

HYPOCALCEMIA AMONG PRETERM AND VERY LOW BIRTH WEIGHT NEONATES IN A TERTIARY CARE NEONATAL UNIT

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ABSTRACT

Objective: To assess the relationship of hypocalcemia with prematurity and low birth weight.

Study Design: Prospective observational study

Place and Duration of Study: Study was conducted in Pak Emirates Military Hospital Pakistan, from Jan 2018 to Jun 2018.

Methodology: Seventy five preterm and very low birth weight neonates were selected for this study. The cut-off values for hypocalcemia were taken as Ionized Calcium level $<1\text{mmol/L}$ and total Calcium level of $<1.75\text{mmol/L}$. The study samples were drawn between 24-72 hrs of life. All babies received prophylactic intravenous calcium gluconate by 4ml/kg/day .

Results: The frequency of hypocalcemia was found to be 50.7% in premature and very low birth weight neonates with 37.3% in early preterm neonates and 13.3% in late preterm. The average ionized calcium levels in hypocalcemic neonates were found to be $0.844 \pm 0.014\text{mmol/L}$ and that in normocalcemic neonates were $1.105 \pm 0.017\text{mmol/L}$. A statistically significant incidence of hypocalcemia was documented in premature and very low birth weight neonates with a p -value <0.001 . However, no definite linearity was established between hypocalcemia and gestational age or birth weight.

Conclusion: Hypocalcemia has an increased frequency in early preterm neonates within 72 hours due to immature hormonal responses and poor calcium reserves. However, a significant direct proportionate relationship between prematurity and low birth weight with early onset neonatal hypocalcemia could not be established through our study.

Keywords: Hypocalcemia, Ionized calcium, Premature neonates, Very low birth weight.

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INTRODUCTION

Hypocalcemia is very commonly observed in neonates in first 72hrs of life due to abruptness of supply of calcium from placental circulation¹. Hypocalcemia when occurs in the first three days of life is termed as early onset hypocalcemia. Underlying pathophysiology can be attributed to an active uptake of calcium from mother to fetus towards the last gestational weeks, which contributes to the fetal skeletal maturity. Hypocalcemia in a premature neonate is defined as serum total calcium level below 7mg/dl ($<1.75\text{mmol/L}$) and serum ionized calcium level less than 4mg/dl ($<1\text{mmol/L}$)². Soon after birth,

calcitonin levels reach their peak levels in absence of parathyroid hormone and thus contributing to hypocalcemia. After 48 hours of life, parathyroid hormone levels gradually normalize in neonate's blood in response to hypocalcemia. Hypocalcemia in a premature neonate is usually asymptomatic but it should be corrected over next 72 hours. This exaggeration of early neonatal hypocalcemia in a preterm neonate is mainly attributed to the immature hormonal response system, impaired calcium intestinal absorption and immature renal reabsorption and decreased intake or supply. When symptomatic it can lead to hypotonia, jitteriness, seizures, tetany and tachycardia.

Hypocalcemia which occurs after 7th day of life is termed as late onset hypocalcemia³. Vitamin D deficiency, hypoparathyroidism,

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hyperphosphatemia, hypomagnesemia, sepsis, metabolic syndromes, renal insufficiency, cow's milk intake, and vitamin D resistance are all amongst etiology of late onset hypocalcemia.

In our study, we have measured the incidence of hypocalcemia in preterm neonates with very low birth weight (<1500gm).

METHODOLOGY

This was a prospective observational study in which we measured serum total and serum ionized calcium levels in preterm (less than 37weeks) and very low birth weight neonates (≤ 1500 grams) being admitted in neonatal intensive care unit of Pak Emirates Military Hospital, Rawalpindi from 1st January 2018 till 30th June 2018. Majority neonates were booked indoor deliveries. Neonates were enrolled in this study after taking informed consent from parents.

Serum Calcium level was sent after 24-48 hours of birth but within 72 hours of life. A total of 75 preterm neonates were enrolled in this study. All neonates with maternal risks of hypoparathyroidism were excluded. Neonates with birth asphyxia, infants of diabetic mother and neonates requiring phototherapy within 48 hrs were excluded from our study. All neonates received prophylactic intravenous calcium infusion at a dose of 4ml/kg/day of 10% calcium gluconate in maintenance fluids or through oral supplementation as orogastric feeds depending upon their clinical status and co-morbid⁴.

A minimal of 1CC blood sample was withdrawn for each test through peripheral venous puncture and dispatched in two sample bottles; one being plain for serum total calcium levels and other being the lithium heparin bottle for the ionized calcium levels. Ionized calcium sample was dispatched with ice pack.

