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A Comparative Study of Blood Glucose Measurements Using Glucometer Readings and the Standard Method in the Diagnosis of Neonatal Hypoglycemia

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ABSTRACT

***Background*:** Hypoglycemia is one of the most common neonatal disorders, associated with severe complications. There has been a great deal of controversy regarding the definition and screening of hypoglycemia. Therefore, in this study, we aimed to determine a cut-off value for blood glucose level in glucometer readings.

***Methods*:** This cross-sectional study was conducted on 238 newborns at risk of hypoglycemia, admitted to Baqiyatallah Hospital of Tehran, Iran in 2012; the subjects were selected via simple sampling. After obtaining informed consents from the newborns' parents, 1 cc blood samples were sent to the laboratory for measuring the blood glucose level. Moreover, venous blood samples, as well as heel-stick blood samples, were obtained for glucometer measurements. Blood glucose measurements were used to determine the cut-off value by the receiver operating characteristic (ROC) curve and make comparisons with the diagnostic criteria for hypoglycemia in the literature.

***Results*:** A total of 238 infants with the mean weight of 2869±821.9 g were enrolled in this study. The mean (±SD) blood glucose levels were 65.1±22.9, 82.9±24.7, and 84.4±24.8 mg/dl, based on the standard laboratory method, glucometer reading of venous blood samples, and glucometer reading of heel-stick capillary blood samples, respectively. The optimal cut-off point for hypoglycemia was determined as 65 mg/dl, using glucometer-based assessment of heel-stick blood samples.

Conclusion: The significant difference in blood glucose levels measured by the laboratory method and outpatient glucometer readings highlights the importance of a cut-off value for rapid assessment and control of blood glucose and timely detection of hypoglycemia. In fact, the cut-off value introduced in the present study could facilitate such measurements.

Keywords: Glucometer, Neonatal hypoglycemia, Screening

Introduction

Hypoglycemia is a common phenomenon in the neonatal period. Since hypoglycemic newborns are usually asymptomatic, their condition may be simply overlooked (1). Hypoglycemia is defined as a serum glucose level of 50-60 mg/dl, depending on the neonate's age; this condition is considered of great significance in the first days of a newborn's life (1).

Given the importance of glucose in brain metabolism, the incidence of hypoglycemia can interfere with structural and functional brain development (2). Complications of neonatal hypoglycemia can be serious and critical. Neurological defects and changes caused by the activation of autonomic nervous system and epinephrine release are among the adverse outcomes of hypoglycemia (1). With respect to these complications, accurate and rapid measurement of blood glucose at birth is one of the most effective measures for the diagnosis of hypoglycemia in newborns without any manifest symptoms (3, 4).

Hypoglycemia may occur as a physiological response at birth; therefore, blood glucose control is not essential for all newborns (5). Based on the standards, the serum glucose level of neonates at risk of hypoglycemia should be measured within the first hours of birth, every 1-2 hours for the first 6-8 hours after birth, and then every 4-6 hours up to 24 hours (4). Although no clear-cut definition has been established for hypoglycemia, blood glucose

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levels < 45 mg/dl on the first day and < 50 mg/dl on the second day are regarded as the standards in routine measurements (4, 6).

The incidence of hypoglycemia varies depending on fetal development and feeding protocols in hospital nurseries (4). In fact, early feeding reduces the occurrence of hypoglycemia, while prematurity, hypothermia, hypoxia, maternal diabetes, and glucose infusion during labor can increase the occurrence of this condition (4, 7). Also, the incidence of hypoglycemia varies depending on the age and weight of neonates. In fact, the highest rates of symptomatic hypoglycemia (25%) have been reported in small-for-gestational-age infants (4, 8).

The symptoms of hypoglycemia may start several hours to several weeks after birth. Irritability and tremor, apathy, episodes of cyanosis, seizure, intermittent episodes of apnea, difficulty in feeding, eye rotations, sweating, sudden pallor, hypothermia, and cardiac arrest or failure are among the most common symptoms, respectively (4).

Infants at high risk of hypoglycemia should be breastfed within the first 1-3 hours after birth or receive dry milk from the mouth or through gavage for 24-48 hours (every 2-3 hours). In case the newborns are resistant to oral feeding or experience transient asymptomatic hypoglycemia, they need to receive intravenous glucose infusions at a rate of 4 mg/kg/min (4).

Several methods have been proposed for blood glucose measurement over the past 40 years. Two common methods used to determine blood glucose level include glucometer readings and routine laboratory assessment (4). Laboratory assessment of blood glucose is based on the evaluation of glucose oxidase, glucose dehydrogenase, glucose hexokinase, and glucose-6-phosphate dehydrogenase (4).

