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Original Research

Risk Factor Assessment and the Incidence of Neonatal Hypoglycemia in the Postnatal Period

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Abstract

Objectives: The aim of this study was to evaluate risk factors used for the assessment of neonatal hypoglycemia and to examine the follow-up outcomes observed in the first 48 hours of postnatal life.

Methods: The records of infants born between 2015 and 2017 (3 years) at Şişli Hamidiye Etfal Training and Research Hospital who had a blood glucose level test performed within the first 24 hours after birth and who had follow-up results for 48 hours were included in the study. Data of gestational age; birth weight; gender; antenatal, natal and postnatal characteristics; blood glucose measurement method and time during the first 48 hours postpartum; glucose values and follow-up; nutritional status; and the need for hospitalization due to a low blood glucose value were recorded. Groups were created based on data of a diabetic mother, small for gestational age (SGA), large for gestational age (LGA), late preterm birth (34-36+6/7 gestational weeks), fetal distress, and feeding intolerance. Blood glucose measurement values and reasons for hypoglycemia and assessment were compared in subgroups.

Results: The data of 9480 infants were reviewed and included in the study. It was determined that blood levels were checked in 28.7% (n=2720). The mean birth weight and gestational age of the infants was 3143±804 g and 37.7±2.5 weeks, respectively. In the study group, 54.7% were male, and 57.5% were delivered via cesarean section. The most frequent factors prompting blood glucose measurement were LGA status (25.9%), prematurity (18%), transient tachypnea (17.3%), and SGA status (11.6%). Results revealed that the blood glucose values of 2009 (73.9%) infants were within normal limits, and there was no further monitoring of blood glucose level during the first 48 hours. In 711 (26.1%), a low blood glucose level finding led to follow-up assessment. The incidence of hospitalization with a preliminary diagnosis of hypoglycemia was 2.5% (n=67). Subgroup analysis indicated that at the first hour, the mean blood glucose value of the patients with multiple factors that were risks for hypoglycemia suggesting further evaluation was lower than those with transient tachypnea and fetal distress ($p<0.001$), and the mean blood glucose value of premature and LGA neonates were significantly lower than the infants of diabetic mothers at the sixth hour ($p<0.001$).

Conclusion: In the postnatal period, the rate of monitoring blood glucose levels in newborn babies was found to be 28.7% and the most commonly predicted risk factor was LGA babies. The frequency of postpartum hospitalization due to hypoglycemia was found to be 2.5%, and blood sugar levels were lower in the first hour in groups with multiple causes.

Keywords: Hypoglycemia; neonates; risk factors.

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Hypoglycemia is one of the most common metabolic problems to occur in the neonatal period. Neonates have high energy requirements, and insufficiency of the enzyme systems and substrates involved in energy production in this period can lead to hypoglycemia.

The incidence of hypoglycemia in newborns is estimated to be 1.3 to 5 per 1000 live births.[1] Most hypoglycemic infants do not have a specific symptom or physical examination finding of hypoglycemia. It is therefore recommended that follow-up protocols be implemented to monitor the blood sugar of infants at risk of hypoglycemia in neonatal units. The primary difficulty is that it is not possible to clearly determine which infants are at risk for hypoglycemia. The American Academy of Pediatrics (AAP) 2011 guidelines suggested risk factors of a late preterm (34-36 6/7 weeks) birth, a diabetic mother (IDM: infant of diabetic mother), low birth weight for gestational age (SGA: small for gestational age), and high birth weight for gestational age (LGA: large for gestational age).[2] The AAP recommended steps to be performed according to the blood sugar values observed in the first 24 hours.[2] However, there is no standardized and accepted protocol of how to monitor neonates who do not have these risk factors or how infants with risk factors should be monitored after the first 24 hours.

