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Management of hypoglycemia in newborn: Turkish Neonatal and Pediatric Endocrinology and Diabetes Societies consensus report

Yenidoğanda hipoglisemiye yaklaşım: Türk Neonatoloji ve Çocuk Endokrinoloji ve Diyabet Dernekleri uzlaşı raporu

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Abstract

Hypoglycemia is one of the most important and most common metabolic problems of the newborn because it poses a risk of neurological injury, if it is prolonged and recurs. Therefore, newborns who carry a risk of hypoglycemia should be fed immediately after delivery and the blood glucose level should be measured with intervals of 2-3 hours from the 30th minute after feeding. The threshold value for hypoglycemia is 40 mg/dL for the first 24 hours in symptomatic babies. In asymptomatic babies, this value is considered 25 mg/dL for 0-4 hours, 35 mg/dl for 4-24 hours, 50 mg/dL after 24 hours and 60 mg/dL after 48 hours. Screening should be performed with bed-side test sticks. When values near the limit value are obtained, confirmation with laboratory method should be done and treatment should be initiated, if necessary. The level targeted with treatment is considered 50 mg/dL in the postnatal first 48 hours before feeding, 60 mg/dL after 48 hours in babies with high risk and above 70 mg/dL in babies with permanent hypoglycemia. In cases in which the blood glucose level is below the threshold value and can not be increased by feeding, a glucose infusion of 6-8 mg/kg/min should be initiated. If symptoms accompany, a mini bolus of 10% dextrose (2 ml/kg/min) should accompany. Incements (2 mg/kg/min) should be performed, if the target level can not be achieved and decrements (2 ml/kg/ min) should be performed, if nutrition and stabilization is provided. The infusion should be discontinued, if the infusion rate decreases to 3-5 mg/ kg/min. If nec-

Öz

Hipoglisemi, uzun sürmesi ve tekrarlaması durumunda nörolojik zedelenme riski nedeniyle, yenidoğanın en önemli ve en sık metabolik sorunlarından birisidir. Bu nedenle, hipoglisemi riski taşıyan yenidoğanlar, doğum sonrası hemen beslenmeli ve beslenme sonrası 30. dakikadan itibaren 2-3 saat aralıklarla kan glukozuna bakılmalıdır. Hipoglisemi eşik değerleri, ilk 24 saat için belirtisi olanlarda 40 mg/dL, belirtisiz olanlarda 0 - 4 saatte 25 mg/dL, 4-24 saat aralığında 35 mg/dL, 24 saatten sonra 50 mg/ dL, 48 saatten sonra ise 60 mg/dL olarak kabul edilebilir. Tarama hastabaşı test çubukları ile yapılmalı, sınıra yakın değerlerde, laboratuvar yöntemi ile doğrulama yapılırken, gerekliyse tedavi başlanmalıdır. Tedavi ile ulaşılması hedeflenen düzeyler, beslenme öncesi postnatal ilk 48 saatte 50 mg/dL, 48 saatten sonra riskli olanlarda 60 mg/dL, kalıcı hipoglisemili olgularda ise 70 mg/dL'nin üstü olarak kabul edilebilir. Kan glukozu eşik değerin altında olan ve beslenme ile yükseltilemeyen durumlarda, 6-8 mg/kg/dk glukoz infüzyonu başlanmalı, belirti eşlik etmesi durumunda ise 2 ml/kg %10 dekstroz minibolus eşlik etmelidir. Hedef düzeye ulaşılamaması durumunda artışlar ve beslenme ile stabilizasyonun sağlanması durumunda azaltmalar 2 mg/kg/dk olarak yapılmalı, infüzyon hızının 3-5 mg/kg/dk'ye inmesi durumunda ise infüzyon sonlandırılmalıdır. Gerekliyse ayırıcı tanı açısından kan örnekleri hipoglisemi sırasında alınmalı ve araştırma,

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essary, blood samples should be obtained during hypoglycemia in terms of differential diagnosis and the investigation should be performed following a 6-hour fasting period in babies fed enterally and at any time when the plasma glucose is <50 mg/dL in babies receiving parenteral infusion. The hypoglycemic babies in the risk group whose infusions have been terminated can be discharged, if the plasma glucose level is found to be at the target level for two times before feeding and babies with permanent, severe or resistant hypoglycemia can be discharged, if the plasma glucose level is >60 mg/dL following a 6-hour fast.

