

Hypoglycemia Frequency in Babies Identified as at Risk

Risk Belirlenen Bebeklerde Hipoglisemi İnsidansı

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ABSTRACT

Objective: The aim of this retrospective study was to determine the frequency of hypoglycemia in babies at risk and to examine our follow-up results up to 48 hours postnatally. It is also aimed at comparing the demographic characteristics of babies with and without hypoglycemics.

Material and Methods: The newborns screened with hypoglycemia ICD code were evaluated in terms of risk factors, and the patients were grouped according to risk factors. All babies at risk were screened up to 48 hours post-natally. Hypoglycemia was defined as a blood glucose concentration <47 mg/dl, regardless of the age of the baby.

Results: Blood glucose concentration first 48 hours after birth was measured in 823 babies with the hypoglycemia ICD code. Hypoglycemia was detected in 251 (30.4%) of these babies. 215 (26%) out of 823 babies were screened for having at least one risk factor for hypoglycemia. Hypoglycemia was detected in 149 (69.3%) of them. frequency of hypoglycemia increased in all babies at risk except infant of diabetic mother. Even through although almost all of the babies at risk developed hypoglycemia in the first 24 hours, we detected hypoglycemia in 7 of them(4.6%) during postnatal 24-48 hours. There were statistically significant differences in demographic characteristics of babies at risk who did and did not become hypoglycemic.

Conclusion: Hypoglycemia is common in babies at risk. Without early detection and timely diagnosis and treatment can cause negative consequences of neurological and developmental. Therefore, continuous monitoring of blood glucose level in babies at risk should be performed to reduce its impact.

Key Words: Hypoglycemia frequency, Risk factors

ÖZ

Amaç: Bu retrospektif çalışmanın amacı risk altındaki yenidoğanlarda hipoglisemi sıklığını belirlemek ve doğum sonrası 48 saate kadar sonuçlarını değerlendirmekti. Ayrıca hipoglisemi olan ve olmayan yenidoğanların demografik özelliklerini karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Hipoglisemi ICD kodu ile taranan yenidoğanlar risk faktörleri açısından değerlendirildi ve hastalar risk faktörlerine göre gruplandırıldı. Risk altındaki tüm bebekler doğum sonrası 48 saate kadar tarandı. Hipoglisemi, kan şekeri konsantrasyonunun 47 mg/dl'nin altında olması olarak tanımlandı.

Bulgular: Hipoglisemi tanı kodu olan 823 yenidoğanın postnatal ilk 48 saat içinde ölçümlenen kan şekeri konsantrayonları değerlendirildi. 251'inde (% 30.4) hipoglisemi saptandı. 823 yenidoğanın 215'i (% 26) hipoglisemi



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için en az bir risk faktörüne sahip olduğu için tarandı. Bunların 149'unda (%69.3) hipoglisemi saptandı. Diyabetik anne bebekleri dısında risk altındaki tüm yenidoğanlarda hipoglisemi insidansı artmıstır. Bununla birlikte, risk altındaki bebeklerin tamamına yakını ilk 24 saatte hipoglisemi gelistirmesine rağmen, 7'sinde (%4.6) postnatal 24-48 saat icinde hipoglisemi tespit ettik. Hipoglisemik olan ve olmayan Riskli venidoğanların demografik özelliklerinde istatistiksel olarak anlamlı farklılıklar vardı.

Sonuç: Hipoglisemi riskli yenidoğanlarda yaygındır. Erken tarama zamanında teşhis ve tedavi olmadan, nörolojik ve gelişimsel olumsuz sonuçlara neden olabilir. Bu nedenle, nörogelişimsel olası etkilerini azaltmak için risk altındaki yenidoğanlarda kan sekeri düzeyinin sürekli olarak izlenmesi gerekmektedir.

Anahtar Sözcükler: Hipoglisemi sıklığı, Risk faktörleri

INTRODUCTION

Due to the metabolic adaptation process, most healthy newborns experience low blood glucose levels in the first hours of life (1,2). This temporary decline guickly improves within hours and reaches normal ranges. However, some newborns experience a more prolonged, recurrent and severe hypoglycemia particularly in the presence of specific risk factors. Repeated episodes can cause brain damage if they are not detected early and diagnosed and treated at the right time (3,4). Therefore, assessment and treatment of prolonged/ recurrent hypoglycemia are important to prevent negative neurological and developmental consequences.