The diagnosis and treatment of neonatal hypoglycemia continues to be a complicated and challenging endeavor. There is no single blood glucose threshold for the definition of hypoglycemia. In term infants without risk factors, blood sugar values normally decrease in the 1 to 2 hours after delivery during a transition period, and may decrease to levels of 30 to 36 mg/dL in 3 to 6 hours when nutrition is not provided.[3] Although it is accepted that these values have no negative effect on development in healthy term babies, there is still a need for additional guidance on the threshold to be used for evaluation and treatment.[4]

In a study conducted with infants with symptomatic hypoglycemia, a blood glucose value of <47 mg/dL was determined to be the limit that would indicate motor and cognitive development effects.[5] However, another study found that in long-term follow-up, an early blood glucose value of <47 mg/dL did not lead to any difference in intelligence, numerical skills, or behavioral status.[6]

Another problem is the deviation of ±10-20 mg/dL in glucometer measurements. This can lead to unnecessary interventions in many infants. Routine blood glucose measurement in infants without risk factors is not recommended since it causes unnecessary separation of mother and baby and disruption to breastfeeding.[4]

The aim of this study was to investigate the reasons for checking blood glucose levels shortly after birth, to determine the procedures and follow-up applied according to blood glucose values, and to define the blood glucose values obtained in newborns according to risk factors.

Methods

The records of infants born at Şişli Hamidiye Etfal Training and Research Hospital between 2015 and 2017 (3 years) were examined retrospectively.

Study Group

Infants who had blood glucose level testing performed within the first 24 hours of life and had data of 48 hours of follow-up were included in the study. The gestation period; birth weight; sex; antenatal, natal, and postnatal characteristics; method and reason for checking blood sugar; time of testing; result of blood sugar evaluation; follow-up values; feeding status; the need for hospitalization due to hypoglycemia; and follow-up findings for the first 48 hours in infants with low blood sugar levels were recorded and analyzed.

The infants in the study were divided into subgroups according to characteristics of IDM, SGA, LGA, late preterm birth (34-36+6/7 gestational weeks), fetal distress, and feeding intolerance. Blood glucose values and causes of hypoglycemia and follow-up in subgroups were examined.

Infants with a gestational age of less than 22 weeks and below the viability limit, infants who were urgently admitted to intensive care without checking blood glucose level, and neonates with major congenital anomalies (gastroschisis, anencephaly, hydrops fetalis, etc.) were not included in the study. Infants without follow-up data for the first 48 hours after birth were also excluded.

Blood glucose measurement: Capillary blood samples were measured with a bedside Accu-Chek Inform II meter (F. Hoffmann-La Roche Ltd., Basel, Switzerland).

Transient tachypnea: The definition used in this study was postnatal tachypnea followed by adequate spontaneous respiration, normal blood gas values, and complete resolution of tachypnea on 4-hour follow-up and could be followed up while remaining with the mother.

Statistical Analysis

SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Descriptive statistics of number and percentage were calculated for the categorical variables, and mean, SD, minimum and maximum for numerical variables. Comparisons of numerical variables in independent groups were performed using the Mann-Whitney U test for 2 groups and the Kruskal-Wallis test for more than 2 groups without normal distribution. The level of statistical significance applied was $p<0.05$.

Results

The total number of live births in the hospital during the study period was 10.220. Thirty-eight infants were excluded from the study because the gestational age was less than 22 weeks and below the viability level. Another 702 neonates who required emergency intervention after birth and were taken to the intensive care unit without blood glucose testing in the first hour of life due to the need for urgent care were also excluded. The study was completed with a total of 9480 infants. A flow diagram of the study is presented in Figure 1.

Blood glucose levels were determined in 28.7% (n=2720) of the infants in the study group. The mean birth weight and gestation period of those who had blood glucose assessment was 3143±804 g and 37.7±2.5 weeks, respectively. The sex distribution was 54.7% male and the delivery type was 57.5% cesarean section. The distribution of risk factors and follow-up results are presented in Table 1. The most common factors prompting blood glucose monitoring were the characteristics of LGA, prematurity, transient tachypnea, and SGA.