Keywords: Glucose, hypoglycemia, infusion, newborn

enteral beslenen bebeklerde 6 saatlik beslenmeme periyodu sonrasında, parenteral infüzyon alanlarda ise plazma glukozunun <50 mg/dL olduğu herhangi bir zamanda yapılır. İnfüzyonları sonlandırılan riskli gruptaki hipoglisemik bebekler, plazma glukoz düzeyleri beslenme öncesi iki kez hedef düzeylerde saptanması durumunda, kalıcı, ciddi ya da dirençli hipoglisemili bebekler ise, plazma glukoz düzeyleri 6 saatlik açlık sonrası >60 mg/dL olması durumunda taburcu edilebilirler.

Anahtar sözcükler: Glukoz, hipoglisemi, infüzyon, yenidoğan

The frequency and importance of neonatal hypoglycemia

Hypoglycemia is one of the most common metabolic problems of the newborn. In most healthy newborns, a reduction in the blood glucose level due to the process of metabolic adaptation is observed in the first hours of life (1). Newborns at risk for hypoglycemia should be screened because risk of cerebral injury occurs if this condition, which can be compensated in healthy newborns with having adequate endogenous sources, prolongs or recurs (2, 3).

The frequency of hypoglycemia may vary by the group screened, the measurement method, and the threshold value used. For example, the frequency increases to 80% in large-for-gestational-age (LGA) babies at different hypoglycemia values (4). Therefore, screening of babies who carry a risk is important. In addition, currently, the frequency has increased because of reasons including problems related to gestational diabetes screening, increase in late preterm and early term deliveries, preference for cesarean section, and delayed breastfeeding.

Fetal glucose metabolism

In fetal life, glucose is derived from the mother and is transferred from the placenta by way of facilitated diffusion. The plasma glucose concentration is generally 70-80% of the maternal venous plasma glucose level. The mean glucose use is approximately 4-6 mg/kg/min in term babies and about 8-9 mg/kg/min in fetuses in the early gestational weeks and in preterm babies (5). Insulin and glucagon do not cross the placenta. The fetal insulin levels increase towards term and the glucagon level stays low. In fetal life, an increased insulin/glucagon ratio suppresses lipolysis and leads to glycogen storage and glycogen stores become sufficient in the 3rd trimester. Gluconeogenesis and glycogenolysis are inactive unless severe fasting develops in the mother. Insulin is involved in growth rather than glucose metabolism in fetal life.

Postnatal glucose metabolism

With birth, transition to intermittent enteral feeding and a change in the energy source occur instead of glucose being provided from the mother in intrauterine life. After delivery, insulin is suppressed and glucagon and epinephrine increase. Thus, glucose secretion from glycogen and stimulation of enzymes for gluconeogenesis are provided. The body tries to keep the blood glucose level constant by way of activated gluconeogenesis (glucose synthesis from lactate, glycerol, and amino acids). If early feeding is enabled, glycogenolysis and gluconeogenesis are not required. If feeding cannot be provided, glycogenolysis activated, but the stores are depleted at the end of a 6-12–hour period.

Ketone bodies are alternative energy sources in the newborn and the brain can use ketone bodies as fuel. This is important in terms of protection of neurologic functions. Blood glucose levels are lower and the rate of ketone bodies is higher in babies who are breastfed compared with babies who are fed with formula (6). In preterm babies, the gluconeogenesis and ketogenesis pathways are relatively immature in addition to the insufficient glycogen and fat stores.

Transient neonatal hypoglycemia

With clamping of the umbilical cord, glucose transfer is discontinued, but suppression of insulin cannot be provided fully. The reason for this is the fact that the glucose level required to suppress insulin secretion is lower in newborns. Fetal insulin, which continues to be secreted, causes a reduction in blood glucose in the first hours of life. In healthy newborns, the blood glucose value reaches its lowest levels in the 2nd hour after birth. It may take 2-3 days (frequently, 24-48 hours) for the blood glucose value to reach normal levels (70-100 mg/dL); this is known as transient neonatal hypoglycemia (7). Transient neonatal hypoglycemia is hypoketotic hypoglycemia because suppressed insulin also prevents the formation of ketone bodies (8, 9). Transient hypoglycemia can be compensated by way of endogenous sources in healthy and well-nourished newborns and hypoglycemia screening is not needed in these newborns.

Babies who are at risk for hypoglycemia and who should be screened

These babies have a delayed normal metabolic adaptation process after birth and they may develop hypoglycemia. Causes belonging to the mother and baby are helpful in defining these babies and these are called risk factors.

