CODEN [USA]: IAJPBB **ISSN: 2349-7750**

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2542794

Available online at: http://www.iajps.com ***Review Article***

AN OVERVIEW NEONATAL HYPOGLYCEMIA MANAGEMENT APPROACHES

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Abstract:

Background: *Hypoglycemia remains to stand for a usual metabolic problem dealing with the neonatal populace. Both healthy and ill-appearing neonates could be impacted by hypoglycemia throughout the very first days of life. Severe neonatal hypoglycemia (HG) leads to neurologic damage, mental retardation, epilepsy, personality disorders, impaired cardiac performance and muscle weakness.*

Objective: *The goal of this review is to highlight the background of the inborn errors of metabolism that present with neonatal hypoglycemia to understand more and discuss management of neonatal hypoglycemia.*

Methodology: *We conducted a search using electronic databases; MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), up to November, 2018.*

Conclusion: *Neonatal HG is important factor in the general neonatal death. HG could additionally create serious invalidity. Treatment of the hypoglycemic infant may begin while investigations continue.*

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Please cite this article in press Muruj Mohammed Kamili et al., ***An Overview Neonatal Hypoglycemia Management Approaches.,*** *Indo Am. J. P. Sci, 2019; 06(01).*

INTRODUCTION:

Over 50 years back, Cornblath et al. identified that low-blood glucose degrees in tiny for gestational age (SGA) as well as preterm babies were associated with seizures [1]. It became obvious that symptomatic hypoglycemia might cause lasting neurologic deficits. Nonetheless, the meaning of medically significant hypoglycemia stays among one of the most confused as well as contentious issues in neonatal medicine [2]. We still have actually restricted evidence-based consensus relating to the screening and also management of babies in danger for hypoglycemia. Although there is agreement that persistent extreme hypoglycemia results in brain injury, there have been few high-quality studies to clarify the neurodevelopmental results connected to transient neonatal hypoglycemia [2].

Signs of hypoglycemia can take place via neuroglycopenic or autonomic pathways. Autonomic signs and symptoms, which result in considerate activation, can include, but not limited to, tachycardia, anxiety, tremors, sweating, nausea/vomiting, and hypothermia. Neuroglycopenic signs as a result of impacts of lowered glucose availability to the main nerves involve indications such as headaches, lethargy, and motor/sensory/visual disturbance, among others [3]. These symptoms, together with counter-regulatory actions, can be impacted by clinical status, age, gender, as well as drug usage, among others [3]. With chronic hypoglycemia, blunted counter-regulatory feedbacks might occur. This is described hypoglycemia linked autonomic failure or, "hypoglycemia unawareness" and also this need to be determined and examined if this occurs [3].

The screening and also management for neonatal hypoglycemia remains a complex and controversial concern in neonatology. In this review we aim to discuss the available and reliable information of diagnosing, symptoms and managing the neonatal hypoglycemia which can cause both adrenergic (as tachycardia,lethargy and diaphoresis) and neuroglycopenic signs (as seizure,come,apnea and hypothermia) .

METHODOLOGY:

We performed comprehensive search using biomedical databases; Medline, and Embase, for studies concerned with neonatal hypoglycemia published with English language up to, November 2018. keywords used in our search through the databases were as; “neonatal hypoglycemia”, “diagnosis”, “management”. More relevant articles were recruited from references lists scanning of each included study.

DISCUSSION:

- **Pathophysiology**

Before birth the fetus receives a constant intravenous supply of glucose, which goes across the placenta by carrier-mediated assisted in diffusion from the mother's circulation. Throughout labour and also delivery the secretion of stress hormonal agents such as glucocorticoids as well as catecholamines causes a rise in fetal blood glucose concentrations, so that cord blood glucose concentrations are frequently high [4].

When the umbilical cord is reduced, the exogenous supply of glucose stops, and blood glucose concentrations drop. This fall in blood glucose results in a reduction in insulin secretion as well as boost in counter-regulator hormones such as glucagon, catecholamines and also glucocorticoids. All together, these alterations initiate fetal endogenous glucose generation by means of glycogenolysis as well as gluconeogenesis, with a resultant stabilisation of blood glucose concentrations, although adult concentrations are not reached until approximately 72 hours old [4].

