

Original Research Article

A comparative study of blood glucose and serum calcium levels in term IUGR neonates and normal neonates: a cross sectional study

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ABSTRACT

Background: Hypoglycemia and hypocalcemia are common metabolic problems occurring in the newborn and have direct consequences in the early neonatal period, prompt identification and treatment prevents severe neurodevelopmental outcomes. The primary objective was to compare blood glucose and serum calcium levels in term Intrauterine growth restriction (IUGR) babies with term appropriate for age (AGA) babies and secondarily to compute number of term IUGR babies with hypoglycemia and hypocalcemia.

Methods: Fifty term IUGR and 50 term AGA babies delivered at SDMCMSH, Dharwad during the study period of one year were included as cases and controls respectively after considering the inclusion and exclusion criteria. Two ml of peripheral venous blood was analyzed at 3 hours and 24 hours of life. Serum calcium was measured by calorimetric test method and blood glucose by auto analyzer. Statistical analysis was done using SPSS-17.

Results: At 3 hours of birth, 24% of term IUGR and 4% of AGA neonates had hypoglycemia. The mean RBS of cases at 3rd hour was 61.36 ± 23.56 mg/dl, significantly lower than control group (75.90 ± 22.57 mg/dl). The mean RBS among cases at 24 hours of life was 70.42 ± 16.14 mg/dl compared to 78.84 ± 15.90 mg/dl among controls. Both correlations were statistically significant. 8% cases had hypocalcemia at 3 hours and 6% had at 24 hours. The mean serum calcium level was lower in cases (8.50 ± 1.40 mg/dl) than controls (8.63 ± 1.14 mg/dl) at the 3rd hour of life and 24 hours of life [cases (8.42 ± 1.07 mg/dl) versus controls (8.64 ± 0.91 mg/dl)].

Conclusions: Significantly lower blood glucose levels were identified in term IUGR neonates. This association was apparent at 3 hours of life. The measurement of serum calcium & glucose in IUGR babies could predict a poorer outcome in these patients. Identifying and treating these biochemical abnormalities can avoid short term as well as long term sequelae.

Keywords: AGA, Hypoglycemia, Hypocalcemia, IUGR

INTRODUCTION

Nearly one third of neonates born in India are low birth weight (LBW), weighing less than 2500 grams at birth. A baby's low birth weight is either the result of preterm birth (before 37 completed weeks of gestation) or due to intrauterine growth restriction (IUGR).¹ IUGR is akin to malnutrition and may be present in both term and preterm

infants. Neonates affected by IUGR are usually malnourished, undersized and therefore have lower birth weight. Two-third LBW neonates born in India fall in this category. Since IUGR neonates are more likely to suffer complications like hypoglycemia, it is important that these infants are identified and managed appropriately at birth. Even after recovering from neonatal complications, they remain more prone to poor physical growth, poor

neurodevelopmental outcome, recurrent infection and chronic diseases (hypertension, hyperlipidemia, diabetes mellitus and coronary heart disease) later in life.² Hypoglycemia as a consequence of IUGR is a major risk factor for neurodevelopmental impairment. The factors that predispose these patients to hypoglycemia include failure of counter-regulation, immaturity of the enzyme systems regulating glycogenolysis, gluconeogenesis, ketogenesis, reduced adipose tissue stores, hyperinsulinism or increased sensitivity to insulin.³ 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.⁴

Ionic calcium is crucial for many biochemical processes including blood coagulation, neuromuscular excitability, cell membrane integrity, and many of the cellular enzymatic activities. Hypocalcemia is a frequently observed clinical and laboratory abnormality in neonates.⁵ Risk factors for early-onset hypocalcemia include prematurity, being small for gestational age (including IUGR), maternal diabetes, and perinatal asphyxia. Symptoms and signs of neonatal hypocalcemia rarely occur unless total serum calcium is <7 mg/dL. Signs include hypotonia, tachycardia, tachypnea, apnea, poor feeding, jitteriness, tetany, and seizures.⁶

Healthy term infants undergo a physiological nadir in serum calcium levels by 24-48 hours of age. This nadir may drop to hypocalcemic levels in high-risk neonates including preterm infants and term IUGR.⁷ Since hypoglycemia and hypocalcemia are associated with direct consequences in the early neonatal period, prompt identification and treatment could prevent severe neurodevelopmental outcomes.

