Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is rare, but an important cause of hypoglycemia in infants, associated with a number of structural abnormalities of the endocrine pancreas is collectively termed as “Islet cell dysmaturation syndrome.” We present the anesthetic management in a clinically diagnosed case of PHHI in a 22 days old full term child, undergoing Subtotal Pancreatectomy. We have discussed the challenges faced in the intra-operative period in managing this neonate for pancreatic resection surgery with focus on intra-operative management of blood glucose levels.

**Key words:** Anesthesia, neonate, persistent hyperinsulinemic hypoglycemia

**Introduction**

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is one of the rare causes of hypoglycemia in infancy. Infants with hypoglycemia may present with grunting, irritability, listlessness, nausea, vomiting, tachypnea, apnea, hypothermia, and with long-term sequel such as seizures, developmental delay, focal neurologic deficits or death secondary to severe, prolonged hypoglycemia.1 Hence, it is a medical emergency, which needs immediate intervention and definitive management is surgical in most of the cases.2 Anesthetic management of a 22-day neonate presenting with similar complaints, undergoing subtotal pancreatectomy, for PHHI, is described here.

**Case Report**

A 22-day neonate (4 kg) was admitted with a history of repeated episodes of convulsions since day 3 of life. She was delivered at full term by elective caesarean section. She had repeated episodes of generalized tonic convulsions with blood glucose level as low as 21 mg/dl and was managed symptomatically with 10% dextrose at 10 ml/kg/min, to maintain blood glucose more than 40 mg/dl. Critical insulin sample analysis showed insulin:glucose ratio 0.7 (normal < 0.4). Ultrasonography Abdomen showed no significant findings. The biochemical and urinary analysis (serum metabolic screens, pH, lactate, ammonia and urinary ketones, amino acids, reducing-substance, serum cortisol, growth hormone levels during periods of normoglycemia) to rule out other metabolic and endocrinal conditions with similar presentation, were normal. The neurological assessment was unremarkable and no Electroencephalogram or other Imaging studies were performed. This led to a clinical diagnosis of PHHI. The neonate was managed with intravenous (IV) 10% dextrose10 ml/kg/min (150 ml/kg/day), two hourly feed through nasogastric (NG) tube, oral Diazoxide (8 mg/kg/dose) 8 hourly and hydrochlorothiazide (25 mg/alternate day). As hypoglycemia persisted even with maximum doses of diazoxide and hydrochlorothiazide, IV octreotide was started at 2 mcg/kg/once a day. This patient was scheduled electively for subtotal pancreatectomy due to persistence of symptoms in spite of aggressive medical management. The 2 hourly NG tube feeds were stopped 6 h prior to surgery and the IV infusion of 10% dextrose along with all the other drugs was continued. Blood sugar checked every 30 min by portable glucose analyzer remained between 100 and 200 mg/dl. 24 G IV cannula was secured on right upper limb. Anesthesia was induced with IV glycopyrolate (4 mcg/kg), fentanyl (2 mcg/kg) followed by propofol (2 mg/kg), atracurium (0.5 mg/kg)
and airway secured with 3.5 uncuffed endotracheal tube. Anesthesia was maintained with oxygen, air, isoflurane with circle absorber system and intermittent doses of atracurium. Right internal jugular vein was cannulated by double lumen No. 4 Fr central venous catheter. Regional analgesia was provided with lumbar epidural catheter inserted by using 19 G Touhy’s needle pediatric set at L3 ± L4 level and fixed at mark 9 cm. Bupivacaine 0.25% (4 ml) was used in epidural block as a bolus. Monitoring included electrocardiogram, non-invasive blood pressure, pulse-oximetry, capnography, central venous pressure, and temperature. Ringer’s lactate 10 ml/kg/h was used as replacement fluid and glucose was supplemented as 4 mg/kg/min. The blood sugar was estimated every 15 min., which was always between 100 and 200 mg/dl as shown in Figure 1. Intra-operative blood loss was 20 ml. and surgery lasted for 75 min. Intra-operative hemodynamic parameters were stable and procedure was uneventful. Residual neuromuscular blockade was reversed with glycopyrrolate (8 mcg/kg), and Neostigmine (0.05 mg/kg). Trachea was extubated and patient shifted to neonatal intensive care unit. Blood sugar level was stabilized between 90 and 100 mg/dl with oral feeds over next 5 days. Post-operative analgesia was provided by 0.25% bupivacaine (1 ml/kg) 6 hourly for next 3 days along with the paracetamol suppository (20 mg/kg) 8 hourly. Histopathological examination of specimen confirmed diagnosis of PHHI.

