newborns had a glucometer blood glucose level of less than 40 mg/dL at one hour, and 2.2% of these exhibited symptomatic hypoglycemia.

In the present study cohort of at-risk newborns, the authors found notable differences in hypoglycemia incidence depending on the method of glucose measurement. When assessed by glucometer, the incidence of hypoglycemia, of 60 mg/dL or less, was 10.8%. However, when assessed by the standard laboratory method, the incidence was significantly higher at 48.9%.

To further analyze the present study data, the authors divided the newborns into two groups based on standard plasma glucose before discharge of 60 mg/dL or less versus more than 60 mg/dL, and found no differences in baseline characteristics, including gestational age, birth weight, and risk factors (Table 1).

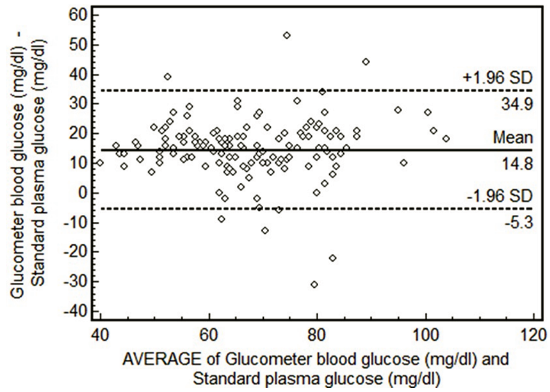

Figure 1. Agreement between glucometer blood glucose and standard plasma glucose levels.

When comparing clinical and laboratory data before discharge, discharge weight was significantly lower in the 60 mg/dL or less group, and a higher proportion of infants had a discharge weight of 2,500 g or less (Table 2). Feeding methods differed significantly (p=0.045) and the lower glucose group was more likely to receive mixed feeding, while breastfeeding rates were similar. Hematocrit, total bilirubin, and the proportion of infants with 7% or more weight loss compared with birth weight did not differ significantly between groups.

Logistic regression revealed a significant association between discharge weight of 2,500 g or less and hypoglycemia (Table 2). The adjusted odds ratio was 2.46 (95% CI 1.09 to 5.57). The authors also investigated the impact of feeding methods on hypoglycemia risk, with breastfeeding as the reference group. For infants fed formula, the adjusted odds ratio was 0.17 (95% CI 0.03 to 1.00). Infants receiving both breastfeeding and formula had an adjusted odds ratio of 1.27 (95% CI 0.52 to 3.12), which was not statistically significant.

The agreement between POC glucometers and standard plasma glucose levels in neonatal hypoglycemia screening was assessed using a Bland-Altman plot, as shown in Figure 1. Blood glucose levels measured by glucometer were higher than those obtained by the standard method in 92.8% of the infants. The mean difference between these measurements was 14.8 mg/dL (95% CI 13.08 to 16.52). To further investigate this discrepancy, the authors conducted a subgroup analysis according to standard plasma glucose levels (Table 3). For newborns with standard plasma glucose levels of

Table 1. Characteristics of the enrolled newborns aged 48 to 60 hours categorized by standard plasma glucose levels before discharge

Factors	Standard plasma glucose before discharge ≤60 mg/dL (n=68)	Standard plasma glucose before discharge >60 mg/dL (n=71)	p-value
Male sex; n (%)	37 (54.4)	39 (54.9)	0.951
Gestational age (weeks); mean±SD	37.57±1.27	37.92±1.19	0.104
Birthweight (g); mean±SD	2,918.94±510.35	3,079.08±588.1	0.089
Mode of delivery; n (%)			0.760
Spontaneous delivery	27 (39.7)	30 (42.3)	
Cesarean section	41 (60.3)	41 (57.7)	
Risk factors; n (%)			
Maternal DM	34 (50.0)	43 (60.6)	0.210
Small for gestational age	18 (26.5)	19 (26.8)	0.969
Late preterm	12 (17.6)	9 (12.7)	0.413
Large for gestational age	9 (13.2)	10 (14.1)	0.884
Antenatal steroids	1 (1.5)	1 (1.4)	0.975
Total number of risk factors; n (%)			0.230
1 risk factor	62 (91.2)	60 (84.5)	
2 risk factors	6 (8.8)	11 (15.5)	
Maternal DM; n (%)			0.809
GDM	32 (47.1)	41 (57.7)	
Overt DM	2 (2.9)	2 (2.8)	
Treatment of maternal DM; n (%)			0.930
Diet control	25 (36.8)	32 (45.1)	
Insulin	9 (13.2)	11 (15.5)	
Maternal age (years); mean±SD	30.69±5.11	31.31±6.08	0.518
Maternal BMI (kg/m^2); mean±SD	24.95±6.42	26.26±11.43	0.421
Weight gain during pregnancy (kg); mean±SD	12.31±7.35	12.68±13.41	0.843
Hypoglycemic symptoms at 1 hour; n (%)	1 (1.5)	2 (2.8)	0.594
1st pre-feed BG (glucometer BG at 1 hour) (mg/dL); mean±SD	62.51±17.11	64.72±20.69	0.496
1st pre-feed BG <40 mg/dL (glucometer BG at 1 hour <40 mg/dL); n (%)	4 (5.9)	6 (8.5)	0.558
2nd pre-feed BG (mg/dL); mean±SD	77.28±15.58	76.97±14.47	0.904
3rd pre-feed BG (mg/dL); mean±SD	80.09±13.37	81.36±12.6	0.567
4th pre-feed BG (mg/dL); mean±SD	80.24±15.29	79.6±13.49	0.797
5th pre-feed BG (mg/dL); mean±SD	79.29±14.57	79.17±9.50	0.964
Postnatal age at pre-discharge glucose (hours)	49.49±4.94	50.04±4.12	0.470
Standard plasma glucose before discharge (mg/dL); mean±SD (min, max)	48.86±7.39 (33, 60)	71.29±8.43 (61, 94)	<0.001*
Type of feeding before discharge; n (%)			0.045*
Breastfeeding	12 (17.6)	13 (18.3)	
Infant formula	2 (2.9)	10 (14.1)	
Mixed feeding	54 (79.4)	45 (63.4)	
Discharge weight (g); mean±SD	2745.15±478.37	2927.49±581.07	0.046*
≤2,500 g; n (%)	24 (35.3)	14 (19.7)	0.039*
>2,500 g; n (%)	44 (64.7)	57 (80.3)	
Hematocrit before discharge (%); mean±SD	51.06±5.46	50.35±5.58	0.452
Total bilirubin before discharge (mg/dL); mean±SD	9.98±2.15	10.03±2.14	0.907
Weight loss compared with birth weight (%); mean±SD	5.9±2.34	5.0±3.10	0.056
<7%; n (%)	44 (64.7)	52 (73.2)	0.277
≥7%; n (%)	24 (35.3)	19 (26.8)	