Failure of this series of physical adjustments can result in hypoglycaemia, which is most usual in the first couple of hours after birth. In the majority of infants this hypoglycaemia is transient, recovering over a couple of hours to days, as well as is generally termed transitional hypoglycaemia [4]. In a smaller number of infants the hypoglycaemia persists for days to weeks, and a few of these will turn out to have consistent neonatal hyperinsulinism and also call for added interventions. There is some proof that even transitional hypoglycaemia is likely to be because of relative hyperinsulinaemia [5].

Although management of hypoglycaemia is mostly focused on managing blood glucose concentrations, it is important to remember that the real objective is to relieve the danger of brain injury. Glucose is the significant fuel for the brain, and also for a neonate with a relatively large brain, mostly all of the estimated total body glucose consumption can be represented by the brain. Because brain glucose uptake is directly proportional to flowing concentrations, in the lack of alternate brain fuels, any kind of reduction in blood glucose concentrations leads to a decrease in available brain oxidative substrates. Consistent hyperinsulinaemia is therefore crucial, due to the fact that it may restrict the manufacturing of alternate cerebral fuels such as ketones that might be otherwise neuroprotective

during hypoglycaemia [5].

- **Risk Factors For Hypoglycemia**

Neonates at increased threat for developing neonatal hypoglycemia ought to be routinely monitored for blood glucose levels regardless of the mode of feeding. At-risk neonates fall into two major categories:

- 1. Excess utilization of glucose, which includes the hyperinsulinemic states
- 2. Inadequate production or substrate delivery [6].

Infant risk factors for hypoglycemia are listed in Table 1.

Table 1. At-risk infants for whom routine monitoring of blood glucose is indicated [6-8].

Small for gestational age
Babies with clinically evident wasting of fat and muscle bulk
LGA(Large gesation age)
Discordant twin: weight 10%<larger twin
All infants of diabetic mothers, especially if poorly controlled
Low birth weight (<2,500 g)
Prematurity (<35 weeks, or late preterm infants with clinical signs or extremely poor feeding)
Perinatal stress: severe acidosis or hypoxia-ischemia
Cold stress
Polycythemia (venous Hct>70%)/hyperviscosity
Erythroblastosis fetalis
Beckwith–Wiedemann's syndrome
Microphallus or midline defect
Suspected infection
Respiratory distress
Known or suspected inborn errors of metabolism or endocrine disorders
Maternal drug treatment (e.g., terbutaline, beta-blockers, oral hypoglycemics)
Infants displaying signs associated with hypoglycemia

- **Clinical Manifestations**

The clinical indications of hypoglycemia are nonspecific, occurring with different other neonatal issues. Even in the existence of an arbitrary low glucose level, the doctor should examine the basic standing of the infant by observation as well as physical checkup to rule out various other ailment entities as well as procedures that might need added laboratory examination and also treatment. Some common medical indicators are listed in Table 2.

Table 2. Clinical manifestations of possible hypoglycemia [6-8].

Irritability, tremors, jitteriness
Exaggerated Moro reflex
High-pitched cry
Seizures or myoclonic jerks
Lethargy, listlessness, limpness, hypotonia
Coma
Cyanosis
Apnea or irregular breathing
Tachypnea
Hypothermia; temperature instability
Vasomotor instability
Poor suck or refusal to feed

A current study identified that of the 23 maternal/infant threat aspects as well as baby signs/symptoms studied; only jitteriness as well as tachypnea was statistically significant at forecasting reduced blood glucose-- not also maternal diabetic issues [8]. A diagnosis of hypoglycemia likewise needs that indicators abate after normoglycemia is recovered (the exception being if brain injury has already been endured).

- **Therapeutic Management**

There are several therapy choices attainable for the management of neonatal hypoglycemia (Table); nevertheless, choosing the appropriate treatment can be challenging as the underlying cause may take weeks to detect. Consequently, during the analysis process, it is necessary to stop or lessen periods of hypoglycemia in an initiative to mitigate possible adverse neurological outcomes brought on by inadequate glucose accessibility for ideal brain function.