Most hypoglycemic infants do not have a specific symptom or physical examination finding of hypoglycemia. So, neonatal units should be able to monitor glucose. Recently, the American Academy of Pediatrics (AAP) published a guideline for screening and management of hypoglycemia in newborns at risk (5). This guideline defined babies at risk for hypoglycemia as late preterm (34-36 6/7 weeks) birth, to have 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). Optimum screening approaches are suggested depending on the risk factors and the blood glucose values observed in the first 24 hours (5). 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.

In our study, we aimed to determine the frequency of hypoglycemia in babies at risk and also detect any differences in the frequency related to different risk factors. We also compared the demographic characteristics of babies at risk with and without hypoglycemia and planned to evaluate the consistency between our approach to infants at risk of hypoglycemia and current recommendations.

MATERIALS and METHODS

This observational and retrospective study was conducted in Başkent University between 1 January 2016-1 April 2019.

The newborns screened with hypoglycemia ICD code were assessed in terms of risk factors, and the patients were grouped based on the risk factors. Risk groups were determined according to recommendations of the AAP (5):

- Small-for gestational-age (SGA) infants: birth weight 10 percentile [according to the Fenton
- growth curve] (6).
- Large-for-gestational-age (LGA) infants: birth weight >90 percentile [according to the Fenton growth curve] (6).
- Infant of diabetic mother (IDM): maternal type 1 or type 2 diabetes mellitus or gestational diabetes mellitus [according to the criteria published by the American Diabetes Association in 2010] (7).
- Late preterm infant (LPI): a premature infant born between 34-36 6/7 gestational weeks

Infants of diabetic mothers were included in the IDM group regardless of their birth weight to avoid overlapping of patients while grouping. LPTs group was formed based on gestational age regardless of the babies' SGA or LGA status.

Infants who had any disease other than hypoglycemia (sepsis, polycythemia) or who suffered from congenital malformations and perinatal asphyxia were excluded from the study.

All infants were breast or formula-fed in the first hour after birth. Later on, they were fed with intervals of two or four hours. Babies with hypoglycemia were encouraged to be fed with breast-milk. Babies who refused to suck were given expressed breast milk, infant formula or dextrose 10% via syringe and the alucose concentration was re-checked half an hour later. I.V. glucose treatment was started in those who did not have any changes in their glucose concentration.

Capillary blood samples were obtained by nursing staff via heel-/ finger-pricking. Blood glucose concentrations were determined using the "Accu-check Glucometer" (ACON Laboratories INC. eUSA) and test strips.

We defined hypoglycemia as a blood glucose concentration <47 mg/dl and severe hypoglycemia as <35 mg/dl (8-11). An episode of hypoglycemia was as defined as one or more consecutive blood glucose concentrations <4 mg/dl. Recurrent hypoglycemia was defined as a further episode of hypoglycemia after successful treatment within 24h.

Although the babies at risk did not experience hypoglycemia in the first 24 hours of the study, intermittent blood glucose measurements were performed for 48 hours after birth. Within 24-48 hours, the level of blood glucose was routinely measured before every two to three feedings. The study was approved by the local ethics committee (Başkent University of Medicine, 28.05.2010. 94603339-604.01.02/20009).

RESULTS

Blood glucose concentration in the first 48 hours after birth was measured in 823 babies with the hypoglycemia ICD code. Hypoglycemia was detected in 251 (30.4%) of these babies. Of them, 215 were screened for having at least one risk factor for hypoglycemia. Hypoglycemia was detected in 149 (69.3%) of them. Of the babies, 66 (30.7%) with at least one risk factor, but not with hypoglycemia, were included in the control group (Figure 1).