Neonatal hypoglycemia is often associated with intrauterine growth restriction (IUGR), premature birth, and maternal diabetes mellitus. In general, hypoglycemia screening is recommended for high-risk cases. Breastfeeding is one of the effective measures in asymptomatic cases, while intravenous dextrose infusion is the main treatment option for symptomatic cases.

The incidence of hypoglycemia varies depending on fetal development and lactation protocols in neonatal intensive care units. Early nutrition reduces the incidence of hypoglycemia, while factors such as prematurity, hypothermia, hypoxemia, maternal diabetes, glucose infusion during labor, and IUGR can increase the risk of this condition.

Serum glucose level decreases 1-3 hours after birth, while the blood glucose level spontaneously returns to the normal level after this period. In healthy and term infants, blood glucose level is rarely below 35 mg/dl, 40 mg/dl, and 45 mg/dl within the first three hours of life, 3-24 hours after birth, and > 24 hours after birth, respectively. Also, depending on the severity and duration of hypoglycemia, premature infants are equally at risk of developmental and neural defects due to low blood glucose level.

The incidence of symptomatic hypoglycemia is 1-3 cases per 1000 live births. Also, this condition has been reported in 5-15% of newborns with developmental disorders. A set of episodic symptoms often appears due to hypoglycemia. Since these clinical symptoms can have various causes, the serum glucose level needs to be measured to determine whether glucose release is sufficient to relieve the symptoms. In case the symptoms are not improved, other conditions should be considered.

Glucose monitoring is performed within one to two hours after birth in infants at risk of hypoglycemia. In case of clinical symptoms, blood samples should be obtained before breastfeeding. Also, blood glucose measurement in neonates with blood glucose levels < 45 mg/dl should continue until the blood glucose level is stabilized (10).

Most hospital nurseries use glucometer devices for rapid and simple measurement of blood glucose level, although the reported results can be inconsistent, particularly in newborns with low blood glucose levels (11, 12). Therefore, low blood glucose level depicted by glucometer readings must be confirmed by laboratory tests (10).

Nelson Textbook of Pediatrics defines hypoglycemia as blood glucose level < 40 mg/dl, < 45 mg/dl, and ≤ 50 mg/dl in the first three hours of birth, 3-24 hours after birth, and after the first day of birth, respectively (13). Accurate diagnosis of hypoglycemia is of great importance for a more effective screening of high-risk cases (14).

Since the primary objective of the present study was to compare blood glucose levels, hypoglycemia was defined as blood glucose level < 45 mg/dl for all newborns. Although several studies have been conducted on this subject, the results have been contradictory, indicating the need for further research (4-6, 15, 16). Therefore, in this study, we aimed to compare glucometer readings and laboratory test results in order to evaluate the status of hypoglycemia in newborns.

Methods

This cross-sectional study was conducted on newborns at Baqiyatallah Hospital of Tehran, Iran in 2013. The sample size was determined, using the following formula:

$$n = \frac{2\left(z_{1-\alpha/2} - z_{1-\beta}\right)^2 \sigma^2}{d^2}$$

According to the literature and the abovementioned formula, the sample size was determined as 238 subjects; the participants were selected via simple sampling. In this study, newborns delivered at Baqiyatallah Hospital were examined by a pediatrician after birth.

The inclusion criteria were as follows: 1) neonate's age of 1-29 days; 2) diabetes mellitus in mothers; 3) birth weight > 4000 or < 2500 g; 4) clinical symptoms suggesting the risk of hypoglycemia including prematurity, maternal diabetes, IUGR, perinatal asphyxia, hypothermia, and lack of breastfeeding in the first hours after birth; and 5) symptoms of neonatal hypoglycemia such as tremor, irritability, apathy, and cyanosis. On the other hand, the exclusion criteria were lack of parental consent and age above one month.

According to the Declaration of Helsinki, consent forms were obtained from the newborns' parents for participation in the study. Venous blood samples (1 ml) were obtained by skilled nurses. After obtaining the venous blood samples, a drop of blood was spilled on a test strip and the results were recorded. The rest of the blood sample was sent to the laboratory for further assessments. The capillary blood samples from the heel were simultaneously obtained and examined by the glucometer, and the results were recorded. All examinations were conducted using the Gluco-Test Plus TD-4230 mg/dl.

Data analysis

After data collection, SPSS version 17 was used for the statistical analysis. To determine the relationship between quantitative variables, one-way ANOVA test was used. Also, Chi-square and Fisher's exact test were used to determine the relationship between quantitative and qualitative variables. Moreover, correlation tests were used to describe the correlation between variables such as weight and blood glucose level. The ROC curve was used to determine the sensitivity and specificity of the cut-off value.

