



Neonatal Hyperglycemia, which threshold value, diagnostic approach and treatment?: Turkish Neonatal and Pediatric Endocrinology and Diabetes Societies consensus report

Yenidoğan hiperglisemisi, hangi eşik değeri, tanısal yaklaşım ve tedavi?: Türk Neonatoloji ve Çocuk Endokrinoloji ve Diyabet Dernekleri uzlaşısı raporu

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Cite this article as: Gökşen Şimşek D, Ecevit A, Hatipoğlu N, et al. Neonatal Hyperglycemia, which threshold value, diagnostic approach and treatment?: Turkish Neonatal and Pediatric Endocrinology and Diabetes Societies consensus report. *Turk Pediatri Ars* 2018; 53(Suppl 1): S234-S238.

Abstract

Hyperglycemia has become an important risk factor for mortality and morbidity in the neonatal period, especially with increased survival rates of very low birth weight neonates. Hyperglycemia in the neonatal period develops as a result of various mechanisms including iatrogenic causes, inability to suppress hepatic glucose production, insulin resistance or glucose intolerance, specifically in preterm neonates. Initiation of parenteral or enteral feeding in the early period in preterm babies increases insulin production and sensitivity. The plasma glucose is targeted to be kept between 70 and 150 mg/dL in the newborn baby. While a blood glucose value above 150 mg/dL is defined as hyperglycemia, blood glucose values measured with an interval of 4 hours of >180-200 mg/dL and +2 glucosuria require treatment. Although glucose infusion rate is reduced in treatment, use of insulin is recommended, if two blood glucose values measured with an interval of 4 hours are >250 mg/dL and glucosuria is present in two separate urine samples.

Keywords: Glucosuria, hyperglycemia, newborn, preterm, Very low birth weight baby

Öz

Yenidoğan döneminde özellikle çok düşük doğum ağırlıklı bebeklerin yaşamda kalmaya başlamaları ile birlikte, hiperglisemi morbidite ve mortalite için önemli bir risk etmeni olmuştur. Yenidoğan döneminde özellikle preterm bebeklerde hiperglisemi, iyatrojenik nedenler, karaciğerde glukoz üretiminin baskılanmaması, insülin direnci ya da glukoz intoleransı gibi mekanizmalar sonucu gelişmektedir. Preterm bebeklerin erken dönemde parenteral ya da enteral beslenmeye başlanması; insülin yapımını ve duyarlılığını artırır. Yenidoğan bebekte kan şekerinin 70-150 mg/dL arasında olması hedeflenmektedir. Kan şekeri düzeyi >150 mg/dL olması hiperglisemi olarak tanımlanırken; 4 saat ara ile bakılan kan şekerinin >180-200 mg/dL olması ve +2 glukozüri olması tedaviyi gerektirmektedir. Tedavide glukoz infüzyon hızı azaltılmasına rağmen; 4 saat ara ile bakılan 2 kan şekeri değeri >250 mg/dL ve alınan iki ayrı idrar örneğinde glukozüri varsa insülin kullanılması önerilmektedir.

Anahtar sözcükler: Aşırı düşük doğum ağırlıklı bebek, glukozüri, hiperglisemi, preterm, yenidoğan

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DOI: 10.5152/TurkPediatriArs.2018.01821

Glucose balance in the neonatal period

In early postnatal period, newborn infants provide to maintain glucose homeostasis via glycogenolysis and gluconeogenesis. It is important for the central nervous system just after birth. In very-low-birth-weight (VLBW) neonates and preterms, the balance is impaired when a limited reserve is combined with the increased energy requirement of the newborn. In this period, the frequency of hypoglycemia is increased, but hyperglycemia is not rare. Hyperglycemia develops as a result of the inability of the newborn to decrease endogenous glucose production during parenteral glucose infusion or the inability to increase peripheral glucose use (1, 2).

Definition and follow-up

Although there is no consensus about the safe range of glucose concentration, a blood glucose level of 70-150 mg/dL is targeted. In newborn babies, a blood glucose level above 150 mg/dL is defined as hyperglycemia (3). In the follow-up of VLBW neonates, hyperglycemia is associated with intracranial hemorrhage, stage 2/3 necrotizing enterocolitis (NEC), increased risk for sepsis, retinopathy of prematurity (ROP), conditions where stress load is increased, surgical interventions, ventilator treatment, growth retardation, and increased mortality. Severe hyperglycemia in the early period in VLBW neonates is an independent risk factor for increased mortality. Hyperglycemia should be prevented in all newborn babies. However, there is no established blood glucose level for the development of these outcomes. Although values including 150 -154 -180 -220 mg/dL have been specified in various studies, it has been reported that serious outcomes would develop with long-term increased blood glucose levels (4). Persisting hyperglycemia, which develops suddenly in the absence a change in infusion rate frequently is the result of sepsis or endocrine problems in the neonatal period (4).