This study was designed with the primary objective of comparing the blood glucose and serum calcium levels in term IUGR babies with term appropriate for age (AGA) babies and secondarily to compute the number of term IUGR babies with hypoglycemia and hypocalcemia.

METHODS

A total of 50 term IUGR babies and 50 term AGA babies delivered at S D M Medical College Hospital, Dharwad during the study period of one year were included in the study as cases and controls respectively. The neonates with gestational age of more than 37 completed weeks with a birth weight less than 10th percentile formed the cases and those neonates born with gestational age more than 37 weeks and birth weight more than 2.5 Kg were taken as controls. Gestational age was assessed using New Ballard Score and Lubchenco charts were used to identify IUGR babies.

Exclusion criteria

- Infant of diabetic mothers

- New born babies with moderate to severe perinatal asphyxia
- Congenital anomalies (obvious external anomaly)
- Preterm neonates (AGA, IUGR)
- Newborn babies with sepsis

Sample collection

One to two ml of peripheral venous blood was drawn under aseptic precautions at 3 hours and 24 hours of life and sample was immediately sent to lab. Serum calcium was measured by calorimetric test method expressed in mg/dl. Blood glucose was measured by auto analyser.

Blood glucose levels less than 40mg/dl was defined as hypoglycemia. Hypocalcemia was defined as serum calcium less than 7 mg/dl or ionised calcium less than 4 mg/dl.

Statistical methods

Descriptive and inferential statistical analysis were carried out. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in number (%). Significance was assessed at 5% level of significance. Independent student T test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups (inter group analysis) on metric parameters.

Chi-square/Fisher Exact test were used to find the significance of study parameters on categorical scale between two or more groups, non-parametric setting for qualitative data analysis.

RESULTS

The mean birth weight in the IUGR group was 1.85±0.27 kg, while the mean birth weight in the control group was 3.02±0.28 Kg. Forty-two cases (84%) in the IUGR were low birth weight, 8 cases (16%) were very low birth weight, none of the cases were born extremely low birth weight. At 3 hours of life, 12 cases (24%) had hypoglycemia (<40 mg/dL) while only 2 (4%) among the controls had hypoglycemia. The difference was statistically significant (Table 1).

Table 1: Random blood sugar among cases and controls at 3 hours of life.

| RBS at 3 hrs of life | Cases | | Controls | | P value |
|----------------------|-------|----|----------|----|---------|
| | No. | % | No. | % | |
| <40 mg/dl | 12 | 24 | 02 | 4 | 0.008 |
| >40 mg/dl | 38 | 76 | 48 | 96 | |

One case (2%) and 1 control (2%) had hypoglycemia around the 24th hour of life The mean RBS among cases at the 3rd hour of life was 61.36±23.56 mg/dl,

significantly lower in comparison to that of the control group (75.90±22.57 mg/dl). Similarly, the mean RBS of cases between at 24 hours of life was 70.42±16.14 mg/dl compared to 78.84±15.90 mg/dl among controls. Both correlations were statistically significant (Table 2).

Table 2: Comparison of mean RBS among cases and controls.

| RBS | Cases (mg/dl) | Controls (mg/dl) | P value |
|-------------------|---------------|------------------|---------|
| 3rd hour of life | 61.36±23.56 | 75.90±22.57 | 0.002 |
| 24th hour of life | 70.42±16.14 | 78.84±15.90 | 0.010 |

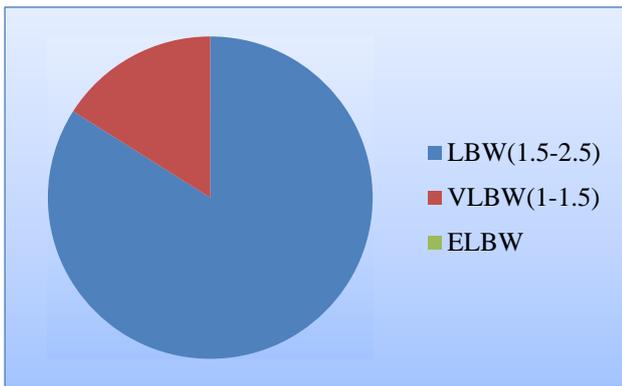


Figure 1: Distribution of cases based on birth weight.

Four cases (8%) had hypocalcemia at the 3rd hour of life and 3 cases (6%) had hypocalcemia at 24 hours of birth. Whereas, none among the control population had hypocalcemia. However, this comparison was not statistically significant.