IDM was found in 71 (47.6%), LPI in 45 (30.2%), SGA in 26 (17.4%) and LGA in seven (4.7) in the hypoglycemic group and not in the hypoglycemic group, IDM was found in 50 (75.7%), LPI

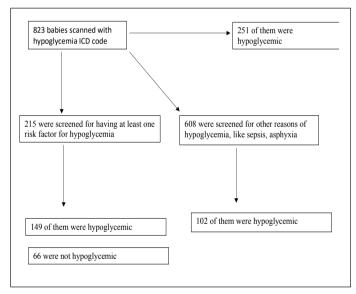


Figure 1: Selection of the hypoglycemic babies at risk.

in eight (12.1%), SGA in seven (10.6%) and LGA in one (1.5%) when the babies were grouped according to the risk factors (Table I). There were significant differences in the demographic characteristics of babies at risk who did and did not become hypoglycemic. The results were summarized in Table II. Male babies were found to be more likely to become hypoglycemic. The majority of hypoglycemic babies (129/149, 86.5%) showed no clinical signs, however, 14 hypoglycemic babies (12.2%) were too sleepy to feed, five had difficulty sucking and one was noted to be jittery.

The frequency of hypoglycemia increased significantly in all risk groups except for the IDM group. The most commonly predicted risk factors were found to be in the LGA babies. Infants of diabetic mothers who did not develop hypoglycemia had significantly lower birth weights and higher singleton pregnancy rates. Blood glucose levels of almost all mothers were regulated by diet and their Hba1c values were significantly lower (p<0.001).

The time of hypoglycemia was assessed according to the groups. Most babies who carried a risk developed hypoglycemia 107/149, (72%) in the first 4 h. Hypoglycemia was detected mostly in the LGA and IDM groups in the first 4 hours after birth and recurred in 4-24 hours in 28 babies (26%). Between 4-24 hours, 64 babies developed hypoglycemia. We observed hypoglycemia in only seven babies within 24-48 hours after birth. Of them, four were in the LPI group, two in SGA and one in LGA.

Recurrent hypoglycemia was observed in 24% of all babies. Of the 98 recurrent episodes, 34 (34.6%) occurred within eight hours of the initial episode and 82 (83.6%) within 24 hours. Of the babies, 19% had severe hypoglycemia which occurred in the first four hours in almost half of them. Although there were recurrent mild hypoglycemia attacks, none of the babies experienced severe hypoglycemia after 24 hours. The occurrence times according to risk groups and recurrent, prolonged and severe hypoglycemia frequency were presented in Tables III and IV.

Table I: Distribution of babies who did and did not become hypoglycemic according to the risk factors.

All newborns at risk (n=215)	Hypoglycemic n=149 (%)	Not hypoglycemic n=66 (%)
IDM group	71 (47.6)	50 (75.7)
LPIs	45 (30.2)	8 (12.1)
SGA infants	26 (17.4)	7 (10.6)
LGA infants	7 (4.7)	1 (1.5)

n: number of patients; IDM: Infant of diabetic mother; LGA: Large-for-gestational-age; SGA: Small for gestational age; LPI: Late preterm infant.

Table II: Demographic data for babies at risk who did and did not become hypoglycemic and their mothers.				
	Hypoglycemic	Not hypoglycemic	р	
Maternal age ^a	35 (24-51)	32 (21-43)	<0.001	
Parity ^a	1 (1-6)	2 (1-6)	< 0.001	
BMI at booking (kg/m²)	28.5±7	29.3 ±7.9	0.035	
Weight change during pregnancy (kg)	14.3±7.1	12.5±7.3	< 0.001	
Diabetes Diet controlled Insulin Hba1c (mmol/l)	42/149 (28.1%) 27/42 (64.3%) 15/42 (35.7%) 7.08 ± 1.12	50/60 (83.3%) 43/50 (86%) 7/50 (14%) 5.9 ± 0.98	<0.001 <0.001 <0.001 <0.001	
Babies (n)	149	66		
Male (n)	85 (57%)	24 (36.3%)	< 0.001	
Birth weight ^a	2600 (960-5070)	3240 (1645-4920)	0.001	
Gestation age (week) ^a	36.6 (29.4-41.3)	38 (34-40.2)	0.031	
Singleton	111 (74.4%)	59 (%89.3)	0.017	
Apgar score at 5 minutes ^a	8 (3-9)	8 (4-9)	0.001	
Cesarean delivery, n (%)	132 (88.5%)	58 (87.8%)	NS	

Table III: Distribution of the hypoglycemia according to the risk groups and hypoglycemia occurrence time.