Risk factors in neonatal hypoglycemia

- **Maternal risk factors**
  - Pregestational or gestational diabetes
  - Preeclampsia/eclampsia, gestation-related hypertension
  - Medical treatment (β-blockers, oral hypoglycemic agents, β-agonist tocolytics, late antepartum and intrapartum dextrose)

- **Risk factors belonging to the baby**
  - Prematurity
  - Intrauterine growth retardation
  - LGA or small-for-gestational-age babies (low birth weight for gestational week-SGA)
  - Postmaturity
  - Perinatal asphyxia, meconium aspiration syndrome (MAS)
  - Infection
  - Polycythemia
  - Hypothermia
  - Drug usage (IV indomethacin)
  - Immune hemolytic disease (Rh incompatibility)
  - Congenital heart diseases
  - Endocrine disorders
  - Special feature on physical examination findings
  - History of sibling with hypoglycemia
  - Malnutrition

Screening time and period in babies at risk

In babies who are at risk, 80% of hypoglycemias were observed in the first 24 hours and 19% were observed in the first 24-48 hours. In 37% of these babies, a hypoglycemia attack was found subsequently, although the first three measurements were found to be normal (10). It has been reported that a single blood sample may be sufficient to exclude subsequent hypoglycemia in 50% of LGA babies, which means that the initial values are more valuable in predicting hypoglycemia, whereas early glucose levels are less reliable in predicting subsequent hypoglycemia in SGA babies (11). Low sensitivity and specificity of the initial measurements in terms of hypoglycemia suggest that the initial blood glucose levels, which are normal initially, may decrease subsequently in SGA babies and therefore, screening should be continued for a longer period.

Table 1. Management protocol (AAP) in the first 24 hours in newborns at risk of hypoglycemia (late preterm, term SGA, infant of diabetic mother, LGA above 34 weeks) (12)

Screening and Treatment for Postnatal Glucose Homeostasis in Late Preterm, Term SGA, Infant of Diabetic Mother and LGA Newborns

Late preterm (34-36 6/7) and SGA newborns (screening 0-24 hours)
Infants of Diabetic Mothers and LGA (>34 weeks) newborns (screening 0-12 hours)

Symptomatic and <40 mg/dL → IV glucose			
ASYMPTOMATIC			
0-4 hours		4-24 hours	
FEED IN THE FIRST HOUR Measure blood glucose 30 minutes after first feeding		Continue feeding with intervals of 2-3 hours Measure blood glucose before each feeding	
Initial blood glucose <25 mg/dL		Blood glucose <35 mg/dL	
Feed and check in one hour		Feed and check in one hour	
<25 mg/dL ↓ IV glucose*	25-40 mg/dL ↓ Feed again/ IV glucose if needed	<35 mg/dL ↓ IV glucose*	35-45 mg/dL ↓ Feed again/ IV glucose if needed
Target blood glucose before routine feeding >45 mg/dL *Blood glucose =200 mg/kg (2 mL/kg 10% dextrose) and/ or infusion rate 5-8 mg/kg/min (80-100 mg/kg/day). Reach a blood glucose level of 40-50 mg/dL			
Symptoms: Irritability, tremor, jitteriness, exaggerated Moro reflex, high-pitched cry, convulsion, hypotonia, lethargy, cyanosis, apnea, feeding difficulty			

Original table should be added (ref. 12)

In a baby who has been fed in the first hour after birth, the blood glucose level should be measured 30 minutes later and one should comply with the recommendations of the American Academy of Pediatrics (AAP) (Table 1) (12). If normoglycemic values are obtained, the measurement should be repeated with intervals of 2-3 hours before feeding. Screening can be terminated if the values obtained in a screening time of 12 hours are normal in LGA babies and if the values obtained in a screening time of 24 hours are normal in SGA babies.

Methods of glucose measurement and influencing factors

Bedside test strips can be used with the objective of screening hypoglycemia in babies at risk. In the bedside glucose measurement test, the peroxidase method is used frequently. This method is inexpensive and practical, but shows a marked difference compared with the actual blood glucose levels and is not reliable, especially at low glucose concentrations (13). If the peroxidase method has been performed using bedside test strips for screening, the diagnosis should be confirmed with a measurement performed with glucose oxidase, dehydrogenase or hexokinase methods in the laboratory when values close to the threshold value are obtained. However, treatment should be initiated immediately without waiting for the test result after sending a blood sample to the laboratory if the level measured in screening is at the threshold value for treatment. The hexokinase method is the gold standard in the diagnosis of hypoglycemia, but it is not applicable as a screening method because of its long process time. A faster result can be obtained with the oxidase method, but there should be no problem related to oxygenation in the baby in order to use this measurement method. The disadvantages for this method include blood loss, which may occur as a result of obtaining blood, the need for repeating blood sampling, and repeated sampling.