Table 3. Pharmacological agents for treatment of neonatal hypoglycemia [9-24].

Agent	**Dosing**	**Administration**	**Side Effects**
Dextrose	4-8 mg/kg/min (max:20-30 mg/kg/day)	Continuous infusion	
Diazoxide	10-15 mg/kg/day	Orally(once every 8hr)	Hirsutism, heart failure, fluid retention, nausea, vomiting
Glucagon	Bolus:200 mcg/kg 1mg/day	Intermittent infusion Continuous infusion	Hyponatremia, thrombocytopenia
Glucocorticoids			Growth suppression, hypertension
Dexamethasome	0.25 m/kg 1-2.5 mg/kg/dose	Intravenous (once every 12hr) Intravenous(once every 6hr)	
Hydrocortisone	50 mg/m^2 /day		
Nifedipine	Initial:0.25-0.3 mg/kg/day Final:0.5-0.8 mg/kg/day	Orally (once every 8hr)	None reported
Octreotide	7-12 mcg/kg/day (max: 40mcg/kg/day	Subcutaneous (every 4-6hr) May be given continuously Intravenous	Cholelithiasis

DEXTROSE:

Hyperinsulinism is one of the most popular reason for both temporal and persistent/permanent types of neonatal hypoglycemia. Management of dextrose titrated to keep euglycemia is one of the most sensible as well as expedient preliminary strategy [9]. Dextrose infusions may be used regardless of the existence of enteral feeds. Traditionally, a 2 mL/kg to 3 mL/kg (200 − 300 mg/kg) intravenous bolus of 10% dextrose is provided, adhered to by a continual infusion [9]. First glucose mixture rates usually made use of for full-term newborns are 4 to 6 mg/kg/min, while rates for premature newborns may be 6 to 8 mg/kg/min [10]. An isotope tracer research study noted that the glucose generation rate of the liver in a single-term neonate was approximately 5 mg/kg/min [10]. Glucose infusion rates ought to be titrated to attain euglycemia, and also hypoglycemic infants might need substantially greater rates.

Dextrose focus of up to 20% to 25% may be called for in order to deliver glucose infusion rates in the 15 to 30 mg/kg/min array [9]. Glucose infusions rates of approximately 30 mg/kg/min have actually been utilized in clients unresponsive to lower rates [11]. The majority of these patients will call for the positioning of central lines in order to provide an adequate quantity of dextrose in a quantity that does not overload the client with fluids. Outer access can be an issue not only from a quantity perspective but additionally as a result of the hypertonicity of dextrose infusions. Concentrations higher than 12.5% have to be provided utilizing a central line [11]. Since these clients need constant serum glucose inspection, it might be prudent to put an arterial line until steady euglycemia is developed to minimize or avoid pain as well as tissue damage to the infants' heels, toes, and also fingers.

GLUCAGON:

Intermittent glucagon doses have been variable. Dosages have varied from 200 mcg/kg to as low as 3 mcg/kg in a single patient [14]. Much more typically, glucagon is given as a continuous mixture over 24 hours. Doses range from 20 to 40 mcg/kg/hr in sick, preterm babies to a flat dosage of 1 mg/day instilled over 24 hrs for babies no matter gestational age or birth weight [13].

Reports of severe hyponatremia with the use of glucagon have actually drawn attention to prospective threats connected with this therapy [12]. Hypertonic saline (3% sodium chloride) has actually been made use of to treat hyponatremia in infants getting glucagon [14]. While using glucagon may contribute to the decline in serum salt, another feasible description is a dilutional effect decline brought on by the huge quantities of intravenous dextrose services along with the quantity needed to carry out the glucagon. There are reports of crystallization of glucagon when supplied in tiny volumes, resulting in occlusion of intravenous catheters. Additional diluting the glucagon solution and also or altering the solution much more regularly than once daily might reduce the concern of crystallization. Monitoring of serum sodium should be carried out while obtaining glucagon treatment. Various other rare unfavorable effects described in case reports include thrombocytopenia and also an uncommon cutaneous paraneoplastic phenomenon, erythema necrolyticum migrans [12].