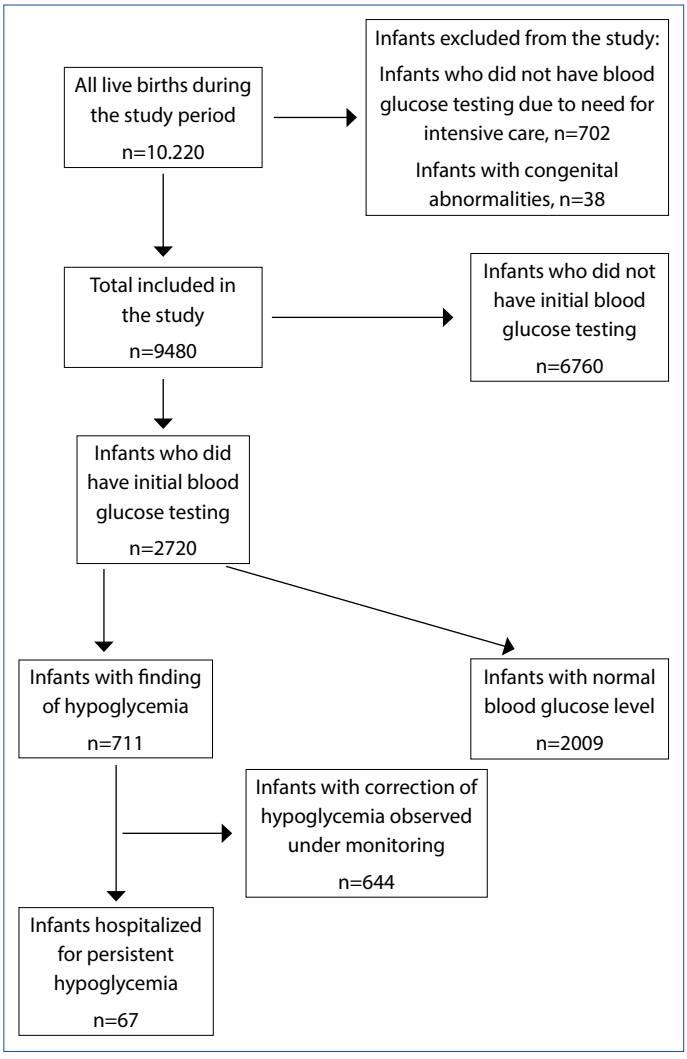

Figure 1. Blood sugar monitoring of infants born in our hospital over a 3-year period.

Of those initially tested, it was determined that the blood glucose values of 2009 (73.9%) infants were within normal limits, and there was no additional blood glucose evaluation performed in the first 48 hours. In all, 711 (26.1%) were followed up due to low blood sugar and 67 (9.4%, 67/711) infants were hospitalized in the neonatal unit due to persistent hypoglycemia (Table 1).

The mean blood glucose values obtained during the first 48 hours postpartum are presented in Table 2. The group with the lowest mean blood sugar at the first hour of life was the group with multiple reasons for testing, whereas the group with the lowest mean blood sugar at the second hour of life was the infants with feeding difficulties. In the 6th and 12th hours of life, the group with the lowest mean blood glucose was the group with fetal distress at birth. Preliminary diagnosis and distribution of blood glucose values of 67 infants hospitalized in the neonatal clinic are presented in Table 3.

Subgroup analyses of the study data were interpreted using the Bonferroni correction. The mean first-hour blood glucose value of the infants with multiple potential reasons for hypoglycemia prompting repeated testing was signifi-

Table 1. Reasons for blood sugar measurement and follow-up results

Reasons	Number of patients n=2720	Percentage of patients %
LGA	705	25.9
Prematurity	489	18
Transient tachypnea	471	17.3
SGA	315	11.6
Infant of diabetic mother (gestational DM + type 1 and type 2 DM)	226	8.3
Twin birth	64	2.4
Fetal distress	45	1.7
Meconium staining	24	0.9
Feeding intolerance	19	0.7
More than 1 reason	143	5.3
Other reasons	219	8.1
Follow-up of blood sugar test results		
Normal, follow-up alongside mother	2009	73.9
Hypoglycemia, blood sugar monitoring	711	26.1
Hypoglycemia hospitalization	67	2.5

LGA: Large for gestational age; SGA: Small for gestational age. DM: Diabetes Mellitus.

