Hypoglycemia in the Newborn

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Abstract

Hypoglycemia in a neonate is defined as blood sugar value below 40 mg/dL. It is commonly associated with a variety of neonatal conditions like prematurity, intrauterine growth restriction, and maternal diabetes. Screening for hypoglycemia in high-risk situations is recommended. Supervised breast-feeding may be an initial treatment option in asymptomatic hypoglycemia. However, symptomatic hypoglycemia should always be treated with a continuous infusion of parenteral dextrose. Neonates needing dextrose infusion rates above 12 mg/kg/min should be investigated for a definite cause of hypoglycemia. Hypoglycemia has been linked to poor neuro-developmental outcome, and hence aggressive screening and treatment is recommended.

Keywords: *Hypoglycemia, Screening, Newborn, Therapy*

Introduction

Hypoglycemia is a common disorder.in neonates.[1] There is, however, no universal definition for this condition.[2] Currently there is insufficient evidence with respect to 'what constitutes hypoglycemia'. The issue is further complicated by the fact that low blood glucose levels (BGLs) are associated with increased cerebral blood flow as a compensatory mechanism. Brain is able to utilize alternative energy substrates to maintain its cerebral energy milieu. Various investigators have empirically recommended different blood glucose levels that should be maintained in neonatal period to prevent injury to the developing brain[3,4] The "normal" range of blood glucose is variable and depends upon factors like birth-weight, gestational age, body stores, feeding status, availability of energy sources as well as the presence or absence of disease.[5,6] Thus, the definition of hypoglycemia should be flexible and encompass all these aspects. Further, there is no concrete evidence to show the causation of adverse long-term outcomes by a particular level or duration of hypoglycemia.[7] Hence, a consensus has been to evolve an "operational threshold".

Definition

The operational threshold for hypoglycemia is defined as *that concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in literature*.[8] This so-called operational threshold values are useful guidelines for clinicians to take appropriate actions. Till proper evidence is generated[9], this value is currently believed to be a blood glucose value of less than 40 mg/dL (plasma glucose less than 45 mg/dL).

Screening for hypoglycemia

Normal blood glucose levels are maintained by glycogenolysis and by gluconeogenesis from a variety of non-carbohydrate energy sources. Neonatal hypoglycemia often occurs in infants with impaired gluconeogenesis, brought about by increased insulin production, altered counter-regulatory hormone production or an inadequate substrate supply.

Screening for hypoglycemia is recommended in high risk infants (Table 1).

Table 1: High risk situations where screening is recommended[10]	
1	Low birth weight infants (<2000 grams)
2	Preterm infants (≤35 weeks)
3	Small for gestational age infants (SGA) : birth weight <10th percentile
4	Infant of diabetic mothers (IDM) - insulin dependent and gestational diabetes
5	Large for gestational age (LGA) infants: birth weight >90th percentile*
6	Infants with Rh-hemolytic disease
7	Infants born to mothers receiving therapy with terbutaline/propranolol/lebatolol/oral hypoglycemic agents
8	Infants with morphological IUGR. This group includes neonates with birth weight between 10th – 25th and possibly up to 50th percentile with features of fetal under-nutrition such as three or more loose skin folds in gluteal region, decreased overall subcutaneous fat, and head circumference to chest circumference difference greater than 3 cm
9	Any sick neonate such as those with perinatal asphyxia, polycythemia, sepsis, shock etc, when they are in active phase of illness. The screening may be discontinued once their condition gets stabilized.
10	Infants on total parenteral nutrition

** LGA infants because of constitutional reasons such as infants of constitutionally large parents may also be exempted from routine screening*

Time schedule for screening

There is a paucity of the literature that looks into optimal timing and the intervals of glucose monitoring. Lowest blood sugar values are seen at 2 hours of life. IDMs frequently experience asymptomatic hypoglycemia very early viz. 1 to 2 hours and rarely beyond 12 hours (range 0.8 to 8.5 h), supporting early screening for this population.[11] However, preterm and SGA may be at risk up to 36 h (range 0.8 to 34.2 h).[12] Some SGA and preterm infants may develop hypoglycemia when feeding is not established. Based on these assumptions and current knowledge, Table 2 elaborates the schedule and frequency of monitoring in different situations

Table 2: Schedule of blood glucose monitoring

	Symptomatology of infants	Time schedule for screening
	At risk neonates (S. No 1-8 in Table 1)	2, 6, 12, 24, 48, and 72 hrs
	Sick infants Sepsis, asphyxia, shock in the active phase of illness	Every 6-8 hrs (individualize as needed)
	Stable VLBW infants on parenteral nutrition	Initial 72 h: every 6 to 8 hrs; after 72 hrs in stable babies: once a day
Infants exhibiting signs compatible with hypoglycemia at any time also need to be investigated.		

Education and counseling of caregivers regarding the screening

Parents should be made aware that their infant is at-risk and therefore requires blood tests at regular intervals. This will ensure appropriate parental participation in monitoring and allay fears if further interventions are required.