DM=diabetes mellitus; GDM=gestational diabetes mellitus; BMI=body mass index; BG=blood glucose; SD=standard deviation
* Statistically significant at p<0.05

Table 2. Clinical predictive factors of low standard plasma glucose at hospital discharge of newborns

Factors	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Type of feeding before discharge		
Breastfeeding	Reference	Reference
Infant formula	0.22 (0.04 to 1.20)	0.17 (0.03 to 1.00)
Breastfeeding and infant formula	1.30 (0.54 to 3.13)	1.27 (0.52 to 3.12)
Discharge weight		
>2,500 g	Reference	Reference
≤2,500 g	2.22 (1.03 to 4.78)	2.46 (1.09 to 5.57)

CI=confidence interval

Table 3. Difference between glucometer blood glucose levels and standard plasma glucose levels

	n	Mean difference (95% CI)
Total	139	14.80 (13.08 to 16.52)
Plasma glucose ≤60 mg/dL	68	17.56 (15.74 to 19.38)
Plasma glucose >60 mg/dL	71	12.15 (9.37 to 14.94)

CI=confidence interval

60 mg/dL or less, the mean difference between glucometer and standard plasma glucose was 17.56 mg/dL (95% CI 15.74 to 19.38), whereas for those with standard plasma glucose levels of more than 60 mg/dL, the mean difference was 12.15 mg/dL (95% CI 9.37 to 14.94).

Treatment was guided by bedside POC glucose levels. Fifteen infants (10.8%) had POC glucose levels of 60 mg/dL or less, all within the range of 40 to 60 mg/dL. None of these infants exhibited clinical signs of hypoglycemia. The lowest recorded glucose value was 45 mg/dL. All infants were managed according to protocol with enteral feeding of 30 mL of milk. Follow-up monitoring showed glucose levels greater than 60 mg/dL both at one-hour post-feeding and before the next feeding. These infants required an additional hospital stay of about four to six hours for observation.

Discussion

Currently, there is no consensus on hypoglycemia thresholds or screening recommendations before discharge. The PES recommends that high-risk neonates older than 48 hours maintain glucose levels greater than 60 mg/dL[10] while the CPS suggests targets of greater than 47 mg/dL for infants younger than 72 hours after birth and greater than 60 mg/dL for those older than 72 hours[6]. Furthermore, the CPS proposes that screening once or twice on day 2 is reasonable when more than one glucose value smaller than 47 mg/dL has occurred in the first 24 hours. This lack of consensus poses challenges for clinicians in determining the optimal approach to managing at-risk newborns. The present study aimed to address this gap by providing evidence-based data to inform future guidelines. In this study, the incidence of hypoglycemia, defined as a plasma glucose level of 60 mg/dL or less, was 48.9% when measured by the standard laboratory method and 10.8% when measured by POC glucometer. These results are consistent with previous studies that assessed glucose levels before discharge in preterm infants that reported a hypoglycemia prevalence of 18% to 26.5%[11,12]. Other studies have reported significant incidences of hypoglycemia in newborns. Karbalivand et al.[8] screened 150 asymptomatic infants aged 24 to 48 hours, including both high-risk and low-risk groups. They reported an overall hypoglycemia incidence of 10%, with four cases in low-risk infants and 11 in high-risk groups. Furthermore, these findings align with the Glucose in Well Babies (GLOW) study, which examined glucose concentrations in 67 healthy term newborns during their first five days of life. The GLOW study reported that 46% of normal infants aged 48 to 72 hours had plasma glucose of 60 mg/dL or less at 48 hours. The mean and 10th percentile glucose levels were 60 mg/dL and 47 mg/dL, respectively[13]. Moreover, the incidence of low glucose concentrations did not significantly differ between healthy term neonates and those identified as at risk, suggesting that transient low plasma glucose levels between 48 and 60 hours may represent a normal metabolic transition in term infants.