In preterm and VLBW babies, a blood glucose level of >180-200 mg/dL indicates the presence of a problem, but clinically important hyperglycemia is defined as osmotic diuresis and glucosuria. It has been reported that it is more important to monitor the blood glucose level in association with monitoring of development of osmotic diuresis, rather than monitoring the blood glucose level alone. In clinical practice, the presence of glucosuria (>1% glucosuria) (1000 mg/dL) is defined as the marker of osmolarity change, which necessitates close glucose monitoring (2).

A blood glucose level measured as >180-200 mg/dL with a 4-hour interval and glucosuria of +2 necessitates treatment.

Causes of hyperglycemia (1-16):

1. Iatrogenic hyperglycemia: Erroneous calculation of intravenous (IV) fluids may lead to hyperglycemia. Parenteral glucose treatment is administered in neonatal intensive care units (NICUs) in preterm babies (long-term in small preterms) and ill term-newborns because of delayed enteral feeding. This may generally create a risk in terms of hyperglycemia in newborns and iatrogenic hyperglycemia may take time. The initiation of glucose infusion at a dosage of 4-6 mg/kg/min on the first day with the objective of preventing hypoglycemia in preterms or in all ill newborns protects babies from hypoglycemia and potential hyperglycemia.

2. Inability to metabolize glucose: Hyperglycemia may be related to prematurity. In very young infants who often receive total parenteral nutrition, hyperglycemia may develop secondary to glucose intolerance or secondary to sepsis and stress.

3. Impaired glucose homeostasis: VLBW neonates (<1000 g) have increased fluid requirement because of underdeveloped renal function and excessive insensible fluid loss. Therefore, giving excessive glucose in association with high volume fluid may lead to hyperglycemia in these neonates. In addition, these neonates have insulin resistance and delayed insulin response. Even in the absence of a high glucose infusion rate, hyperglycemia may be observed because of inadequate insulin secretion and inability to suppress glucose production in the liver. In addition, impaired glucose homeostasis may lead to transient hyperglycemia in "small-for-gestational-age" (SGA) babies.

4. Giving hyperosmolar formula: Hyperosmolarity may develop as a result of preparing formula with less water than needed. This may lead to transient neonatal glucose intolerance in the baby. Severe dehydration, hypernatremia, and hyperglycemia may develop in relation to gastroenteritis.

5. Convulsions: Hyperglycemia may develop due to catecholamine secretion.

6. 46, XXDq deletion of chromosome 13: Hyperglycemia may be observed.

7. Lipid infusion: Hyperglycemia may develop even if the rate of glucose administration is low in infants receiving lipid infusions. Increased plasma free fatty acid concentration may lead to hyperglycemic response which in turn inhibits the peripheral use of glucose and inhibit the effects of insulin.

8. Protein intake in the early period: Early protein intake influences the release of insulin-like growth factor-1 (IGF 1). IGF 1 lowers blood glucose by increasing the use of peripheral glucose, increasing glycogen synthesis and suppressing hepatic glucose production. Relative insulin deficiency in the preterm infant causes a low level of IGF 1, which prevents the development of pancreas and beta cells and develops hyperglycemia.

9. Sepsis: If hyperglycemia develops in normoglycemic and clinically stable neonates without a change in glucose infusion rate, the possibility of sepsis and NEC should be considered.

10. Stress: Conditions including pain, hypoxia, and respiratory distress cause hyperglycemia secondary to increased cortisol and catecholamine levels in the neonates. The blood glucose level may increase after surgical procedures.

11. Drugs: Maternal use of diazoxide and neonatal use of caffeine, steroids, and phenytoin may lead to hyperglycemia.

12. Diabetes mellitus in newborns

Diagnostic approach

Physical examination:

There are no significant, specific findings related to hyperglycemia. Physical examination may reveal signs of sepsis such as temperature instability and peripheral perfusion.

Laboratory:

1. Serum glucose level: Measurements with “dextrostix” have a high probability of yielding erroneous results. Serum glucose level must be measured before starting treatment.

Which method should be used to measure the blood glucose level in the neonatal period?

ASPEN recommends the use of venous blood glucose measurements rather than capillary blood glucose measurement because capillary blood indicates the level in whole blood, which is 15% lower and is influenced by dilution with alcohol and by increased hematocrit value. However, it is appropriate to monitor blood glucose by capillary measurements because it will not be possible to obtain venous blood each time blood glucose measure-

ment is needed in NICUs (15). Continuous glucose measurement (CGM) systems may be used because the number of interventions is high, the risk for hypoglycemia and hyperglycemia cannot be determined, and interim measurements cannot be found with capillary blood glucose measurements. CGM devices are also useful in demonstrating glucose trends other than showing glucose values. (17, 18).

2. Detection of glucose in urine: Glucosuria is a finding of osmotic diuresis. A glucose value of 2+ or higher in the urine increases the risk on osmotic diuresis. Each 18 mg/dL increase in blood glucose increases serum osmolarity by 1 mOsm/L. Normal osmolarity is 280-300 mOsm/L.