	IDM group	LPIs	SGA infants	LGA infants
	n=71 (%)	n=45 (%)	n=26 (%)	n=7 (%)
Hypoglycemia within first 4 h	62 (87.3%)	23 (51%)	16 (76.9%)	6 (85.7%)
Hypoglycemia in 4-24 h	27 (38%)	25 (55.5%)	15 (57.6%)	1 (14.3%)
Hypoglycemia in 24-48 h	0 (0%)	4 (8.8%)	2 (7.7%)	1 (14.3%)
Severe hypoglycemia within first 4 h	6 (20%)	5 (33.3%)	2 (20%)	1 (14.3%)
Severe hypoglycemia in first 4-24 h	8 (22.%)	6 (21.4%)	2 (25%)	0 (0%)

n: number of patients; IDM: Infant of diabetic mother; LGA: Large-for-gestational-age; SGA: Small for gestational age; LPI: Late preterm infant.

Table IV: Distribution and	comparison of the incide	ence of hypoglycemia	according to risk groups.

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	IDM group (n=71)	LPIs (n=45)	SGA infants (n=26)	LGA infants (n=7)
Severe hypoglycemia, n(%)	37 (52.1%)	11 (24.4%)	10 (38.4%)	1 (14.2%)
Prolonged hypoglycemia, n(%)	5 (7%)	8 (17.7%)	6 (23%)	0 (0%)
Reccurent hypoglycemia, n(%)	15 (21.1%)	9 (20%)	10 (38.4%)	1 (14.2%)

n: number of the hypoglycemia episodes; IDM: Infant of diabetic mother; LGA: Large-for-gestational-age; SGA: Small for gestational age; LPI: Late preterm infant.

DISCUSSION

The present study was conducted to determine the frequency of hypoglycemia in newborn babies at risk and detect the differences of the frequency related to different risk factors. In our study, the frequency among all screened babies was 30.4% (251/823) while it was 59.3% (149/215) among babies identified as being under risk. The frequency of hypoglycemia varied between the risk groups. The reasons for being under risk and the number of risk factors did not affect the frequency of hypoglycemia.

Routine measurement of blood glucose is recommended to prevent neonatal hypoglycemia for newborns at risk (5). Therefore, it is aimed to prevent the negative neurological and

developmental effects of hypoglycemia. There is a significant difference in the screening for hypoglycemia between clinicians and nurseries regardless of the recommendations (9). Various results have been obtained in the frequency of hypoglycemia due to different approaches. This variability depended on many factors such as the definition of hypoglycemia, feeding status and timing of the blood glucose test.

Neonatal hypoglycemia was more common in our study than the previously reported, which might be due to several reasons. Firstly, our standard approach was to strictly control the blood glucose levels of newborns who were under risk for 48 hours after birth, thus, we had an increased opportunity to detect hypoglycemia. Another reason was that we defined <47 mg/ dl as the limit of hypoglycemia. The frequency increased in line with the limit blood glucose value determined for hypoglycemia. Stark et al. (10) defined hypoglycemia as a blood glucose concentration of < 40mg/dl and reported a 27% frequency in admitted babies who were under risk. When they recalculated the frequency based on the Swiss and the AAP guidelines, namely <45 mg/dL instead of <40 mg/dL, they found that the frequency increased from 27 to 43%. Harris et al. (8) reported the frequency of hypoglycemia to be 51% when they accepted the hypoglycemia limit value as 47 mg/dl (5,11). The frequency of hypoglycemia in babies under risk was 17.8% by Hosağası et al. (12) in the first 24 hours according to the AAP guideline.

Duration of monitoring blood glucose is important to determine the frequency of hypoglycemia. Continuous glucose monitoring may provide more accurate information. The current screening guidelines recommend that infants with diabetes and large babies should have monitoring discontinued 12 hours after birth (if the blood glucose is > 47 mg/dl) and late preterm babies and small babies after either 24 or 36 hours (5,13). Contrary to these recommendations, we performed intermittent glucose measurement in all babies under risk for 48 hours. Also, only seven babies developed moderate hypoglycemia after 24 hours and the length and frequency of blood glucose monitorization time increased the frequency.