Consequently, term at-risk neonates with glucose levels of 47 to 60 mg/dL and discharge weight greater than 2,500 g may not require immediate intervention, particularly in the absence of symptoms. The present study also identified risk factors associated with low blood sugar in at-risk newborns before discharge. Logistic regression revealed a significant association between discharge weight of 2,500 g or less and hypoglycemia risk. Infants with a discharge weight of 2,500 g or less were more than twice as likely to experience hypoglycemia compared with those weighing more than 2,500 g. In contrast to previous studies identifying maternal diabetes, excessive postnatal weight loss, and exclusive breastfeeding as significant risk factors, the findings did not demonstrate significant associations between these factors, including multiple risk factors, SGA, preterm birth, type of feeding, or weight loss greater than

7%, and hypoglycemia in the present study cohort. These discrepancies may be explained by differences in study populations, timing of glucose assessment, or use of different cutoff values for hypoglycemia. The significance of discharge weight of 2,500 g or less may be attributed to reduced glycogen stores, similar to those observed in SGA and low-birth-weight infants[12].

A significant discrepancy between capillary blood glucose measured by glucometer and standard laboratory plasma glucose levels was observed in the present study. Based on glucometer readings, hypoglycemia at 60 mg/dL or less, was detected in only 10.8% of cases, whereas laboratory analysis indicated a much higher incidence of 48.9%. A previous study[14] also found that glucometers tend to overestimate glucose levels when plasma glucose is low. This suggests that glucometer readings may underestimate the true prevalence of hypoglycemia. Clinicians should interpret glucometer results with caution and confirm abnormal readings with laboratory plasma glucose testing. Although glucometers are not reliable for diagnosing hypoglycemia, they may be useful for initial screening and management, consistent with previous studies[15,16]. This finding aligns with international guidelines recommending glucometers for initial screening to avoid delays in diagnosis and treatment[2]. However, because glucometers consistently overestimate blood glucose, a low reading is likely to reflect true hypoglycemia. Conversely, a normal glucometer reading does not exclude low plasma glucose. Therefore, confirmatory laboratory testing is recommended for accurate diagnosis. The Bland-Altman analysis showed narrower limits of agreement in neonates with glucose greater than 60 mg/dL, suggesting greater reliability of glucometer readings at higher glucose levels. This implies that POC testing may provide more accurate estimates of plasma glucose when levels are above the hypoglycemic threshold, while discrepancies are greater at lower levels.

The strengths of the present study include its prospective design and focused on asymptomatic at-risk neonates aged 48 to 60 hours. Moreover, the authors used both POC glucose testing and laboratory blood glucose analysis. POC testing provides immediate results, allowing rapid clinical decision-making, while laboratory analysis remains the gold standard for confirmation. The limitation of the present study is that the authors did not follow infants after discharge and were therefore unable to evaluate long-term outcomes, which is crucial for understanding the impact of neonatal hypoglycemia.

In conclusion, the present study highlights the high incidence of hypoglycemia among at-risk neonates aged 48 to 60 hours, particularly in those with discharge weight of 2,500 g or less. While the clinical significance of plasma glucose levels between 47 and 60 mg/dL remains uncertain, the findings suggest that not all cases require immediate intervention, particularly in the absence of symptoms. Glucometer readings may underestimate the true prevalence of hypoglycemia. Therefore, confirmatory plasma glucose testing is essential for accurate diagnosis and management. Further studies with long-term follow-up are needed to clarify the clinical implications of hypoglycemia in this population.

Conclusion

There is a high incidence of hypoglycemia among asymptomatic neonates identified as at risk before discharge, and newborns with a discharge weight of 2,500 g or less are at significantly increased risk of developing hypoglycemia, even in the absence of clinical symptoms.

What is already known about this topic?

- Neonatal hypoglycemia is one of the most common metabolic disorders in newborns, particularly among at-risk infants.
- Current guidelines primarily focus on screening and management during the first 24 hours of life.

What does this study add?

- Hypoglycemia is highly prevalent in asymptomatic at-risk neonates aged 48 to 60 hours.
- Discharge weight of 2,500 g or less is a significant risk factor for hypoglycemia.

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Authors' contributions

Kansuda A contributed to the conceptualization and design of the study and developed the statistical analysis plan. RP and JK were responsible for acquiring clinical and laboratory data. Kanokwan A. performed the data analysis and drafted the manuscript. Kansuda A. interpreted the findings and finalized the manuscript. Kansuda A. and Kanokwan

A. revised and approved the final version. All authors reviewed and approved the submitted version.

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Conflicts of interest

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. The authors have nothing to disclose.

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