It should be stated from which site the blood sample was taken because the site of blood sampling may also affect the result as well as the measurement method. For example, whole blood glucose levels are 10-15% lower compared with plasma glucose levels. Glucose concentrations in arterial blood samples are slightly higher compared with venous and capillary blood samples. The presence of capillary stasis and alcohol applied to the skin also affect the result in addition to increased hematocrit, bilirubin, and triglycerides in the blood. Warming the heel before blood sampling eliminates the possibility of obtaining lower venous glucose concentrations because of stasis and facilitates the procedure of blood sampling. In addition, it should be kept in mind that the glucose level may reduce in relation to metabolization of glucose by the erythrocytes in the sample if whole blood is kept at room temperature. Although the reduction rate is frequently accepted to be 5-6 mg/dL/hour, it has been reported that it may increase up to 20 mg/dL/hour (13, 14). In order to prevent this, samples should be placed in tubes containing fluoride or kept in ice if they are not going to be studied immediately.

Continuous subcutaneous glucose monitoring systems can be used with the objective of reducing the number of blood sampling procedures in very small preterms, especially under intensive care conditions (15, 16). It provides more detailed information by showing real-time variance trends in the blood glucose. Its disadvantages include low reliability at low blood glucose levels and the need for calibration four times daily.

Causes in neonatal hypoglycemia

In newborns, hypoglycemia has two main causes; reduction in glucose production or an increase in glucose consumption. The reduction in glucose production is related to limited glycogen stores and insufficient gluconeogenesis. Increased consumption is related to increased insulin or anaerobic glycolysis. In some cases, multiple mechanisms may be involved. For example, an increase in glucose requirement may be involved because of a low gluconeogenic rate, perinatal hypoxia, and relatively large brain in addition to an increase in glycogen consumption in hypoglycemia observed in intrauterine growth retardation (IUGR).

In newborns, an increase in insulin may be responsible for hypoglycemia in transient hypoglycemia as well as permanent hypoglycemia, especially in SGA babies (7). The frequency of hyperinsulinemia in SGA babies with hypoglycemia ranges between 10% and 94% (17). The frequency of hyperinsulinemia in permanent hypoglycemia varies from country to country (between 1/2500 and 1/50,000) (18). Although the exact frequency in our country is not known, a higher frequency may be expected because the frequency of consanguineous marriage is about 20-25%.

Symptoms of hypoglycemia in newborns

Hypoglycemic newborns are frequently asymptomatic. Associated symptoms are mostly related to neuroglycopenia and autonomic nervous system activation and screening and immediate treatment of hypoglycemia in symptomatic babies is important in terms of preventing a neurologic injury process because the presence of symptoms may indicate poor neurodevelopmental prognosis. However, most newborns stay asymptomatic with very low blood glucose levels, while some others may be symptomatic with similar or higher blood glucose levels when compared with asymptomatic babies. In preterm babies, symptoms may not be observed or may be masked. In addition, the fact that symptoms are not specific for hypoglycemia renders association with hypoglycemia difficult. When evaluating if symptoms are associated with hypoglycemia, disappearance of symptoms when the blood glucose is normalized may be helpful and this is named the Whipple triad (19).

Hypoglycemia symptoms
- Lethargy
- Irritability
- Jitteriness
- Coma, convulsion, hypotonia
- Poor suck
- Tachypnea
- Apnea
- Bradycardia
- Cyanosis
- Paleness
- Hypothermia
- A high-pitched voice cry
- Abnormal eye movements

Relationship between the presence of symptoms and hypoglycemic injury

Hypoglycemia is not manifested clinically if alternative sources can be used immediately after the blood glucose is reduced. This stage is called the appropriate metabolic adaptation and biochemical hypoglycemia stage (1st stage). If the blood glucose is not corrected, non-specific findings including lethargy and irritability occur because alternative sources will be consumed. At this stage metabolic adaptation is impaired (2nd stage) and permanent damage does not occur if intervention can be performed. However, at the 3rd stage in which metabolic adaptation does not exist, severe clinical findings including coma and convulsion occur if hypoglycemia continues (20). In conclusion, presence of neurologic symptoms in a hypoglycemic newborn shows that metabolic adaptation cannot be provided and there is a potential for injury. Therefore, hypoglycemia in symptomatic newborns should be corrected rapidly.