When should be screening is stopped

- At risk infants (Table no 1) : At the end of 72 hours.
- In an infant on IV fluids: Has two consecutive values >50 mg/dL on total oral feeds after stopping of the IV fluids.
- Infant whose blood sugar normalized on oral feed: Consider at risk and monitor for 48 hours

Infants in whom screening is not required

Screening for hypoglycemia is not recommended in term healthy breast-fed appropriate-for-gestational age (AGA) infants. However, term infants with poor feeding, presence of inadequate lactation or presence of cold stress may be considered for screening.

Method of Glucose estimation

a. *Bed side reagent strips (Glucose oxidase):* Though widely used and is an important 'point of care' method, glucose estimation by this method is unreliable especially at levels where therapeutic intervention is required such as BGL 40-50 mg/dL. They are useful for

screening purpose but low values should be always confirmed by formal laboratory analysis. However, treatment may be initiated based on the results of the reagent strips. It is important to also consider the variations between capillary and venous, blood and plasma, and immediate and stored samples (whole blood sugar is 10-15% less than the plasma sugar, the glucose levels can fall by 14-18 mg/dL per hour in blood samples that await the analysis).[13] Arterial samples have slightly higher value compared to venous and capillary samples.

The first generation strips focused on change in color of enzyme on application of blood drop. The color can be read by naked eye or more recently by reflectance meters. The readings tend to get affected by hematocrit values, acidosis, presence of bilirubin, presence of edema etc. The newer generation glucose reagent strips generate a current on reaction of glucose with enzymes such glucose oxidase or glucose dehydrogenase. The amount of current is proportional to amount of sugar present in plasma. Though these second generation glucose readers are more accurate than the previous version, they are still not entirely reliable. Any abnormal BGLs by this technique must be confirmed by standard laboratory methods.

b. Laboratory diagnosis: This is the most accurate method. In the laboratory (lab), glucose can be measured by either the *glucose oxidase* (calorimetric) method or by the *glucose electrode method (as used in blood gas & electrolyte analyzer machine)*. Blood samples should be analyzed quickly to avoid erroneously low glucose levels.

Clinical signs associated with hypoglycemia

a. Asymptomatic: It is well known that low BGL may not manifest clinically and be totally asymptomatic. These infants should also be treated in view of the possible adverse long term effects.[14,15] However, there is considerable controversy with regards to if asymptomatic hypoglycemia results in a neuronal damage.

b Symptomatic: Clinical signs of hypoglycemia in order of frequency are stupor, jitteriness, tremors, apathy, episodes of cyanosis, convulsions, intermittent apneic spells or tachypnea, weak and high pitched cry, limpness and lethargy, difficulty in feeding, and eye rolling. Episodes of sweating, sudden pallor, hypothermia and cardiac arrest have also been reported.

Diagnosis

a. Asymptomatic hypoglycemia: It is said to be present when the blood glucose level is less than 40 mg/dl (to be confirmed by laboratory estimation) and the infant does not manifest any clinical features

b. Symptomatic hypoglycemia: This diagnosis should be made if hypoglycemia coexists with clinical symptomatology. Neonates generally present with nonspecific signs that result from a variety of illnesses. Therefore, careful evaluation should be done to look for all possible causes especially those that can be attributed to hypoglycemia.

If clinical signs attributable to hypoglycemia persist despite intravenous glucose, then other causes of persistent / resistant hypoglycemia should be explored.

Management of asymptomatic hypoglycemia

Table 3: Management plan of infants with asymptomatic hypoglycemia on screening	
Blood sugar 20-40 mg/dL	Trial of oral feeds (expressed breast milk or formula) and repeat blood test after 1 hour. If repeat blood sugar is more than 50 mg/dL, two hourly feeds is ensured with 6 hourly monitoring for 48 hrs If repeat blood sugar is <40 mg/dL, IV Dextrose is started and further management is as for symptomatic hypoglycemia
Blood sugar levels <20 mg/dL	IV Dextrose is started at 6 mg/kg/min of glucose;further management is as for symptomatic hypoglycemia

Oral feeds – issues

Direct breast-feeding is the best option for trial of an oral feed. If the infant is unable to suck, expressed breast milk may be used. Breast milk promotes ketogenesis (ketoacids are important alternate sources for the brain along with less important pyruvate, free fatty acids, glycerol, and amino acids). If breast milk is not available, then formula feeds may be given in at-risk neonates. If oral feeds are contraindicated, start glucose infusion.

Some of the randomized clinical trials in SGA[16] and appropriate-for-gestational age[17] infants found that the sugar or sucrose fortified milk (5 g sugar per 100 mL milk) raises blood glucose and prevents hypoglycemia. Such supplementation may be tried in the asymptomatic neonates with blood sugar levels between 20 to 40 mg/dL. However, this practice carries a potential to compromise breast feeding rates, and therefore one should be prudent in exercising this option.

All symptomatic infants should be treated with IV fluids

Management of symptomatic hypoglycemia

For symptomatic hypoglycemia including seizures, a bolus of 2 mL/kg of 10% dextrose (200 mg/kg) should be given. This mini-bolus helps to rapidly achieve the steady state levels of blood glucose.[15] Immediately after the bolus, a glucose infusion at an initial rate of 6-8 mg/kg/min should be started. Check blood sugar after 30 to 60 min and then every 6 hour until blood sugar is >50 mg/dL.