Table 3: Serum calcium levels among cases and controls.

| Serum Calcium (mg/dl) | Cases (n=50) | | Controls (n=50) | | P value |
|-------------------------------------|--------------|------|-----------------|-------|---------|
| | No | % | No | % | |
| 3rd hour of life | | | | | |
| <7 | 4 | 8.0 | 0 | 0.0 | 0.221 |
| 7-11 | 46 | 92.0 | 50 | 100.0 | |
| 24th hour of life | | | | | |
| <7 | 3 | 6.0 | 0 | 0.0 | 0.242 |
| 7-11 | 47 | 94.0 | 50 | 100.0 | |

Table 4: Comparison of mean serum Calcium in the two groups of patients studied.

| Serum Calcium | Cases | Controls | P value |
|-------------------------------|-----------|-----------|---------|
| 3 rd hour of life | 8.50±1.40 | 8.63±1.14 | 0.595 |
| 24 th hour of life | 8.42±1.07 | 8.64±0.91 | 0.225 |

The mean serum calcium level was lower in cases (8.50±1.40 mg/dl) than controls (8.63±1.14 mg/dl) at the

3rd hour of life (Table 3). Similarly, the mean calcium level was also lower in cases (8.42±1.07 mg/dl) compared to controls (8.64±0.91 mg/dl) at 24 hours of life (Table 4). However, the difference was not statistically significant.

Table 5: General characteristics.

| Parameter | Cases | Controls |
|------------------------------------|------------|------------|
| Total number of subjects | 50 | 50 |
| Gender distribution; (Male:Female) | 3:2 | 3:2 |
| Birth weight (kg) | 1.85±0.27 | 3.02±0.28 |
| Age of mother (years) | 25.58±4.12 | 25.28±2.98 |
| Apgar score | | |
| 1 minute | 7.22±0.58 | 7.18±0.44 |
| 5 minutes | 8.26±0.44 | 8.42±0.54 |
| New Ballard score | 35.22±2.38 | 38.74±2.48 |

The general characteristics of the study subjects has been tabulated in Table 5.

DISCUSSION

Intrauterine growth and its aberrations are a major concern of obstetrics as well as neonatology. The birth weight is one of the strongest known indicators of perinatal mortality.⁸ The significance of analyzing birth weight as a function of gestational age is established by the fact that this association has a direct effect on perinatal mortality and morbidity. Williams et al showed that within fixed gestational age strata, perinatal mortality is related inversely to birth weight.⁹ As far as the morbidity in such cases is concerned, the incidence of neurodevelopmental impairment in both pre-term and term growth retarded infants is considerably increased.

Hypoglycemia is the most common metabolic problem occurring in newborn in the presence of certain risk factors especially in IUGR neonates. Since the symptoms of hypoglycemia are highly nonspecific, more so in small sick neonates, it can be easily missed clinically. Therefore, hypoglycemia must always be confirmed biochemically and by response to treatment.

Calcium ions in ECF and ICF are essential for many biochemical processes. Significant aberration in calcium levels are frequently observed in the neonatal period. Once the baby is born, its calcium levels now depend on PTH secretion, dietary calcium, renal resorption, skeletal stores and vitamin D.

Hence after delivery, calcium levels start decreasing and return to normal by the 3rd day of life. However, the efficacy of intestinal absorption and renal handling matures by 2-4 weeks. This transition is responsible for the high incidence of hypocalcemia in neonates, especially in high risk neonates like IUGR babies. Infants with IUGR may have hypocalcemia if they were born

preterm or have had perinatal asphyxia. SGA is not an independent risk factor for early onset Neonatal Hypocalcemia (ENH).¹⁰

Since hypoglycemia and hypocalcemia are associated with direct consequences in the early neonatal period and may cause irreversible neurological sequelae later, this study was aimed at identifying these metabolic alterations in the high risk IUGR neonate.¹¹

The mean birth weight among cases in our study was 1.85 ± 0.27 kg (ranging from 1.25 kg to 2.3 kg) and that of the controls was 3.02 ± 0.28 kg (ranging from 2.5 kg to 3.5 kg). In both groups 60% of the subjects were male. These findings were very similar to a study done in 2012.⁸ The incidence of hypoglycemia in IUGR babies has been well established. Several studies indicate that hypoglycemia is among the commonest metabolic disorders affecting IUGR babies.¹²