In a study in which the relation of presence of symptoms with neurodevelopmental outcomes was investigated, hemorrhage and infarction were found with a rate of 94% (48% cortical, 42% basal ganglia) on magnetic resonance imaging (MRI) performed on the 8th day in symptomatic term babies 60% of whom had symptomatic transient hypoglycemia. Impairment of cognitive functions and an increased frequency of epilepsy were observed at the age of two years in 65% of the subjects (21).

Relationship of hypoglycemia with neurodevelopmental disorder

Glucose is an essential fuel for brain metabolism. Many mechanisms including changes in cellular energy characteristics, activation of N-methyl-D-aspartate (NMDA) receptors, increased production of free radicals, and apoptosis have been proposed to be involved in cellular injury triggered by hypoglycemia (21, 22). However, hypoglycemic cerebral injury should be addressed as a multifactorial condition. These factors include cerebral blood flow, cerebral glucose use, and the presence of alternative substrates including lactate and ketone (5, 12, 21, 23, 24). Therefore, hypoglycemia may cause greater harm in conditions including hypoxic ischemic encephalopathy in which cerebral blood flow and glucose supply decrease. In favor of this, low pH in the cord blood, application of resuscitation, intubation, and low Apgar score in hypoglycemic babies have been defined as independent variables in terms of poor neurologic outcomes (25). In addition, there are studies supporting that hypoglycemia accompanying neonatal encephalopathy contributes to poor motor and cognitive outcomes (26, 27). It has been reported that maturation and growth status might also be effective in terms of outcomes, as well as prolonged or recurrent hypoglycemia (2, 3, 28). In a study conducted with 661 preterm babies with a gestational age below 32 weeks, the period of hypoglycemia and recurring hypoglycemia (<47 mg/dL) showed a strong correlation with reduced motor and mental development scores in the 18th month when other confounding factors were corrected (2). Less severe, but recurring hypoglycemia attacks may be more important compared with a severe and single hypoglycemic attack in terms of long-term negative effects. Developmental scores were found to be lower at the age of 3.5 and 5 years in babies who had recurrent hypoglycemia in the neonatal period when compared with babies who had a single and severe hypoglycemic attack (3). In the LOLLIPOP study, factors that influenced outcomes in hypoglycemic preterm babies who had a gestational age of 32-36 weeks were investigated and it was shown that hypoglycemia in the neonatal period was associated with delayed development at the age of four years; the effective factors in the multiple variance analysis included hypoglycemia and SGA, and hypoglycemia was still effective when SGA was excluded (28).

However, the relationship between hypoglycemia level and injury risk is still not clearly understood. In one study, the newborns born between 1990 and 1991 with a gestational age below 32 weeks whose hypoglycemia lasted for three days or longer (<45 mg/dL) were compared with the babies matched in terms of hospital care, gestational age, and birth weight who did not have hypoglycemia at the age of 2 and 15 years and no difference was found between the two groups in terms of developmental and physical disability (29). In another large-scale study involving preterm, late preterm, and term babies published recently, it was reported that academic performance at the age of 10 years was poorer in babies who had early

transient hypoglycemia compared with normoglycemic babies when perinatal factors were adjusted (30).

Management of hypoglycemic newborn

The Endocrine Society recommends that the blood glucose level should be maintained in the first 48 hours and etiologic investigations should be performed later because it would be difficult to differentiate neonatal transient hypoglycemia, which is frequently observed in the first 48 hours and does not require investigation, from non-transient hypoglycemia, which requires further investigations and treatment (7). Therefore, management in the first 48 hours in babies at risk should involve early feeding (especially breastfeeding) and close monitoring in terms of hypoglycemia symptoms. Early feeding in the first hours of life enables appropriate maintenance of blood glucose during transfer from the fetal period to the neonatal period, and recognition of symptoms is essential for injury prevention with appropriate interventions.