Ethical considerations

Written consent forms were obtained from the parents of newborns for participation in the study. No additional costs were imposed on the parents for the treatment or hospitalization of the neonates. The newborns' information remained confidential and the results were anonymously published.

Results

A total of 238 infants with the mean weight of 2869±821.9 g (range: 410-4900 g) were enrolled in this study (Table 1). The weight of 94 (40.5%), 106 (45.7%), and 32 (13.8%) neonates was below 2500 g, between 2500 and 4000 g, and above 4000 g, respectively. In terms of maternal diabetes, 153 (65.4%) mothers had no previous history of gestational diabetes, 77 mothers had gestational diabetes, and four mothers had diabetes before pregnancy (Table 1).

Among 94 low-birth-weight infants, 19 (21.21%) cases had blood glucose levels < 45 mg/dl. Among 106 newborns with a normal birth weight, only 16 (15.09%) cases had blood glucose levels < 45 mg/dl. In addition, 9 (28.12%) out of 32 large-for-gestational-age infants had blood glucose levels < 45 mg/dl.

In total, 218 (92.4%) and 18 infants were asymptomatic and symptomatic during sampling, respectively. Based on the laboratory assessment, the mean glucose level was 65.01±22.09 in venous blood samples. On the other hand, according to glucometer readings, the mean glucose level was 89.28±24.71 in venous blood samples and 84.41±24.81 in capillary blood samples from the heel (Table 1).

Table 1. Characteristics of the participants

No.	Variables	Amount
1	Number	238
2	Weight	2869±821 g
3	< 2500 g	94 (40.5%)
3	2500-4000 g	106 (45.7%)
4	> 4000 g	32 (13.8%)
5	Blood glucose level	65.01±22.09 mg/dl
6	Blood glucose level in glucometer readings (venous blood samples)	82.98±24.71 mg/dl
7	Blood glucose level in glucometer readings (heel-stick blood samples)	84.41±24.81 mg/dl
8	Gestational diabetes mellitus	78 (32.7%)

The mean blood glucose level determined by the laboratory assessment was significantly different from the glucose level measured by the glucometer (P=0.045); however, the mean values calculated by the glucometer were not significantly different (P=0.67). Based on the laboratory assessment, 45 (19.4%) cases had hypoglycemia, among whom 39 cases were asymptomatic and only six infants presented with the clinical symptoms of hypoglycemia (P<0.05).

The ROC curve was used to determine the cut-off point for serum glucose level (Figure 1 & Table 2). By introducing hypoglycemia as blood glucose level < 45 mg/dl, the area under the curve for blood glucose in venous and heel-stick blood samples was 0.816 and 0.814, respectively; the reported values were considered acceptable.

Considering the sensitivities and specificities presented in Table 2, 65 mg/dl of blood glucose in heel-stick capillary blood samples was regarded as the cut-off value for hypoglycemia, based on the glucometer readings. Based on the introduced cut-off value, 45 (19%) newborns had hypoglycemia, which was not significantly different from the results obtained by the laboratory method (n=45, 19.4%) (P=0.13) (Table 3). Table 4 shows the cut-off value in different glucose measurements with respect to weight.

Table 2. Specificity and sensitivity of glucometer readings of blood glucose level in heel-stick samples

Blood glucose level (mg/dl)	Specificity	Sensitivity
45.5	6.8%	98.2%
50.5	13.6%	97.9%
55	18.2%	95.7%
59	31.8%	92.5%
65	45.5%	87.2%
68	50%	83.4%
75	74.2%	77.3%
90	97.5%	36.9%

