ORIGINAL RESEARCH PAPER

Neonatology

ROLE OF UMBILICAL CORD BLOOD C-PEPTIDE LEVEL IN EARLY PREDICTION OF HYPOGLYCEMIA IN HIGH RISK NEONATES

KEY WORDS:

Mudita Suman* Resident Doctor *Corresponding Author

Riya Mittal Resident Doctor

M.L.Gupta Sr. Professor And Unit Head

ABSTRACT

Background: Hypoglycemia is a common metabolic problem in high risk newborn i.e. IDM,LBW, Preterm, SGA,LGA, IUGR, and neonates with sepsis. Hyperinsulinimic hypoglycemia is a major Cause of hypoglycemic brain injury. C-Peptide is an useful marker of insulin production As it is secreted from pancreas along with insulin as byproduct, in equimolar concentration. **Aim:** To find out any relation between umbilical cord blood c peptide levels and hypoglycemia in high risk neonates To know the role of umbilical cord c peptide levels in early prediction of hypoglycemia in high risk newborn. **Method:** Study type: Prospective comparative observational study. This prospective comparative observational study done at pediatrics department of SMS medical college jaipur with 110 High risk newborns in two groups and with another 55 newborns with no risk for hypoglycemia and there c Peptide level considered as reference level. In this study umbilical cord blood c peptide level sent at the time of birth of all high risk newborns. Then blood glucose monitoring done at birth, 30 min., 1hr, 3hr, 6hr,12hr,18hr,24hrs. Then divided into two groups each of 55 ,First is High risk hypoglycemic neonates (BS<45mg/dl) and another high risk normoglycemic (BS>45 mg/dl). Another 55 newborns with no risk and normal blood glucose were also enrolled and there mean c peptide level was considered as reference level. Then comparison of c Peptide levels was done. **Result:** Mean cord blood c peptide level of newborns with no risk for hypoglycemia was 1.35±0.12 ng/ml, which is considered as reference level.Mean cord blood c Peptide level of High risk hypoglycemic newborns 6±0.37ng/ml, which is significantly higher from High risk normoglycemic group c peptide level I.e. 1.46±0.14ng/ml Umbilical cord blood c peptide levels were significantly higher in High risk hypoglycemic neonates as compared to high risk normoglycemic group. **Conclusion:** Umbilical cord blood c Peptide levels are high in high risk hypoglycemia. Umbilical cord blood C Peptide level can be used for early prediction of hypoglycemia in high risk Newborns. And can be used for prediction of NICU admission and prediction of frequent assessment of blood sugar is required or not. And early prediction of hypoglycemia by c peptide can be helpful in preventing hypoglycemia related morbidity and mortality.

INTRODUCTION

Hypoglycemia is a common metabolic problem in newborns.

Infants are at risk for more severe or prolonged hypoglycemia due to one or a combination of the following underlying mechanisms[1,2]

1. Insufficient glucose supply, with low glycogen or fat stores
2. Poor mechanisms of glucose production
3. Increased glucose utilization caused by excessive insulin production
4. Increased metabolic demand
5. Failure of counter-regulatory mechanisms (i.e., pituitary or adrenal failure)

Neonatal hypoglycemia most commonly affects the following groups of infants[3]

- Intrauterine growth restriction or small compared to gestational age infants
- Infants of diabetic mothers or large for gestational age infants
- Preterm infants (32 to 36.6 weeks gestational age)

Preterm, intrauterine growth restricted and small for gestational age infants are at risk for hypoglycemia because they are born with decreased glycogen stores, decreased adipose tissue and experience increased metabolic demands because of their relatively large brain size.[2,4]

In very low birth weight (<1000 g) preterm infants, the enzymes involved in gluconeogenesis are expressed at low levels; thus their ability to produce endogenous glucose is poor, contributing to their risk of severe or prolonged low glucose concentrations.[2]

Infants of diabetic mothers (IDM) and large for gestational age infants experience fetal hyperinsulinism and increased peripheral glucose utilization, putting them at risk for hypoglycemia in the immediate postnatal period.[2,4] The placenta supplies the fetus with a direct source of glucose via facilitated diffusion, such that fetal glucose concentrations are proportional to maternal levels. Prolonged elevations in maternal glucose concentrations result in fetal hyperglycemia and pancreatic overstimulation to increase endogenous fetal insulin production.[2] These elevated levels of fetal insulin persist after birth and, in the absence of a continuous exogenous glucose source, result in increased glucose utilization and lower blood glucose concentrations. IDM have a decreased ability to mobilize glycogen stores after birth and experience a relative adrenal insufficiency with decreased levels of catecholamines, further contributing to the risk of low blood glucose levels.[2]

Infants experiencing perinatal stress (e.g., fetal distress, perinatal ischemia, maternal preeclampsia/eclampsia, sepsis, hypothermia) or those with congenital heart disease have increased metabolic energy requirements, which puts them at risk for hypoglycemia.[2,4,5] Perinatal stress causes a state of 'hypoglycemic hyperinsulinism' that can persist for days to weeks, resulting in persistently low glucose concentrations requiring ongoing interventions to maintain euglycemia.[4]