Although the amount and carbohydrate content of the colostrum secreted in the first days of life is limited, its fat content is high and ketones are formed through demolition of fatty acids contained in the colostrum. Ketones are an alternative fuel for the neonatal brain during fasting or hypoglycemia and protects the brain from the harms of hypoglycemia. In a study in which metabolic adaptation responses in the first weeks of life were compared between term babies and preterm babies with a gestational age of 31 weeks, it was shown that the concentrations of ketone bodies were lower in preterm babies compared with term babies (31). When babies who were breastfed were compared with babies who were fed with formula in this study, it was found that the blood glucose level was lower in babies who were breastfed, but ketone bodies showed a negative correlation with blood glucose. This correlation is prominent on the 2nd and 3rd days of life; in this period, which is critical in terms of hypoglycemia, breastfeeding is more appropriate in terms of metabolic adaptation of the newborn. Therefore, special effort should be made to enable early feeding and breastfeeding in all babies independent of the presence of the risk for hypoglycemia.

In the early postnatal period, babies should be protected against the harmful effects of hypoglycemia as well as unnecessary investigations and treatment. It may cause to separate the baby from the mother with an unnecessary evaluation and this may cause disruption of adaptation that could be provided with breastmilk, changing to formula feeding, opening vascular access, and unnecessary hospitalization of the baby. In a Cochrane meta-analysis in which two studies were evaluated, it was reported that use of 40% dextrose gel in the treatment of newborns with hypoglycemia prevented separation of the baby from the mother, and when compared with placebo gel, increased the rate of breastfeeding after discharge (32). Evidence related to its adverse effects in the neonatal period or at the adjusted age of two years has not been found and it has been reported that it might be recommended for the first-line treatment of hypoglycemia (33). However, it is not yet available in Turkey. The therapeutic efficacy and preventive efficiency of the use of dextrose gel was investigated and it was shown that its use in the first hour after birth in babies at risk (0.5 mL/kg or 200 mg/kg) prevented neonatal hypoglycemia and intensive care unit admissions (34, 35).

Operational threshold value and target values which are desired to be achieved with treatment

In recent years, the phenomenon of the "operational threshold value" has been emphasized in relation with hypoglycemia treatment (1). The operational threshold value is defined as the whole blood or plasma glucose concentration at which intervention should be performed because of the possibility of neurologic injury in view of the present evidence, and this value is somewhere between the level that is thought to lead to organ injury and the target level desired. The operational threshold value is a value used to determine the need for intervention. It has no diagnostic importance, nor is it predictive for negative neurologic sequelae.

The definition of clinically important hypoglycemia continues to be one of the most complicated and controversial issues in newborns (1). Although there is no consensus, a threshold value of 47 mg/dL has been widely accepted. In a prospective cohort study (the CHYLD study), it was reported that keeping the blood glucose level above 47 mg/dL in hypoglycemic (blood glucose <47 mg/dL) term and late preterm babies (n=2.16) did not lead to neurodevelopmental impairment at the age of two years (36).

However, it is also not clear at which value neurologic injury and permanent brain damage can develop and which method is the best. A consensus related with the definition of neonatal hypoglycemia has not been made, either (37). Evidence has been obtained from cohort and case control studies and this decreases the strength of the evidence.

It is not possible to apply a single threshold value for all babies (38). As mentioned before, it may vary depending

on individual values, adaptation response, contributing factors, and underlying pathologies. However, in light of current information, each neonatal intensive care unit must have an management and treatment protocol specified for babies with a risk of hypoglycemia and for babies with permanent hypoglycemia. This protocol should also include operational threshold values and target values. The recommendations of the AAP and the Pediatric Endocrinology Society (PES) may be considered in specifying this protocol (9, 12).

The recommendations of the AAP for the threshold and target values in the first 24 hours for babies at risk are shown in the table below (Table 1). As can be seen in the table, the management and the threshold and target values used in treatment in the first 24 hours for babies at risk vary depending on the presence or absence of symptoms. The operational threshold value in the first 24 hours is 40 mg/dL if the baby is symptomatic, whereas it is 25 mg/dL in the first 4 hours and 35 mg/dL between the 4th and 24th hours if the baby is asymptomatic. The AAP recommends that babies at risk should be fed in the first 1 hour and the blood glucose level should be measured 30 minutes later; feeding should be repeated, if the blood glucose level is below 25 mg/dL in the first measurement, and intravenous treatment should be initiated if the blood glucose level is below 25 mg/dL in the second measurement. Feeding should be repeated once again if the first measurement shows a value between 25 and 40 mg/dL and intravenous treatment should be initiated if it does not increase on the follow-up measurement. In the postnatal 4-24 hours, it is recommended that feeding should be enabled with intervals of 2-3 hours, and feeding should be repeated if the first measurement shows a value below 35 mg/dL before feeding; a follow-up measurement should be performed in 1 hour and intravenous treatment should be initiated if the follow-up measurements persist below 35 mg/dL. Feeding should be repeated if it is between 35 and 45 mg/dL and intravenous treatment should be initiated if it persists at the same level.

