

Neonatal Hypoglycemia: Article Review

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Abstract

Introduction: Neonatal hypoglycemia is one of the most common metabolic problems in newborns and is defined as a plasma glucose level of less than 30 mg/dL in the first 24 hours after delivery and further up to 45 mg/dL. It poses a risk of neurological injury, mental retardation, recurrent seizure activity, personality disorders, and developmental delay in newborn babies. In this condition, the newborn should be fed immediately after the delivery as well their blood glucose level should be measured within 2 - 3 hours, half an hour after the feeding. Despite being one of the common problems after birth, the management of low blood glucose levels remains challenging due to the lack of a definitive approach provided by healthcare professionals. With the establishment of the right definitive approach, both transient and neonatal hypoglycemia can be treated well. There are various treatment options included, such as dextrose infusion, glucagon, glucocorticoids, diazoxide, octreotide, and nifedipine. With the emergence of more new treatment modalities and a stepwise practical approach can help in the management of these patients.

Aim of the Study: The review discusses the management and treatment modalities of neonatal hypoglycemia.

Methodology: The review is a comprehensive research of PUBMED from the year 1986 to 2018.

Conclusion: Aggressive management of neonatal hypoglycemia is required. A significant population suffers from neurodevelopmental problems if not managed appropriately. Delay in development has also been seen in as many as 30% of patients suffered from neonatal hypoglycemia. Due to such various worst outcomes, it is prudent to aggressively treat neonatal hypoglycemia regardless of the infant's age or the underlying cause. For those in whom a metabolic disorder has been diagnosed, appropriate disease-specific therapy should be ideal for correcting hypoglycemia. With the continuing evolvement of molecular and genetic causes of congenital hyperinsulinism, the discussion would be beyond the scope of review.

Keywords: Dioxide; Hyperinsulinism Hypoglycemia; Nifedipine; Glucagon; Octreotide

Background

Hypoglycemia remains one of the most common metabolic problems in neonates. The possible cause of intractable hypoglycemia in infants is congenital hyperinsulinism (CHI), which is due to dysregulated insulin secretion from pancreatic β -cells. There is increased consumption of glucose and inhibition of glycogenolysis, gluconeogenesis and ketogenesis, depriving the brain of both its primary and secondary energy fuel sources that is glucose and ketone bodies. Since hypoglycemia is known to cause some irreversible neuronal injury; thus the knowledge of glucose homeostasis, appropriate lab investigations, and prompt initiation of medical therapy is important in the management of hyperinsulinemic hypoglycemia (HH) [1,2].

The predisposing factors or cause of neonatal hypoglycemia may include changes in hormone receptors, changes in enzymatic activities. In newborns, there is the inadequate reserve of hepatic glycogen, muscle stores as a source of amino acids for gluconeogenesis and lipid stores for the release of fatty acids. Thus, fetal glucose is derived entirely from the mother through the placenta [3].

Following events happen post-delivery [3]:

- Three to five-fold increase in glucagon concentration within minutes to hours.
- Fall of insulin concentration for several days.
- The strong urge in catecholamine secretion and elevated growth hormones in response to the surge of catecholamines.

The net effect of which is the mobilization of glucose via glycogenolysis and gluconeogenesis, lipolysis, and promotion of ketogenesis. As a result of which glycogen stores rapidly depletes within hours, gluconeogenesis intensifies [3].

Methodology

A comprehensive and systematic search was conducted regarding hypoglycemia in newborns, the risk factors associated, clinical picture and managements. PubMed search engine and Google Scholar search were the mainly used database for search process. All relevant available and accessible articles of all types were reviewed and included.

The term used in search were: neonatal hypoglycemia, infant of diabetic mother, low blood glucose, hyperinsulinism hypoglycemia, nifedipine, glucagon, octreotide.

Clinical presentation

The clinical presentation of neonatal hypoglycemia presents as decreased availability of glucose for brain and the adrenergic stimulation. The symptoms vary from asymptomatic hypoglycemia to severe disturbances in the central nervous system and cardiopulmonary system. Symptoms are as follow [3]:

1. CNS manifestation- Altered level of consciousness or unresponsiveness, lethargy, hypotonia, poor feeding, jitteriness, irritability, stupor, seizure, vomiting.
2. Cardiopulmonary- Congestive heart failure, cyanosis, apnea, high-pitched cry and hypothermia.
3. ANS manifestation- Pallor, diaphoresis, tachycardia, hunger, anxiety, nausea and Vomiting.

4. In contrast to neonates, older children manifest as- mental confusion, behavioral changes, amnesia, headache, decreased visual acuity, diplopia, dysarthria, aphasia, ataxia, difficulty in concentration.