Table 2. Blood sugar values according to the reason for follow-up

	Blood glucose (mg/dL) and time of measurement														
	1st hour			2nd hour			6th hour			12th hour			24th hour		
	n	Mean±SD	Lower-upper limit	n	Mean±SD	Lower-upper limit	n	Mean±SD	Lower-upper limit	n	Mean±SD	Lower-upper limit	n	Mean±SD	Lower-upper limit
Transient tachypnea	404	64.7±18.9	19-152	141	69.8±17.9	25-130	37	70.9±16.9	44-107	6	69.5±14.5	55-96	1	59.0	
Prematurity	208	64.6±19.2	20-141	214	64.0±16.2	15-145	130	65.0±13.2	36-113	60	70.0±11.7	50-101	8	73.9±9.6	60-90
LGA	147	59.6±18.6	22-122	495	66.8±15.6	31-153	301	65.4±12.7	38-111	254	71.3±11.4	43-114	48	67.4±9.0	50-93
Infant of mother with gestational diabetes	116	60.9±16.2	20-103	154	67.5±16.3	34-139	148	71.7±14.8	40-131	45	71.5±14.8	50-133	8	66.8±11.8	52-91
Infant of mother on insulin	34	64.6±25.4	20-151	36	65.3±20.8	22-110	33	72.2±14.9	51-105	9	73.6±13.8	48-89	4	83.8±16.2	74-108
SGA	100	61.3±19.4	20-127	268	67.1±16.0	17-118	207	69.1±16.0	30-127	83	70.1±12.2	33-105	15	78.1±20.8	56-134
Feeding intolerance	5	71.4±18.4	46-95	9	59.1±17.3	26-82	8	65.0±20.6	36-96	6	63.7±10.4	49-74	3		
Twin birth	26	67.6±11.4	47-86	41	68.2±19.3	42-135	30	74.5±18.8	53-149	8	78.0±16.3	53-102	1	60.0	
Fetal distress	35	70.8±19.4	33-135	19	65.8±14.2	48-100	7	61.6±12.6	35-72	5	62.6±21.5	35-94	6	83.0±19.2	61-96
Meconium staining	15	62.9±17.4	35-98	11	62.1±9.8	54-86	10	61.9±8.0	50-75						
Other (maternal drug use, hypothyroidism, etc.)	96	59.8±14.8	20-103	149	63.9±14.7	29-125	128	66.7±12.6	29-102	22	68.4±11.4	50-89	1	72.0±19.8	60-112
More than 1 reason	89	57.0±17.8	20-137	104	66.9±17.0	36-136	91	70.2±14.3	43-113	6	71.9±15.0	52-106	8	76.8±21.9	56-102
p*		<0.001			0.133			<0.001			0.522			0.073	

* Kruskall-Wallis test; Total n=2720; however, because blood glucose measurements were performed at different times, the n value changes in each time period; LGA: Large for gestational age; SGA: Small for gestational age.

Table 3. Blood sugar monitoring time and results of 67 patients hospitalized due to hypoglycemia

	1st hour			2nd hour			6th hour			12th hour		
	n	Mean±SD	Lower-upper limit	n	Mean±SD	Lower-upper limit	n	Mean±SD	Lower-upper limit	n	Mean±SD	Lower-upper limit
Transient tachypnea	21	47.7±25.0	19-134	6	45.0±15.6	25-70						
Prematurity	10	39.9±13.8	26-72	6	48.7±10.6	37-65	3	47.0±14.2	36-63	1	87.0	
LGA	7	60.5±17.9	35-73	4	86.0±40.5	40-120	2	42.0±0.0	42-42			
Infant of mother with gestational diabetes	1	40.0		1	34.0							
Infant of mother on insulin	1	44.0		1	61.0		1	51.0				
SGA	5	46.7±9.1	37-55	5	49.6±13.0	35-67	5	51.8±20.9	30-85	1	64.0	
Feeding intolerance	1	34.0		1	41.0					1	49.0	
Twin birth	3	33.0±2.1	31-35,1	1	59.0		1	35.0	35-35	1	35.0	
Fetal distress	10	47.2±11.8	33-64	7	55.1±30.4	29-98	2	32.0±4.2	29-35	1	62.0	
Meconium staining	8	31.9±8.8	20-42	1	42.0							
Other (maternal drug use, hypothyroidism, etc.)	67	44.2±18.8	19-134	33	53.8±24.1	25-120	14	45.3±14.9	29-85	5	59.4±19.3	35-87
More than 1 reason	21	47.7±25.0	19-134	6	45.0±15.6	25-70						
p*	10	39.9±13.8	26-72	6	48.7±10.6	37-65	3	47.0±14.2	36-63	1	87.0	