Although the management of the AAP for the first 24 hours is specified in detail, it is only recommended that the blood glucose level should be kept above 45 mg/dL for babies aged 24-48 hours. According to the PES, studies conducted with children and adults have indicated a neuroglycopenic threshold value of approximately 50 mg/dL (in terms of brain function impairment) and the same threshold value should be used independent of the postnatal age because the condition may be similar in newborns. In light of these recommendations, the following operational threshold and target values can be used in babies at risk of hypoglycemia and in babies with permanent hypoglycemia.

Operational threshold values

- In asymptomatic babies, a blood glucose level of 25 mg/dL despite feeding in the postnatal 4 hours, 35 mg/dL in the 4-24-hour interval and below 50 mg/dL after the 24th hour.
- In symptomatic babies, 40 mg/dL in the first 24 hours and below 50 mg/dL after the 24th hour.

Target values (values desired to be achieved with treatment):

- 50 mg/dL in the postnatal first 48 hours before feeding, 60 mg/dL after the 48th hour for babies at risk, above 70 mg/dL in patients with permanent hypoglycemia.

Intravenous treatment in hypoglycemia

Intravenous treatment should be initiated in subjects with a blood glucose level below the threshold value and in subjects in whom the blood glucose level cannot be elevated with feeding or in the presence of symptoms associated with hypoglycemia. Even if intravenous treatment is initiated, feeding should not be omitted and it should be kept in mind that enteral nutrition could enable a more balanced increase in blood glucose levels. Although follow-up measurements following treatment initiation or adjustment of treatment can be performed with bedside measurement method (whole blood glucose), measurements should be confirmed with laboratory methods when a treatment decision or treatment adjustment is required. It should be stated what method was used for measurement.

In the presence of symptoms, intravenous glucose treatment is administered as a mini bolus of 10% dextrose at a dose of 2 mL/kg (200 mg/kg) with the accompaniment of an infusion of 6-8 mg/kg/min. If no symptoms accompany, intravenous infusion alone is sufficient. The blood glucose level should be measured 30 minutes after initiation of intravenous treatment and it should be checked if the target level has been reached. In a baby who receiving a glucose infusion, the glucose infusion rate should be increased such that it is 2 mg/kg/min if no symptoms accompany, but if the target level has not been achieved, the measurement should be repeated 30 minutes later. The glucose infusion rate should be increased by 2 mg/kg/min each time until the target level is achieved. When the target level is reached, the next measurement should be performed 4-6 hours later (4 hours later if the baby is fed with intervals of 2 hours; 6 hours later if the baby is fed with intervals of 3 hours) and before feeding.

Table 2. Drugs used in additional treatment

Drug name	Action	Dosage	Preference	Adverse effect(s)
Glucagon (mcg/kg)	Glycogenolysis	200 mcg/kg 1 mg/day	Diagnosis of hyperinsulinism	Hyponatremia Platelet
Diazoxide (mg/kg)	Insulin	5-20	First-line option in treatment of hyperinsulinism	Fluid load Hirsutism Nausea, vomiting
Octreotide (mcg/kg)	Insulin	5-10	Hyperinsulinism treatment	Growth retardation
Hydrocortisone (mg/kg)	Peripheral glucose Gluconeogenesis	5-15	Adrenal failure Limited (1-2 days) use	Hypertension Slowdown in growth

Infusion should not be discontinued suddenly or should not be reduced rapidly. If the blood glucose level is maintained about the target level at the infusion rate used, one should begin to reduce the infusion rate by 2 mg/kg/min in babies who can be fed. If the infusion rate is reduced, the blood glucose level should be measured 30 minutes later and if the level is at the target value, the measurement should be repeated 4 or 6 hours later depending on the feeding status. If the second measurement also shows a value at about the target value, one should continue to reduce the infusion rate (by 2 mg/kg/min). In babies who can be fed, infusion can also be terminated if the glucose infusion rate is reduced to 3-5 mg/kg/min. Increments and decrements in the infusion rate should be performed gradually as mentioned; rapid reductions or discontinuation should be avoided. Babies can be discharged if the plasma glucose levels measured with intervals of 4-6 hours and 2 consecutive measurements before feeding are found to be at target levels in hypoglycemic babies in the risk group after the infusion is discontinued and if the blood glucose levels are >60 mg/dL following a 6-hour fasting period in babies with permanent, severe or prolonged hypoglycemia (7).