Risk factors of neonatal hypoglycemia where screening is recommended [4,5]

Maternal risk factors:

- Pregestational or gestational diabetes
- Preeclampsia/eclampsia, gestation-related hypertension
- Medical treatment, drugs including beta-blockers, oral hypoglycemic agents, beta-agonists tocolytics, late antepartum and intrapartum dextrose.

Risk factors belonging to infant:

- Preterm infants (≤ 35 weeks)
- Low birth weight (< 2000 gm)
- Small for gestational age- birth weight $< 10^{\text{th}}$ percentile
- Large for gestational age- birth weight $> 90^{\text{th}}$ percentile
- An infant with Rh-hemolytic disease
- Infants with IUGR- this includes neonates with birth weight between 10^{th} - 25^{th} and up to 50^{th} percentile with features of fetal undernutrition; these include three or more skin folds in the gluteal region, decreased subcutaneous fat, and difference greater than 3 cm in head to chest circumference
- Perinatal asphyxia, meconium aspiration syndrome (MAS)
- Infection
- Polycythemia
- Hypothermia
- Congenital heart diseases
- Endocrine disorders.

Screening time and period for infants at high risk

For those infants at risk, nearly 80% of hypoglycemic cases are observed in the first 24 hrs and 19% of cases are found in 24 - 48 hrs. A single blood sample may be ample to exclude subsequent hypoglycemia in 50% of LGA babies; thus, initial values are more critical in predicting hypoglycemia and on the other hand, early blood glucose values are of less use in predicting hypoglycemia in SGA babies. In an infant who has been fed in the first hour of birth, the glucose level should be measured after 30 minutes and recommendations of the American Academy of Pediatrics should be complied, as shown in the table below [6,7].

Screening and treatment for Postnatal Glucose Homeostasis in Late Preterm, Term SGA, Infant Diabetic Mother and LGA Newborns [7]:

- Late preterm and SGA newborns (Screening 0 - 24 hrs).
- Infant of diabetic mother and LGA (Screening 0 - 12 hrs).

Transient and persistent hypoglycemia

The events or conditions occurring during the birth are often related to transient hypoglycemia, such as mothers receiving intravenous dextrose during delivery or treated with hypoglycemic agents during pregnancy. Infants born to diabetic mothers secrete a higher amount of insulin to accommodate excess fetal glucose concentration. The preterm infants and those with SGA have fewer glycogen and fat stores than a full-term infant; thus, lack of storage in combination with high insulin puts them at high risk of hypoglycemia. The anaerobic metabolism needed to maintain blood glucose concentration in patients with birth asphyxia and perinatal stress increases the risk of hyperinsulinism; these patients are at high risk of developing transient hypoglycemia in the first hours of life [8,9].

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is a rare condition that can be very challenging to manage. It is associated with persistently elevated levels of circulating insulin, which is caused by over secretion of pancreatic beta-cells and an absence of ketone production. Many other metabolic disorders, such as glycogen storage, gluconeogenesis, and fat oxidation [10].

The treatment procedure depends on the understanding of the glucose adaptation process that occurs right after birth, conditions that leads to transient hypoglycemia, and other possible conditions affecting insulin secretion. Infants with transient hypoglycemia need extensive diagnostic workup. In the case of persistent hyperinsulinism, the diagnostics include plasma insulin, beta-hydroxybutyrate, free fatty acid levels, plasma ammonia levels, plasma acylcarnitine profile, and urine organic acids [11].

Agents	Dosing	Administration	Side Effects
Dextrose	4 - 8 mg/kg/min	Continuous infusion	
Glucagon	Bolus: 200 mcg/kg	Intermittent infusion	Hyponatremia, thrombocytopenia
	1 mg/day	Continuous infusion	
Glucocorticoids			Growth suppression, hypertension
Dexamethasone	0.25 m/kg	IV once every 12hr	
	1 - 2.5 mg/kg/dose	IV once every 6hr	
Hydrocortisone	50 mg/m ² /day		
Nifedipine	Initial: 0.25 - 0.3 mg/kg/day	Orally once in every 8hr	None reported
	Final: 0.5 - 0.8 mg/kg/day		
Octreotide	7 - 12 mcg/kg/day	Subcutaneous every 4 - 6hrs	Cholelithiasis
Diazoxide	10 - 15 mg/kg/day	Orally once every 8hr	Hirsutism, heart failure, fluid retention, nausea, vomiting.

Table 1: Pharmacological agents used in the treatment of neonatal hypoglycemia [12].