GLUCOCORTICOIDS:

Making use of glucocorticoids, as an intense treatment of hypoglycemia, has been supported by some [17]. Information to sustain this usage are limited to instance reports; nonetheless, dosing is found in common tertiary references. Physiologically glucocorticoids lower insulin secretion and increase insulin resistance as well as enhancing both gluconeogenesis as well as glycogenolysis. Theoretically these results must induce an increase in serum glucose concentrations. Dexamethasone and also hydrocortisone have been utilized to deal with hypoglycemia [15], [16]. In case records, patients obtained glucocorticoids at differing stages throughout the therapy process (initially versus salvage). Belik et al. provided a 35-week-gestation newborn dexamethasone at 0.25 mg/kg every 12 hours; nevertheless, the newborn later needed glucagon treatment [12]. A couple of various other researchers, Bhownick et al. as well as Lindley et al., provided hydrocortisone at 2.5 mg/kg/dose intravenously every 6 hrs to a small-for-gestational-age term baby and 50 mg/m2/day intravenously split every 6 hrs to a 31-week pregnancy female, respectively [15], [16]. Both patients called for added therapies after the enhancement of steroids for long term glycemic control.

Systemic glucocorticoid therapy brings substantial dangers. Usual side effects associated with glucocorticoid treatment include growth suppression, feed intolerance, and high blood pressure. Preterm, very-low-birth weight newborns treated with hydrocortisone have actually a raised danger of spontaneous perforation of the gastrointestinal tract [17]. In addition, glucocorticoids may unnecessarily

raise blood pressure in people without hypotension and also may raise the threat for unfavorable neurodevelopmental end results [17].

DIAZOXIDE

Diazoxide is generally launched at 10 to 15 mg/ kg/day orally in 2 to 3 split doses. Some records have actually started treatment at doses as little as 5 mg/kg/day [19]. Doses might then be titrated upward or downward based on laboratory outcomes. Diazoxide responsive individuals often tend to have lower dose requirements than nonresponsive people or those calling for medical treatment [18] Optimum dosages of approximately 30 mg/kg/day have actually been reported; however, efficacy was not increased at doses over 15 mg/kg/day [19]. When efficient, hypoglycemia stabilizes within 2 to 4 days of therapy initiation; nonetheless, because of variants in kinetic specifications, a test of 5 to 8 days is needed prior to judging treatment a failing [18]. Start of activity is within 1 hour of administration, with a period of action of 8 hours, thinking regular kidney functionality. Diazoxide is offered for oral use and also, when effective, is among just two treatments that offer an enteral alternative.

One of the most frequently reported adverse effects associated with diazoxide use is hypertrichosis, which is reported to some extent in almost all individuals [18]. While medically less considerable, this can be rather worrying for parents. An additional typical and also extra clinically considerable adverse effect is fluid retention. Diazoxide brings about an increase in sodium retention while restricting free water clearance. Individuals without structural cardiac deficiencies have established cardiac failure while getting diazoxide treatment. In these people, the cardiac failure dealt with upon discontinuation of therapy [19]. Consequently, caution should be utilized in people with recognized cardiac problems vulnerable to fluid overload.

OCTREOTIDE:

Octreotide is a treatment option that is started in patients for whom diazoxide therapy failed. Octreotide is a long-acting somatostatin analogue. Somatostatin hinders insulin secretion by hyperpolarization of β-cell as well as straight inhibition of VGCC. Endogenous somatostatin has a short half-life (1 − 3 mins) making it a less desirable therapeutic alternative. The half-life of octreotide is around 1.5 hours, which permits periodic dosing in some people. It might be provided as intravenous or subcutaneous periodic dosages or as a continual mixture.