In this study, 50 IUGR neonates who were either given direct breastfeeds or given expressed breast milk (by pallada or tube) and 50 breastfed AGA neonates formed the 2 study groups. All the cases received NICU care in view of LBW and VLBW care. 24% of the term IUGR neonates developed hypoglycemia within the first 12 hours of life (at the 3rd hour), while only 4% of the term AGA babies did so. Hasmasanu et al conducted a study in 2013 which revealed that 27.3% of the IUGR neonates developed hypoglycemia while 4.3% of the AGA babies did so.¹³ Similarly, Mazumder et al studied the correlation of hypoglycemia in IUGR neonates and observed a much higher incidence (46.9%) compared to 3.1% among term AGA neonates.⁸ Lubchenko et al found that 25% of term IUGR neonates presented with hypoglycemia compared to 10% among term AGA neonates.¹⁴ A study done by Bhat MA et al also revealed that 23.9% of term IUGR infants had hypoglycemia in the first day of life.¹⁵ The incidence of hypoglycemia in IUGR babies was higher than AGA babies.

In this study, the incidence of hypoglycemia among VLBW neonates was 37.5% compared to 21.4% in LBW neonates at 3 hours of birth. At 24 hours, none of the VLBW babies had hypoglycemia while 2.3% of LBW babies had hypoglycemia. This finding was comparable to the study conducted by Lubchenko et al suggesting that as birth weight decreases, the incidence of hypoglycemia increases in term IUGR neonates.

However, in this study, a second blood glucose reading was taken at 24 hours of birth and revealed only 2% in each group had hypoglycemia, this can be attributed to the fact that all patients with hypoglycemia were managed with intravenous or oral feeds between the two readings.

The physiological levels of calcium are very unstable in the first few days following birth, due to abrupt interruption of placental supply, low levels of PTH, high

levels of calcitonin and physiological acidosis. Infants with intrauterine growth retardation are especially at risk for developing hypocalcemia. Hypocalcemia is often asymptomatic may remain undiscovered and untreated.¹⁶

Blaga et al in 2011 found that 16% of term IUGR neonates presented with hypocalcemia.¹⁶ An Indian study found that 10% of the cases, which consisted of 200 term IUGR infants had hypocalcemia in comparison to 4% of the normal control population.¹⁷ Mazumder et al also correlated serum calcium with growth retarded neonates, in this study, 9.4% of the term IUGR babies had hypocalcemia versus 6.2% among term AGA babies.⁸ However, a study observed that an incidence of neonatal hypocalcemia in IUGR infants was not increased above the incidence expected from their respective gestational ages unless associated with asphyxia.¹⁸

In this study, 8% of term IUGR neonates had hypocalcemia at the 3rd hour of birth and 6% at 24 hours of life. Although these findings are similar to other studies, none of the patients in the control group had hypocalcemia. Moreover, this correlation was not statistically significant.^{8,16,17}

In this study, the outcomes of neonates with hypoglycemia and hypocalcemia were not followed up and both glucose and calcium levels obtained at 24 hours of life were unreliable as interventions done for correcting these metabolic abnormalities were undertaken due to ethical issues.

Both hypoglycemia as well as hypocalcemia needs close clinical evaluation and biochemical monitoring for timely identification and appropriate management. Hypoglycemia should be treated promptly with early enteral or intravenous nutrition that may prevent adverse neuro-developmental outcome.¹²

CONCLUSION

The aims of this comparative 2 group-controlled study were to estimate blood glucose levels and serum calcium levels in 50 term IUGR neonates and 50 term AGA neonates and to find the number of neonates presenting with these metabolic derangements within the first day of life.

In this study, it was observed that significantly lower blood glucose levels were identified in intrauterine growth restricted term neonates. This association was apparent at 3 hours of life. Since both symptomatic and asymptomatic hypoglycemia have been linked to worse neuro-developmental outcomes later in life, efforts to promptly identify and treat hypoglycemia is warranted.

The measurement of serum calcium in high risk neonates, including IUGR babies could predict a poorer outcome in these patients.

However, there were a few limitations in this study. The natural course and consequence of hypoglycaemia were not observed as all the babies that had hypoglycaemia were treated due to ethical issues. Total calcium levels were measured, which includes ionized calcium and calcium bound to albumin. In this study serum albumin was not measured.

Considering the results of this study as well as those done earlier, identifying and treating these biochemical abnormalities can potentially avoid both short term as well as long term sequelae in these infants.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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