Other iatrogenic causes of transient neonatal hypoglycemia include intrapartum administration of maternal medication (e.g., beta-adrenergic tocolytic agents, valproic acid, propranolol, and conduction anesthetics), delayed feeding, and exogenous insulin administration.[1,2]

Low glucose concentrations beyond the first 48 hours of life raise concern for an underlying disorder as the etiology of hypoglycemia. The underlying physiologic mechanisms that cause pathologic or persistent hypoglycemia are similar to those described above:

Causes of persistent neonatal hypoglycemia include:[2,6]

- Congenital hyperinsulinism
- Congenital syndromes: Beckwith-Wiedemann syndrome, Soto syndrome, Costello syndrome
- Endocrine disorders: congenital hypopituitarism, congenital adrenal hyperplasia, hypothyroidism
- Inborn errors of metabolism: maple syrup urine disease, glycogen storage disorders, hereditary fructose intolerance, galactosemia, fatty acid oxidation disorders

Indication for routine blood glucose screening[7]

1. Low birth weight infants (<2000 grams)
2. Preterm infants (<35 weeks)
3. Infant of diabetic mothers (IDM)
4. Infants with Rh-hemolytic disease
5. Infants born to mothers receiving therapy with terbutaline/propranolol/lebatolol/oral hypoglycemic agents
6. Infants with morphological IUGR.

C peptide is secreted from pancreas in equimolar concentration of insulin . It is unaffected by hemolysis and has a longer half life than insulin,it can be used for marker of insulin concentration in blood.

There are limited studies on umbilical cord blood c peptide level and risk of developing hypoglycaemia in neonates at high risk. Therefore this study was undertaken to evaluate the relationship between umbilical cord blood c peptide level and the risk of developing hypoglycaemia in high risk neonates.

METHOD

This study was conducted The study was conducted in the Department of Pediatrics, SPMCHI and attached hospitals, SMS Medical college, Jaipur From June 2021 to July 2022.

Study Design

Prospective observational hospital-based study.

All the neonates who are at high risk for hypoglycemia (Infant of diabetic mother, gestational age <35 weeks, SGA and LGA,LBW, Any sick neonate) were enrolled for study.

Neonates with no risk for hypoglycemia were also enrolled for study for reference C peptide level.

An informed consent was obtained from parents before enrollment and following characteristics were recorded- maternal profile like gravida, antenatal care, type of delivery, GDM, risk for sepsis, USG etc. And neonate's profile birth weight , height and head circumference, gestational age assessment using Ballard Score within 24 hours of birth.

All the neonates meeting the inclusion criteria were devided into 2 groups

Group A - Newborn with high risk for hypoglycemia with normal blood glucose levels

Group B - Newborn with high risks for hypoglycemia with low blood glucose levels.

Another 55 term neonates with no risk for hypoglycemia and with normal blood glucose levels were also enrolled for reference cord blood c peptide levels

Approximately 3mL of UC blood was collected immediately after delivery from all infants who met the inclusion criteria. The blood was chilled to 4°C, centrifuged as soon as possible, and Umbilical Cord serum C-peptide was measured using a third-generation ELISA at central lab, SMS medical college.

Blood glucose measurements were performed by glucometer at birth, after 30min, and 1, 3, 6, 12, 18 and 24h; follow-up blood glucose evaluations were performed until blood glucose got normalized. Along with this Neonatal outcome for neonates admitted to NICU was recorded.

Hypoglycemia was considered if Blood glucose level <45mg/dl.

Raised c-peptide level was considered if >1.35ng/mL

Quantitative data were represented as mean, standard deviation, median, and range. Data were subjected to student t-test to compare means of two groups. Qualitative data were presented as number and percentage and compared using either the Chi square test or Fisher's exact test.

RESULT

In this study there was no significant difference between both the groups according to neonatal and maternal Characteristics.

In this study, 55 newborns with no risk for hypoglycemia and normal blood glucose were studied and their mean cord blood C peptide level was considered as reference C peptide level. That was 1.35 ng/ml.

In our study, mean C peptide level of high risk normoglycemic group (Group A) was 1.46 ±0.14 ng/ml and mean C peptide level of high risk hypoglycemic group (Group B) was 6±0.37 ng/ml.

Means C peptide level of high risk normoglycemic group (Group A) newborns according to different high risk factors were as follows:
IDM 1.59±1.29 ng/ml, Term LGA 1.45±1.12 ng/ml, full term SGA 1.52±0.91 ng/ml , preterm AGA 1.38±0.70 ng/ml, newborn at risk factor sepsis 0.98±0.30 ng/ml.

Mean C peptide levels of high Group B i.e. high risk hypoglycemic group according to different risk factors were as follows:
IDM 6.66±2.66ng/ml , Term LGA 5.61±2.72 ng/ml, Term SGA 5.11±2.48 ng/ml. Preterm AGA 6.42±2.41 ng/ml, newborn at risk for sepsis were having mean c peptide levels of 5.30±3.06ng/ml.

C peptide levels were significantly higher in hypoglycemic group compared to normoglycemic Group, across all risk factors.