Octreotide demonstrated some effectiveness in supporting glucose concentrations but not constantly avoiding subtotal pancreatectomy in nine individuals [20]. Nine individuals obtained octreotide long-term, approximately 4.3 years with proof of transient malabsorption as well as some compromise in direct growth [20]. Resistance to octreotide occurred in all patients, despite risen dosages. This may be connected to a possible ceiling result at bigger doses. Dose-related hypoglycemia may be seen with escalating dosages. This phenomenon was described in an infant experiencing hypoglycemia once every 5 days while getting 200 mcg/ day. As treatment was intensified to 400 mcg/day, the people experienced enhanced frequency of hypoglycemic episodes (2 − three each day). When therapy returned to the initial dose, hypoglycemia supported and happened when every 4 to 5 days [20]. Glaser et al. reported the use of octreotide in 8 people with an initial starting dosage of 4 to 5 mcg/kg/day separated in 4 doses [22]. Dosages required maintaining euglycemia ranged from 3 to 10 mcg/kg/day either IV or subcutaneously through an insulin infusion pump. For all patients, it was not required to increase the dosage as the patient expanded.

Intermittent dosing of octreotide need to be carried out 1 to 2 hrs adhering to selected feeds [20]. Patient conditions might be managed making use of dosages with every other feed. If individuals do not continue to be euglycemic with recurring application, octreotide may be carried out through constant infusions.

One more essential activity of somatostatin is the inhibition of the release of development hormonal agent. The results of long-term use octreotide on normal development are a concern. When development hormone is measured adhering to the administration of octreotide, a suppression of growth hormonal agent is observed 2 hours following injections. However a rise in development hormonal agent is seen at 4 hrs [12]. A lot of side effects of octreotide are minor and call for no treatments. One report of cholelithiasis in a baby required a reduction of the octreotide dose and initiation of ursodeoxycholic acid [21].

NIFEDIPINE:

Nifedipine has actually been made use of by some

investigators as a restorative alternative in patients for whom diazoxide therapy has actually fallen short with variable success [43,44,47]. At this point, this therapy must be considered investigational due to the few individual case reports published [23]. Calcium is required for appropriate heart contractility in the newborn population. The lasting security of nifedipine has actually not been reviewed and also may put some patients in danger for unexpected heart death triggered by calcium channel blockade.

Calcium channels found on pancreatic β-cell open up to allow an increase of calcium resulting in increased intracellular calcium which causes the secretion of insulin [23]. Use of the calcium channel blocker nifedipine can prevent insulin secretion. This treatment approach has actually been reviewed more just recently in the literary works in patients for whom various other restorative choices have actually stopped working; however, just 4 people have been defined in the published case series [24]. Nifedipine was launched at 0.25 to 0.3 mg/kg/day, orally, separated every 8 hours. Doses were enhanced by 0.1 mg/kg/day up until patients were euglycemic as well as dextrose was discouraged. Effective treatment was attained with nifedipine at 0.5 to 0.8 mg/ kg/day [24].

Safety and security of nifedipine in this populace has not been studied; however, blood pressure was monitored routinely and also was gauged regular for sex and age [24]. The study did not recognize any kind of unfavorable impacts, nevertheless typical negative effects experienced with the use of calcium channel blockers include dizziness, flushing, headaches, and queasiness.

CONCLUSION:

Hypoglycaemia is the commonest metabolic disease of the infant, and also possibly the only easily preventable reason for neonatal brain injury. Regardless of this, monitoring of neonatal hypoglycaemia has for years been based on extremely restricted evidence.

Glucose screening must be done just on at-risk newborns as well as those with medical indicators compatible with hypoglycemia. Keeping the newborn at breast or returning the newborn to the breast immediately is important.

Although administration of hypoglycaemia is greatly focused on handling blood glucose concentrations, it is very important to bear in mind that the actual objective is to relieve the risk of brain injury. Glucose is the major fuel for the brain, as well as for a neonate with a reasonably large brain, almost all of the approximated total body glucose usage can be made up by the brain. Given that brain glucose uptake is directly symmetrical to distributing concentrations, in the lack of alternative brain fuels, any type of decrease in blood glucose concentrations results in a reduction in offered brain oxidative substrates. Relentless hyperinsulinaemia is therefore important, due to the fact that it may restrict the production of alternative cerebral fuels such as ketones that might be or else neuroprotective during hypoglycaemia.

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