Repeat subsequent hypoglycemic episodes may be treated by increasing the glucose infusion rate by 2 mg/kg/min until a maximum of 12 mg/kg/min. After 24 hours of IV glucose therapy, once

two or more consecutive blood glucose values are >50 mg/dL, the infusion can be tapered off at the rate of 2 mg/kg/min every 6 hours with BGL monitoring. Tapering has to be accompanied by concomitant increase in oral feeds. Once a rate of 4 mg/kg/min of glucose infusion is reached and oral intake is adequate and the blood sugar values are consistently >50 mg/dL, the infusion can be stopped without further tapering. Ensure continuous glucose infusion without any interruption preferably using infusion pump.

Do not stop an IV infusion of glucose abruptly; severe rebound hypoglycemia may occur. Avoid using > 12.5% dextrose infusion through a peripheral vein due to the risk of thrombophlebitis.

Recurrent / resistant hypoglycemia

This condition should be considered when there is a failure to maintain normal blood sugar levels despite a glucose infusion of 12 mg/kg/min or when stabilization is not achieved by 7 days of therapy. High levels of glucose infusion may be needed in the infants to achieve euglycemia.

Table no 4 : Important causes of resistant hypoglycemia and investigations

Important causes of resistant hypoglycemia	Investigations to be considered
Congenital hypopitutarism	Serum insulin levels
Adrenal insufficiency	Serum cortisol levels
Hyperinsulinemic states	Growth hormone levels
Galactosemia	Blood ammonia
Glycogen storage disorders	Blood lactate levels
Maple syrup urine disease	Urine ketones and reducing substances
Mitochondrial disorders	Urine and sugar aminoacidogram
Fatty acid oxidation defect	Free fatty acid levels
	Galactose 1 phosphate uridyl transferase levels

Besides increasing the rate of glucose infusion, drugs may also be tried in the treatment of resistant hypoglycemia. Before administration of the drugs, take the samples to investigate the cause (Table no 3). Drugs that are used include the following:

1) Hydrocortisone 5 mg/kg/day IV or PO in two divided doses for 24 to 48 hrs

(2) Diazoxide 10-25 mg/kg/day in three divided doses PO. Diazoxide acts by keeping the K_{ATP} channels of the β-cells of the pancreas open, thereby reducing the secretion of insulin. It is therefore useful in states of unregulated insulin secretion like in insulinomas.

(3) Glucagon 100 μg/kg subcutaneous or intramuscular (max 300 μg) – maximum of three doses. Glucagon acts by mobilizing hepatic glycogen stores, enhancing gluconeogenesis and promoting ketogenesis. These effects are not consistently seen in small-for-gestational age infants. Side effects of glucagon include vomiting, diarrhea and hypokalemia and at high doses it may stimulate insulin release.

(4) Octreotide (synthetic somatostatin in dose of 2-10 μg/kg/day subcutaneously two to three times a day.

Do not use diazoxide and glucagon in small for gestational age infants.

Useful formulae

(a) Infusion rate (mg/kg/min) = $\frac{\text{\% of dextrose being infused x rate (mL/hr)}}{\text{body weight (in kg) x 6}}$

(b) Infusion rate (mg/kg/min) = $\frac{\text{IV rate (mL/kg/day) x \% of dextrose}}{144}$

(c) Infusion rate (mg/kg/min) = Fluid rate (mL/kg/day) x 0.007 x % of dextrose infused

Follow-up and outcome

Lucas in 1988 linked hypoglycemia to long term adverse outcomes in a retrospective multicentric study. Later, a similar relationship of lower head circumference and developmental scores was highlighted by Duvanel *et al*.[18] Further, a systematic review of 18 studies on neurodevelopment after hypoglycemia showed poor methodological quality of all but two studies. None of the studies provided a valid estimate of the effect of neonatal hypoglycemia on neurodevelopment.[19] Though these studies have major limitations, it would seem prudent to follow up all infants who had confirmed hypoglycemia in the high-risk category, till a future optimal study is performed.[19] The outcome of hypoglycemia is determined by factors like, duration, degree of hypoglycemia, rate of cerebral blood flow, and cerebral utilization of

glucose. Special attention should be paid to neuro-developmental outcome, overall IQ, reading ability, arithmetic proficiency and motor performance.

The infants can be assessed at one month corrected age for vision / eye evaluation. At 3, 6, 9, 12 and 18 months corrected age they can be followed up for growth, neurodevelopment, vision and hearing loss. Vision can be assessed with Teller acuity card and hearing should be assessed by Brainstem evoked auditory responses. Neurodevelopment will be assessed by the clinical psychologist using DASII 2. MRI at 4-6 weeks provides a good estimate of hypoglycemic injury and therefore should be considered in follow up of such infants subject to affordability.

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Figure 1. **Algorithm for management of neonatal hypoglycemia**