Table 1: Blood glucose levels in relation to risk factors

Risk Factor	High Risk Normo-glycemic(Group A)		High Risk Hypo-glycemic (group B)		P-value
	N	Mean blood glucose mg/dl Mean±SD	N	Mean blood glucose mg/dl Mean±SD	
IDM	12	90.83±1.29	18	35±8.75	<0.0001
Term (LGA)	18	93.26±14.3	18	32.21±3.92	<0.0001
Term (SGA)	6	81.79±6.19	9	34.25±7.21	<0.0001
Preterm (AGA)	16	97.25±1.12	16	36.5±7.01	<0.0001
Neotates With Risk Factor For Sepsis	25	105.9±16.0	30	37.39±4.94	<0.0001

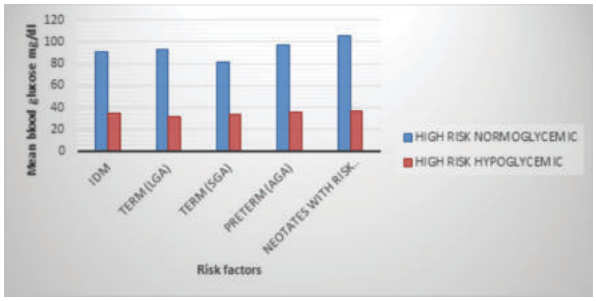

Fig.1

Table 1 and fig 1 shows that Blood glucose levels were significantly lower in group B that is high risk hypoglycemic group compared to group A high risk normoglycemic group .

TABLE 2: C-Peptide Level In Relation To Risk Factors

Risk Factor	High Risk Normo-glycemic (Group A)		High Risk Hypo-glycemic (group B)		P-value
	N	Mean C-peptide Ng/ml Mean±sd	N	Mean C-peptide Ng/ml Mean±sd	
IDM	12	1.59±1.29	18	6.66±2.66	<0.0001
Term (LGA)	18	1.45±1.12	18	5.61±2.72	<0.0001
Term (SGA)	6	1.52±0.91	9	5.11±2.48	<0.0001
Preterm (AGA)	16	1.38±0.70	16	6.42±2.41	<0.0001
Neotates With Risk Factor For Sepsis	25	0.98±0.30	30	5.30±3.06	<0.0001

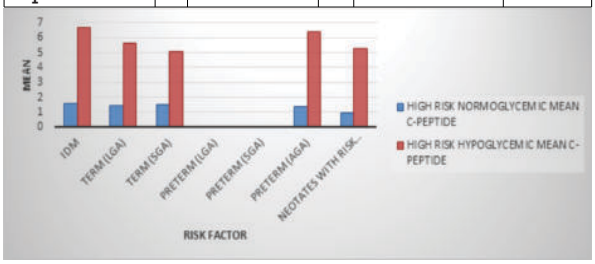

Fig. 2

Table and fig.2 shows that C peptide levels were higher in high risk hypoglycemic group (group B) compared to normoglycemic Group (group A) according to all risk factors ,which was statistically significant.

DISCUSSION

55 newborns with no risk for hypoglycemia and normal blood glucose were studied and their mean cord blood C peptide level was considered as reference C peptide level. That was 1.35 ng/ml.

Mean C peptide level of high risk normoglycemic group (Group A) was 1.46 ±1.14 ng/ml and mean C peptide level of high risk hypoglycemic group (Group B) was 6±0.37 ng/ml. C peptide levels of high risk hypoglycemic group was significantly higher than reference c peptide and normoglycemic group.

Begum MN et al[8] in her study found that C peptide levels were significantly higher in hypoglycemic IDM, that is 4.57± 2.50 ng/ml as compared to normoglycemic IDM that is 2.81± 2.11 which is statistically significant and similar to our study.

Similar findings were also reported by Abdelgadir et al[9], Godard et al[10], fellucca F et al[11]. This significant difference of means of C peptide value indicates that there may be an association between increased cord blood C peptide level with hypoglycemia in IDM.

Metzer BE et al[12] in his study reported that biochemical and clinical hypoglycemia were strongly associated with increased cord serum C peptide levels.

Saber et al[13] found a statistically significant increase in C peptide levels in infants who develop hypoglycemia compared to control group, suggesting that Cord blood C peptide can be used as an early predictor of hypoglycemia in IDM.

Sosenko et al[14] also conducted a study with 79 IDM and 62 non IDM and found that IDM has a higher level of cord blood C peptide which was significantly associated with hypoglycemia.

In our study the cord blood C peptide level was significantly higher in IDM as well as non IDM high risk hypoglycemic newborns.

Above studies shows significant relation between hypoglycemia and raised C peptide levels. These results are similar to our study.

CONCLUSION

To conclude cord blood C peptide levels were significantly higher in high risk hypoglycemic neonates, compared to high risk normoglycemic infants. Hence cord blood C peptide levels may prove to be an important test to predict hypoglycemia in high risk neonates. It will help in identifying neonates who are at risk of developing hypoglycemia and need frequent blood glucose monitoring and NICU admission. This in turn may help in reducing hypoglycemia related morbidity and mortality in neonates.

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