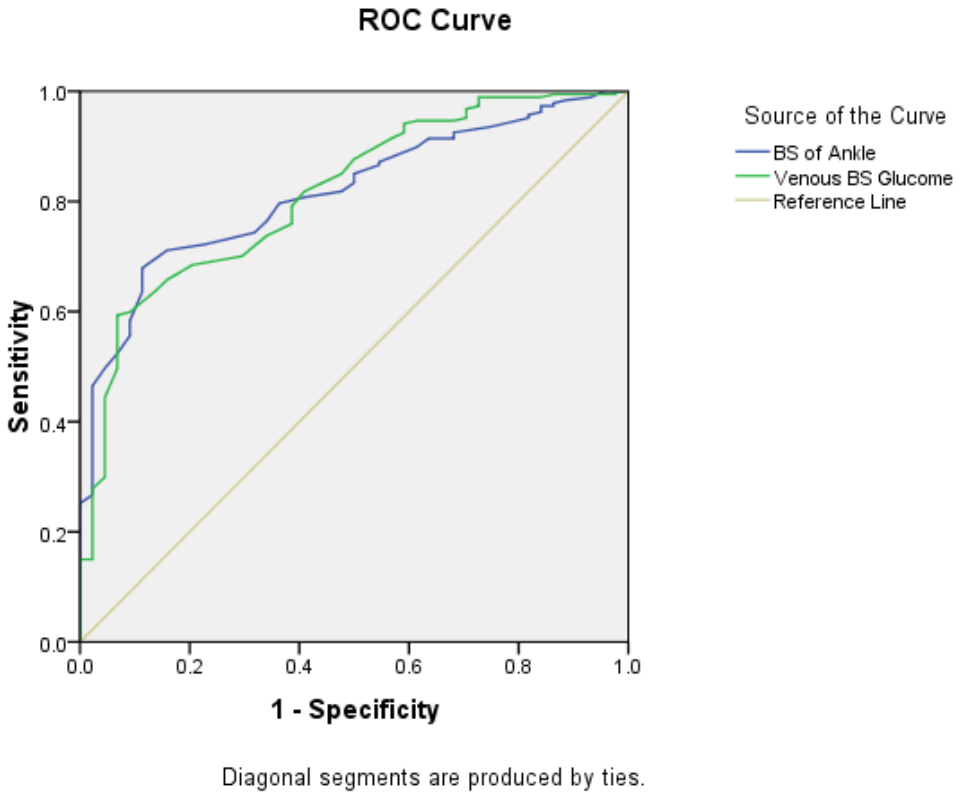

Figure 1. ROC curve for the laboratory method and glucometer readings of blood glucose level in heel-stick and venous blood samples (blood glucose level < 45 mg/dl is indicative of hypoglycemia)

Table 3. Frequency of hypoglycemia using the new cut-off value

Methods of glucose measurement	The introduced cut-off value	The standard cut-off value (< 45 mg/dl)	P-value
Heel-stick blood glucose level	45 (19)	5 (1.2)	<0.001
Venous blood glucose level	48 (2.20)	4 (7.1)	<0.001

Table 4. Frequency of hypoglycemia in terms of neonatal weight

	Weight (g)	Blood glucose level < 45 mg/dl	Heel-stick blood glucose level < 65 mg/dl	Venous blood glucose level < 65 mg/dl	P-value
1	< 2500 g	19	18	17	0.18
2	4000-2500 g	16	18	21	0.09
3	> 4000	9	8	9	0.12
	P-value	0.29	0.39	0.98	

Discussion

The major finding of this study was the significant difference between the laboratory method and glucometer readings of blood glucose level in venous and capillary blood samples; the difference was more evident among newborns on the first day after birth. Accordingly, glucometer readings were not reliable based on the established cut-off value for hypoglycemia (blood glucose level < 45 mg/dl).

Another important finding of this study was the introduction of a new cut-off point for hypoglycemia in venous blood and heel-stick samples (blood glucose level of 65 mg/dl), recorded by the glucometer. The obtained results based on this cut-off value were not significantly different from the standard laboratory measurements; therefore, the introduced value can be regarded as reliable. On the other hand, Hamid et al. noted the lack of correspondence between blood glucose level and glucometer findings and highlighted the need for consistence (as reported in the present study) (5).

According to a study by Barion, Glucotest is an appropriate tool for determining the blood glucose level. In this study, blood glucose level of 68 mg/dl was introduced as the cut-off value for hypoglycemia in glucometer readings. The results of the present study were in consistence with the findings reported by Barion. In fact, the present results were even more significant since the blood glucose level in heel-stick samples was also examined by the glucometer (6).

In this study, only 18 out of 45 cases had symptomatic hypoglycemia, indicating the importance of screening via blood glucose measurements. Another finding of the present study was the significant difference between blood glucose levels recorded in newborns on the first day of birth, which shows the importance of this condition in this age group. Therefore, a more sensitive and accurate cut-off value for blood glucose level is required in the treatment of these infants; however, no study has addressed this need, so far.

Conclusion

Considering the importance of blood glucose level in the diagnosis of hypoglycemia in the first hours of life, an accurate index is required for glucometer readings. Based on the findings, the new cut-off value introduced in the present study is recommended for the detection of hypoglycemia by glucometers, given the significance of timely diagnosis and treatment of hypoglycemia and accessibility of glucometers.

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Conflicts of interest

There was no conflict of interest in this study.

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