Hospitalization was based on 2-, 6-, and 12-hour blood glucose values. In all, 34 infants were hospitalized in the first hour, 19 infants in 2nd hour, 9 infants in the 6th hour, and 5 infants in the 12th hour; LGA: Large for gestational age; SGA: Small for gestational age.

cantly lower than that of those with transient tachypnea or fetal distress (p<0.001), and the mean sixth-hour blood glucose level of premature and LGA infants was significantly lower than babies who had a mother with gestational diabetes (p<0.001).

In this study group, 1897 infants were screened according to the AAP criteria and 33 were hospitalized. Another 823 infants who did not meet the AAP screening criteria were also screened (transient tachypnea, twin birth, perinatal asphyxia-fetal distress, meconium staining, other causes) and 34 of these infants needed inpatient treatment. Only 49.3% of the infants treated for hypoglycemia as inpatients were found to meet the hypoglycemia screening criteria according to the AAP guideline.

Discussion

The aim of this descriptive study was to determine the frequency and reasons for blood sugar monitoring in neonates and examine the follow-up during the initial 48-hour postpartum period.

The AAP 2011 guide addressing the diagnosis and follow-up of neonatal hypoglycemia suggested risk factors for hypoglycemia of late preterm birth, SGA, LGA, or a diabetic mother.[2] In this guide, blood glucose limit values are given lower than the hypoglycemia treatment threshold used by other developed countries.[7, 8] The report was designed as a "pragmatic approach to a controversial issue in which evidence is lacking but guidance is needed," rather than as a definitive evidence-based indicator of the absence of neurological influences. However, many clinicians have since become accustomed to and used the AAP treatment thresholds and recommendations in their clinical practice.

The Pediatric Endocrine Society also published recommendations for the assessment and management of persistent hypoglycemia. Using a different approach to the AAP recommendations, they suggested that due to the period of transitional hypoglycemia, blood sugar should be kept close to the average for a healthy newborn during the first 24 hours of life.[7] It was recommended to maintain a level of >50 mg/dL (2.8 mmol/L), the level at which neuroglycopenic symptoms occur in older children and adults. After 48 hours, >60 mg/dL (3.3 mmol/L) was the suggested target.[7]

Hosagasi et al.[9] examined hypoglycemia in a group of 207 infants comprising 5.7% IDM, 38.1% LGA, 31.8% SGA, and 24.1% late preterm cases. It was reported that hypoglycemia was determined based on the AAP guideline in 17.8% of infants overall: 16.6% in the IDM group, 12.7% in the LGA group, 12.2% in the SGA group, and 34% in the late preterm birth infants. In our study, the most common causes of hypoglycemia were found to be similar. In a retrospective study of 803 infants born with meconium stained amniotic fluid, severe hypoglycemia was found in 1.4% of infants with no significant relationship established between meconium staining and hypoglycemia.[10] Our data also revealed no significant relationship between meconium in the amniotic fluid and hypoglycemia.

Another important issue related to neonatal hypoglycemia is the time of blood glucose testing after birth and the frequency of measurement. In the National Guidelines for Neonatal Hypoglycemia (UK), the recommended algorithm for infants of diabetic mothers is to check blood glucose levels immediately after birth, at 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, and 12 hours, and whenever hypoglycemia symptoms are seen. In addition, it is recommended to monitor the blood sugar level 30 minutes after the start of intravenous perfusion and after dose adjustments during hypoglycemia treatment.[10] In our study, when the blood glucose values of IDM infants were examined in accordance with this algorithm, the lowest blood glucose values were determined at the first hour.