Dextrose

The infants with symptomatic hypoglycemia and presenting with seizures are treated with “mini-bolus” of IV 10% dextrose at 2 ml/kg over 3 min; this is followed by glucose infusion. For confirmation of hyperinsulinemic hypoglycemia, infants need to undergo a controlled reduction in GIR to induce hypoglycemia so as to collect the critical blood samples. In the case of suspected amino acid induces HH, the protein-loading test is suggested [13].

Once the diagnosis of HH is confirmed, all the attempts should be made to wean dextrose infusion as tolerated since transient forms may resolve within 5 - 7 days. But in case of a rise in GIR even after a week of parenteral glucose, a trial of dioxide therapy with thiazide diuretics is initiated. If this still leads to an unachieved level of glucose, a dose increment of diazoxide can be made by 2.5 mg/kg with a maximum dose of 15 mg/kg/day [14,15].

Diazoxide

Diazoxide is the first line of treatment in HH. Diazoxide acts by preventing depolarization cell membranes by acting on the SUR1 sub-unit and K-ATP channel, thereby inhibiting insulin secretion. Diazoxide is given orally in a dose of 5 - 15 mg/kg/day in three divided doses and is embolized in the liver and excreted in kidneys, in this way close monitoring of hepatic and renal functions is needed. In infants with already existing hepatic dysfunction or hypoalbuminemia, a lower dose is initiated as 3 mg/kg/day [16].

Tolerance to the drug is usually good with certain side effects such as hypertrichosis, which is reversible on discontinuation of the drug. Other side effects might include tachycardia, neutropenia, thrombocytopenia and hyperuricemia, pulmonary hypertension, respiratory failure, and structural heart disease [17].

Glucagon

Glucagon is secreted by pancreatic alpha cells as the counterregulatory hormone of insulin. It is usually given intravenously, intramuscularly, or subcutaneously at a dose of 1 - 20 µg/kg/h for short term control patients who are unresponsive to diazoxide [18].

Symptomatic infants with LGA, need intramuscular administration of glucagon as a single dose between 0.5 to 1 mg. Side effects of glucagon are intolerance to feeding and erythema necrolyticum. Since glucagon is an insulin secretagogue in high doses, this a long-term use of it is only recommended with somatostatin analogs [18].

Treatment strategies in a hypoglycemic event of both symptomatic and asymptomatic patients are as follow [12]:

- **Glucocorticoids:** The use of corticosteroids in the management of hypoglycemia is limited. Glucocorticoids are known to reduce insulin secretion and enhance glycogenolysis and gluconeogenesis. According to the current recommendation, glucocorticoids are used when there is hypocortisolism while hypoglycemic or when there is proven adrenal insufficiency by synacthen test [12].
- **Nifedipine:** It is an L-type calcium channel blocker that is used in a dose of 0.25 - 2.5 mg/kg/day in patients whose diazoxide therapy was proven to be unsuccessful in control of hypoglycemia. The clinical response of these drugs vary. For adequate cardiac contractility in infants, calcium is required. The long-term safety of nifedipine is yet to be evaluated, since it may place some patients at risk for sudden cardiac death caused by calcium channel blockade [19].

Calcium channels are present on beta-pancreatic cells, open to allow an influx of calcium, which leads to increased intercellular calcium, which causes the secretion of insulin. Thus, the use of calcium channel blocker nifedipine can inhibit insulin secretion [19].

- **Octreotide:** Again, octreotide is the drug of choice that is initiated in whom diazoxide therapy has failed. Octreotide is a long-acting somatostatin analog that inhibits insulin secretion by hyperpolarization of beta-cell and direct inhibition of VGCC. Since endogenous somatostatin has a short half-life, it makes it less desirable therapeutic option whereas the half-life of octreotide is 1.5hrs compare to endogenous, which is 1 - 3 minutes, this it can be used for intermittent dosing in some infants. It is administrated intravenously or subcutaneously in intermittent doses or continuous infusion.

Intermittent doses of octreotide are given 1 - 2 hourly following selected feeds. If the euglycemic state is not achieved, then the patient is given a continuous infusion. This somatostatin agent releases growth hormones. Thus, a long-term use of octreotide on normal growth is of concern. The side effects of octreotide are minor and require no major attention. Cholelithiasis is reported to be one of the few side effects.

Conclusion

The management of infants at the risk of hypoglycemia and those suffering from hypoglycemia in the first few hours to days of life is essential and of concern for doctors looking after the newborn babies since it comes with the potential risk of neurological as well as developmental disorders. Although there is complexity in overall therapeutic management and navigating the normal glucose levels but choosing an appropriate line of treatment during hypoglycemic state increases the precise diagnosis and recovery and hence eliminating the further risk associated with hypoglycemia.

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