When should further investigations be performed in hypoglycemia?

In presence of the following conditions, diagnostic investigations should be performed in terms of permanent hypoglycemia. However, investigations should be performed after the 48th hour.

- Inability to maintain the blood glucose level above 50 mg/dL in the first 48 hours and above 60 mg/dL after 48 hours
- Presence of severe, resistant or prolonged hypoglycemia
- Positive familial history of congenital hypoglycemia
- Presence of dysmorphic findings (syndromic hypoglycemias)

Severe hypoglycemia: Hypoglycemia accompanied by symptoms.

Resistant hypoglycemia: Hypoglycemia for which high glucose infusion is needed. It is recommended to measure the insulin level if glucose requirement is above 8 mg/kg/min for 24 hours (39). If the requirement is at higher levels, the performance of other investigations in terms of differential diagnosis should be discussed.

Prolonged hypoglycemia: Prolonged hypoglycemia can be defined as continuance of hypoglycemia after the 5-7th day. Prolonged hypoglycemia may be transient or permanent. In the transient type, hypoglycemia may last for a long time but completely recovers subsequently. For example, hypoglycemia observed in SGA babies may last for months and additional treatment may be needed besides glucose infusion, but it is transient (40, 41). Hypoglycemia that lasts for a long time, that does not recover spontaneously and which requires additional treatment besides intravenous glucose is named permanent hypoglycemia (for example, cases of congenital hyperinsulinism). In such cases, a differential diagnosis of hypoglycemia, and a decision for additional treatment and follow-up of the baby should be planned in collaboration with the division of pediatric endocrinology. The list of drugs to be used, if additional treatment is needed, is shown in the following table (Table 2).

Syndromic hypoglycemias: Syndromic hypoglycemias should be considered, if dysmorphic findings accompany hypoglycemia. Some of these syndromes are listed below:

Beckwith-Wiedemann syndrome,

- Costello syndrome,
- Timothy syndrome,
- Kabuki make-up syndrome,
- Ondine syndrome.

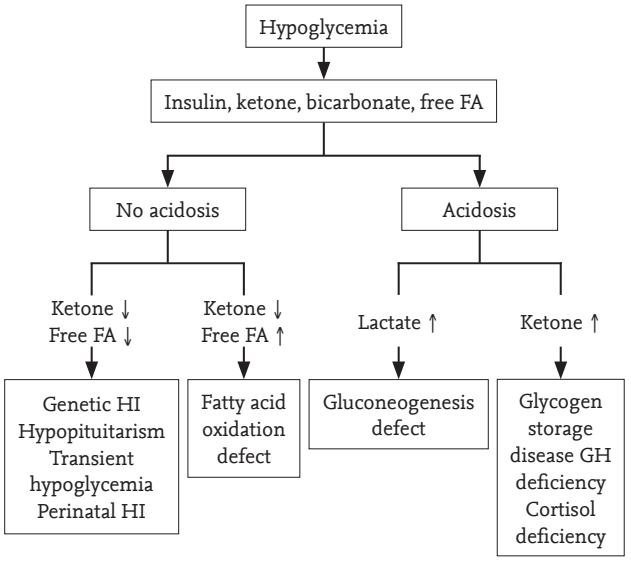

Figure 1. Diagnostic approach in nontransient hypoglycemia (9)
HI: hyperinsulinism; FA: fatty acids

Laboratory tests to be performed in terms of differential diagnosis and drugs used in additional treatment

Blood samples for laboratory tests to be performed in terms of differential diagnosis should be obtained during hypoglycemia. Blood sample can be obtained following a 6-hour fasting period in babies who are being fed enterally and at any time when the plasma glucose level is below 50 mg/dL in babies who are given parenteral glucose infusion.

In the differential diagnosis, insulin, blood gases, lactate and pyruvate levels, beta hydroxypiruvate and/or acetoacetate levels, ammonia, plasma free fatty acids, blood/urine amino acids, acylcarnitine levels, cortisol, C peptide, and urinary organic acid levels are helpful in addition to blood glucose. The Pediatric Endocrinology Association's flow chart for the diagnostic approach is shown in Figure 1 (9). A genetic examination may be needed additionally in permanent and syndromic hypoglycemias.

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