Research has demonstrated that the lowest blood glucose levels occur in the first 12 hours in LGA infants and infants of diabetic mothers, and in the first 24 hours in SGA and late preterm infants.[11] Therefore, it is recommended that LGA and IDM infants should be observed for 12 hours and SGA and late preterm infants for 24 hours.[11] The British guidelines recommend that infants with risk factors should be monitored for at least 4 to 6 hours before feeding, until 2 consecutive values are considered normal.[12]

Hosagasi et al.[9] found in their analysis of the timing of the detection of hypoglycemia that the lowest blood sugar levels were found in late preterm infants during the first 4 hours and in the period of 4-24 hours of follow-up. In our study, the group with the lowest mean blood sugar in the first hour of life was the group with multiple reasons identified as risk factors suggesting testing, while the group with the lowest mean blood sugar in the second hour of life was infants with nutritional problems. In the 6th and 12th hours of life, the group with the lowest mean blood glucose level was the group with fetal distress.

Neonatal hypoglycemia is a common metabolic disorder that can lead to adverse effects but it can be addressed with early diagnosis and treatment. Hypoglycemia that is symptomatic, recurrent, or persistent has been shown to be associated with neuromotor damage.[13] However, a significant association between asymptomatic episodes of hypoglycemia and neuromotor developmental delay or brain damage has not been established. Studies have indicated that irreversible white matter damage was detected in 95%

of 18-month cranial magnetic resonance imaging of patients with symptomatic refractory hypoglycemia.[13] However, another study reported that neonatal hypoglycemia was not associated with an adverse neurological outcome when a blood glucose concentration of at least 47 mg/dL was maintained.[14] Therefore, there is currently no widely accepted blood glucose level that has been identified as an absolute threshold for neonatal hypoglycemia. It is recommended that infants with late preterm, SGA, LGA and IDM infants evaluated in the risk group due to susceptibility to hypoglycemia should be monitored according to AAP hypoglycemia protocols. In this study, all of the newborns delivered at our hospital over a 3-year period whose blood glucose level was examined for any reason were evaluated. In all, 28.7% of the infants had a risk factor for hypoglycemia prompting testing and 2.5% required inpatient treatment for hypoglycemia. Our results indicated that the AAP risk factors did not always result in hypoglycemia and most cases had 2 or more risk factors.

The majority of the infants in this study were identified according to the AAP risk groups; however examination revealed that additional conditions, such as transient tachypnea, birth with fetal distress, meconium staining, maternal drug use, and maternal hypothyroidism were significant. This suggests that the AAP risk factors for hypoglycemia should be expanded.

Conclusion

In conclusion, our research revealed that 28.7% of the newborns in the group had a blood glucose level evaluation in the immediate postnatal period and the most common risk factor for hypoglycemia was LGA status. The frequency of postpartum hospitalization due to hypoglycemia was 2.5%, and the blood glucose value at the first hour was lower in the groups with multiple potential causes of hypoglycemia. It was determined that half of the patients who needed inpatient treatment would have been missed if follow-up was performed according to AAP criteria alone.

We believe that it is appropriate to determine the risk factors according to clinical unit data in the development of hypoglycemia for the first 48 hours postpartum and to establish follow-up criteria, to establish the follow-up guide with the data to be obtained from these babies, and to follow the babies in this guideline.

Disclosures

Ethics Committee Approval: The study was approved by the Sisli Hamidiye Etfal Local Ethics Committee (603-22.12.2015).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.B., L.B.; Design – A.B., S.B.; Supervision – H.S.U., E.T.Ü.; Materials – S.B., Ş.S.; Data collection &/or processing – S.B., Ş.S.; Analysis and/or interpretation – L.B., S.B.; Literature search – E.K.B., E.T.Ü.; Writing – A.B., L.B.; Critical review – H.S.U., E.K.B.

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