Another important issue related to neonatal hypoglycemia is the time and type (breast or formula) of feeding. This could be observed in the study by Heck and Erenburg et al. (14). Although they accepted the cut-off value as 40 mg/dl for hypoglycemia, they found the frequency rate higher. This difference was explained by the researchers with the possible "rebound" hypoglycemic effect of formula feeding. In our study, it was not possible to predict the effect of type of feeding on frequency due to the lack of knowledge. Our hospital was baby-friendly and almost all mothers chose to breastfeed in the first few hours after birth. However, because the anxiety of mothers who could not breastfeed increased the nurses' tendency to feed with the babies with formula, we did not know how successful we were in this. LGA babies whose mothers did not have diabetes mellitus were claimed to be under risk for transient hypoglycemia (15). Our results supported this hypothesis. We detected hypoglycemia in the first postnatal hours in almost all of the LGA babies. Only one baby developed hypoglycemia after 24 hours after birth. Besides, none of the babies had prolonged hypoglycemia. Recurrent and severe hypoglycemia was observed in only one baby. In many studies, the frequency of hypoglycemia was high in the first postnatal hours in LGA babies (12,16). Some researchers even argued that glucose monitoring should not be extended up to 48 hours (17). We cannot support this idea due to the small number of LGA babies in our study. Nevertheless, we had a baby who developed hypoglycemia after 24 hours.

Recent studies have shown that the risk of hypoglycemia was significantly higher in the SGA babies than in LGA and AGA (11, 12, 18). Apart from the increased frequency of hypoglycemia,

low or high birth weight is an important determinant for the severity, recurrence and duration of hypoglycemia. Our data supported this and the severity, recurrence and duration of hypoglycemia were statistically higher in the SGA babies than in LGA.

Infants of diabetic mothers commonly experience hypoglycemia in the first hours after birth. However, the infants of diabetic mothers treated with diet did not have any association with hypoglycemia, while a significant increase in the frequency of hypoglycemia was observed in those born to mothers treated with insulin or oral agents (19,20). Our findings were in line with this result. We can speculate that this may represent objective evidence that strict control of diabetes has long term benefits in the postnatal period. This should be carefully interpreted since we could not compare further glucose levels due to no indication of follow up in controls.

Late preterm infants are physiologically and metabolically immature compared with term infants. Furthermore, the feeding difficulty is another concern in late preterm infants. Therefore, the increased risk of hypoglycemia in the postnatal period is not surprising. The frequency of hypoglycemia in LPIs is reported to be three times of that in term infants, and nearly two-thirds of these late preterm infants require intravenous dextrose (21).

In their prospective study, Celik et al. (22) found absolute hypoglycemia in 14.5% of late preterm infants. This study found an increased risk for hypoglycemia in the postnatal period (between selected groups) in the LPI group and the rate of hypoglycemia among all risk groups was 20.9%.

Of the babies in our study, 19% had severe hypoglycemia which occurred in the first four hours in almost half of them. Severe hypoglycemia was not detected after 24 hours in any of these babies although there were recurrent mild hypoglycemia attacks. Recurrent hypoglycemia, which is important for longterm adverse neurological effects, was observed in 24.1% of all babies with hypoglycemia. Recurrent hypoglycemia was seen more frequently in the SGA babies. Recent studies highlighted the importance of recurrent hypoglycemia and pointed out the necessity of a well-designed follow- up study to determine the developmental outcomes of babies who experienced early/recurrent hypoglycemia (12, 23). Such a study will provide further evidence for the early intervention and strict control of blood glucose. Our study had some limitations and recommendations. The most important limitation of this study was its retrospective and observational design. The low number of babies under risk and some adequacies regarding our records was another limitation of this study. Contrary to the recommendations by the AAP, we accepted 47 mg/dl as the limit value for hypoglycemia and blood glucose measurement of all babies under risk was monitored for 48 hours (5). Therefore, the number of tests was high and some babies were applied avoidable intervention, which also increased the frequency of hypoglycemia considerably. Even the possibility of

rebound hypoglycemia may have contributed to the frequency of hypoglycemia observed in the present study because our nurses often preferred formulas or dextrose while intervening hypoglycemia. Because we did not record how we intervened in hypoglycemia, we could not determine this. Another result of this study was that our nurses tended to feed babies, who could not have breast milk, with formula. Similarly, we cannot predict the outcome of this.

To conclude, neonatal hypoglycemia is common in babies under risk and they should be routinely screened for blood glucose regardless of the recognition of risk factors and early attention should be paid to feeding. Additionally, we believe that it is appropriate to establish follow-up criteria for the first postnatal 48 hours.

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