Discussion

Despite hypoglycemia is a commonly faced the problem in neonates, the threshold for hypoglycemia is still controversial. 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 the literature.”[3]

The operational threshold for hypoglycemia is considered when blood glucose level in Pre-term infants is <30 mg/dl, and <40 mg/dl in full-term infants .[4] The differential diagnosis of neonatal hypoglycemia are shown in Table 1. [4]In neonatal hypoglycemia laboratory studies such as blood glucose, ketone, insulin levels, serum cortisol, growth hormone levels during periods of normoglycemia, and serum metabolic screens, pH, lactate, ammonia and urinary ketones, amino acids and reducing-substances, should be performed to arrive at a definitive diagnosis.[5] Hyperinsulinism in infancy (HI) is the most common cause of recurrent and persistent hypoglycemia in the neonatal period,[6] most cases of which are sporadic. It is characterized by the inappropriate and excessive secretion of insulin from the pancreatic β-cells. The most common cause of HI is due to mutations in the genes regulating the function of the K_ATP channel located on the β-cell membrane.[7] PHHI is associated with a number of structural abnormalities of the endocrine pancreas like multiple diffuse microadenomas, islet cell adenomas, islet cell dysplasia, islet cell hyperplasia (nesidioblastosis). All these conditions are collectively termed the “islet cell dysmaturation syndrome.” The serum glucose level <60 mg/dl, non-ketotic hypoglycemia in association with elevated insulin levels (>10 µU/ml), Insulin/glucose ratio from 0.4 to 2.7 (normal <0.3), sustained glucose requirement in excess of 10 mg/kg/min are confirmatory findings in PHHI.[8] Though surgery is the treatment of choice for PHHI, optimization of blood glucose level prior to surgery is necessary to avoid adverse effects of hypoglycemia. These include seizures, developmental delay, focal neurologic deficits or death secondary to severe, prolonged hypoglycemia. Timely nasogastric feeds, dextrose infusion and drugs like diazoxide, octreotide etc., play an important role in blood glucose level optimization. The aim is to maintain blood sugar level more than 40 mg/dl.

Diazoxide, octreotide[9] and nifedipine[10] are the primary medications used in long-term treatment of PHHI. All these drugs increase serum glucose levels as a well-known adverse effect, but their other therapeutic actions may become a burden in patients with PHHI. Few of them are shown in Table 2. [11] Hence, the exact medication regimen, including doses and selection of drugs, must be highly individualized on the basis of therapeutic response, adverse-effect tolerance, and individual factors.

The Dextrose infusion rate can be calculated by following formulae:[12]

- Dextrose Infusion rate (mg/kg/min) = % of dextrose being infused x rate (ml/hr) body weight (in kg) x 6
- Dextrose Infusion rate (mg/kg/min) = IV rate (ml/kg/day) x % of dextrose/144
In these patients, maintenance of blood sugar level is the main concern. In the normal neonate the glucose requirement is 4-6 mg/kg/min and the fluid requirement is 100-150 ml/kg/day. To balance both these requirements, a 5-10% dextrose solution is the maintenance fluid for neonates. In hyperinsulinemia, glucose requirement increases to 10 mg/kg/min. When glucose is supplemented with boluses of high concentration dextrose containing fluid, blood glucose level could exceed renal threshold for glucose causing glycosuria and osmotic diuresis. Hence, it is preferred to use the dextrose containing fluid as maintenance and ringer lactate as replacement solution. We need to be very careful while supplementing dextrose as use of increased volume can cause volume overload in neonates. Maximal concentration of glucose that can be given through peripheral IV line is D12.5%. If infant requires IV dextrose concentrations >12.5%, insertion of central venous catheter is helpful. Umost care should be taken not use D25% or D50% IV or large IV volume boluses as this creates rebound hypoglycemia and hyperosmolarity in infants who are hyperinsulinemic. Intra-operatively blood glucose level can also act as a guide for tumor removal.

Table 1: Differential diagnosis of neonatal hypoglycemia

| Hypopituitarism, hypothyroidism |
|---------------------------------|
| PHHI=
| PHHI=
| Adrenal insufficiency
| Infant of diabetic mother
| Growth hormone deficiency
| Multiple endocrine neoplasia
| IUGR
| Inborn error of metabolism
| Small for gestational age
| Patau syndrome, beckwith-wiedemann syndrome

Table 2: Adverse effects of therapeutic agents used to increase blood sugar levels pre-operatively

| Drug       | Mechanism of action                      | Side-effects                      |
|------------|-----------------------------------------|-----------------------------------|
| Diazoxide  | Inhibits pancreatic insulin release      | Hypotension, fluid and Na retention, hyperglycemia, tachycardia |
| Nifedipine | Ca channel blocker                       | Edema, dizziness, flushing        |
| Octeotride | Somatostatin analog; decreases GH secretion | Dysglycemia, hypothyroidism, ECG changes |
| Chlorothiazide | Inhibits Na reabsorption in distal renal tubules | Hyperglycemia hypertension hyperuricemia |
| Glucagon   | Insulin antagonist, accelerate hepatic glycogenolysis | Nausea vomiting |}

Conclusion

Avoiding long term complications of hypoglycemia like neurological damage is of prime importance in management of PHHI. Though uncommon but PHHI is clinically important cause of hypoglycemia in neonates, and must be considered in a patient with a presumptive pre-operative diagnosis of insulinoma. 

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