3. Complete blood count: Complete blood count is essential for differential diagnosis of sepsis.

4. Serum electrolytes: Hyperglycemia causes electrolyte loss in urine by leading to osmotic diuresis. Electrolyte levels should be monitored in patients with hyperglycemia.

5. Serum insulin level: Serum insulin levels may be low or low-normal in transient diabetes mellitus in newborns.

6. Serum and urine C-peptide levels: These levels are used in the differential diagnosis of monogenic diabetes and Type 1 diabetes.

Treatment

In the treatment of hyperglycemia; reducing the amount of glucose given or initiating insulin therapy or both should be performed together (19).

Most infants who are not fed are initially given 4-6 mg / kg / min iv glucose to maintain normal blood glucose levels. Blood glucose is generally measured every 4-6 hours in these neonates. Testing glucose in each urine enables obtaining less blood tests in neonates with hyperglycemia (19).

1. Positive glucose in urine: When glucosuria is ≥ 1 (+) in urine, there is a risk for osmolarity change. If urine glucose is ≥ 2 (+), the amount of glucose in the IV fluid is reduced by 1-2 mg / kg / min every 2-4 hours to reduce the amount of glucose to 4 mg / kg / min (3).

2. Negative glucose in urine: If glucose is required for calories, high glucose (200 mg / dl) levels are acceptable

as long as there is no glucose excretion or 1+ in urine. Blood glucose and urine glucose should be monitored every 4 to 6 hours with dextrostix.

Currently, treatment of hyperglycemia that does not cause an increase in osmolarity and osmotic diuresis is not supported.

Sepsis should definitely be considered in all babies with hyperglycemia.

- The neonates should be fed immediately if they can be fed.
- Parenteral nutrition with high amino acid content should be initiated in the early period (4)

INSULIN is recommended if blood glucose levels > 250 mg / dl and if glucosuria is present in 2 separate urine samples taken at 4 hours intervals and weight gain is not sufficient despite the reduction of glucose infusion (20, 21).

Bolus insulin therapy is not recommended considering the development of hypoglycemia. Insulin infusion treatment has been defined as appropriate for preterm newborns in Cochrane database and in a randomized, controlled study. Insulin treatment causes an increase in weight as well as controlling hyperglycemia.

Insulin treatment without bolus insulin:

- Insulin infusion at a rate of 0.01-0.05 U/kg/h is initiated.
- Insulin is increased by 0.01 U/kg/h up to a maximum dose of 0.1 U/kg/h.
- The objective is to maintain the blood glucose level between 150 mg/dL and 200 mg/dL
- If the blood glucose level decreases to 180-200 mg/dL, insulin infusion is reduced by 50%.
- If the blood glucose level is <180 mg/dL, insulin infusion is discontinued.
- If the blood glucose level is <150 mg/dL, insulin is discontinued and glucose infusion is increased by 2 mg/kg/min.

The blood glucose level should be measured half an hour after each change in insulin infusion.

If hypoglycemia develops, insulin infusion is discontinued and 2 ml / kg IV bolus is administered with 10% Dx. For rebound hyperglycemia the patient should be monitored (20, 21).

Is insulin infusion necessary to prevent hyperglycemia in the early period?

In a study conducted with continuous glucose measurement devices in VLBW babies, it was reported that subjects who received standard hyperglycemia treatment and early insulin infusion in the early period experienced more hypoglycemia though they were hyperglycemic for a shorter period, NEC and ROP development and growth parameters were similar they developed sepsis at around 28 days; however, mortality was higher and it was stated that there was no need for insulin infusion to prevent hyperglycemia in the early period (16).

Drugs causing hyperglycemia

1. The serum theophylline level should be measured in babies who receive theophylline in terms of toxicity resulting in potential hyperglycemia. If the level is high, theophylline should be discontinued or its dose should be adjusted.
2. Maternal use of diazoxide: this drug may cause hypotension and tachycardia as well as hyperglycemia. Toxicity in babies is self-limiting and rare.
3. Caffeine and phenytoin should be discontinued, if possible.
4. Steroid: their frequency and dose may be decreased.
5. Catecholamines

Hyperosmolarity: Rehydration is necessary. Formula is discontinued if hyperosmolarity is secondary to hyperosmolar formula. Detailed formula use is explained.

In conclusion, in the neonatal period:

- The glucose value should be kept between 70 and 150 mg/dL
- A blood glucose level of >150 mg/dL in term babies should be defined as hyperglycemia
- Early enteral nutrition should be initiated
- Parenteral amino acids should be initiated in the early period to prevent hyperglycemia
- Insulin should be used in persistent hyperglycemia despite decreased glucose infusion rate in newborns receiving parenteral nutrition treatment
- Insulin infusion is not needed in the early period to prevent hyperglycemia.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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