The cut-off range for hypocalcemia in our study was defined as serum total calcium level <1.75mmol/l and serum ionized calcium level <1mmol/l. Serum total calcium levels were not corrected for albumin levels. All babies were labelled to have hypocalcemia when either both

serum total calcium and ionized calcium levels or only ionized calcium levels were found to be below cut-off values².

The data was recorded on forms provided and then saved in IBM SPSS (Statistical Package of Social Sciences) Statistics version 21.0. Two major categories were made on basis of gestational age namely <32 weeks and ≥ 32 weeks - 36+6 weeks. Similarly weight was also recorded by dividing the premature neonates into two groups; 1000-1500grams and <1000grams. The risk factors associated with prematurity were also recorded along with gender and sepsis screen.

The data was analyzed by frequency, percentages, one sample t-test, comparison of means and Correlation co-efficient. The percentages of hypocalcemia amongst the two gestational groups were also recorded. Significance of data was measured by calculating *p*-value.

RESULTS

A total of 75 preterm and very low birth weight neonates were enrolled in our study. The values of plasma total calcium and ionized calcium levels were measured in this study. The average serum total calcium values in premature neonates were found to be 2.04mmol/L in <32 weeks (early preterm) and 2.03mmol/L in >32 weeks (late preterm) which is above the cut-off value of 1.75mmol/L for hypocalcemia when total calcium level is considered (table-I). Whereas the average plasma ionized calcium levels were found to be 0.965mmol/L in <32 weeks babies (Early Preterm) and 0.989mmol/L in >32 weeks babies (Late Preterm) which is below cut-off value for hypocalcemia i.e. 1mmol/L (figure). In this study's data, although we gathered total calcium levels without albumin correction, we have labelled patients to have hypocalcemia when only ionized calcium levels were found to be less than designated cut off value of 1.0 mmol/L.

In hypocalcemic patients, the mean plasma total calcium was 1.922 ± 0.030 mmol/L and mean ionized calcium levels were 0.844 ± 0.014 mmol/L. The normocalcemic group had a mean total

calcium value of 2.149 ± 0.030 mmol/L and a mean ionized calcium value of 1.105 ± 0.017 mmol/L. The ionized calcium values for the hypocalcemic group was 1.4 times lower than the normocalcemic group.

The study data as previously mentioned was divided in two groups based on gestational

and 58.7% delivered via Cesarean section. The gender distribution was 56% males and 44% females; and it had no significant correlation with incidence of hypocalcemia. (table-II).

One sample t-test showed a statistically significant total hypocalcemia in preterm neonates in the current study with a *p*-value of less than

Table-I: Comparison of total and ionized calcium levels among the two gestational age groups.

Gestational Age	Mean Total Calcium Level (mmol/L)	Mean Ionized Calcium Level (mmol/L)	Hypocalcemia (% age)
<32 weeks	2.04	0.965	56
>32 to <36 + 6 weeks	2.03	0.989	40

Table-II: Gender wise and mode of delivery wise distribution.

Gender	Mode of Delivery			
	Spontaneous Vaginal Delivery		Lower Segment C-section	
	Male	Female	Male	Female
	17 (54.8%)	14 (45.2%)	25 (56.8%)	19 (43.2%)

Table-III: Comparison of frequency of hypocalcemia based on birth weight vs gestational age.

Hypocalcemia	Incidence based on birth weight (grams)		Incidence based on gestation (weeks)	
	VLBW (1000-1500gms)	ELBW (<1000gms)	Late Preterm (32 wks - 36+6wks)	Early Preterm (<32 wks)
Present	48.4% (31)	63.6% (7)	40% (10)	56% (28)
Not Present	51.5% (33)	36.3% (4)	60% (15)	44% (22)

age and birth weights separately. Out of the total 75 neonates, 50 (66.6%) were <32 weeks and 25 (33.3%) neonates were in 32-36+6 weeks age group. Amongst the neonates with hypocalcemia; 28 (73.7%) babies were below 32 weeks of gestation and 26.3% were between 32nd and 36+6 week of gestation. In babies with normocalcemia; 22 (59.5%) were <32weeks and 15 (40.5%) were from 32-36+6 weeks.

On the basis of weight; 11 (14.7%) neonates weighed <1000grams and 64 (85.3%) neonates weighed between 1000-1500grams range. The percentage distribution of hypocalcemia group on basis of weight was calculated to be 18.4% in <1000 grams and 78.9% of babies had weight between 1000 to 1500grams. Thus showing no linear relation between hypocalcemia and birth weight (table-III).

The risk factors associated with prematurity were also determined showing an increased relation of prolonged rupture of membranes with prematurity. Out of the total data; 41.3% delivered through spontaneous vaginal delivery

0.01 and a mean difference in ionized calcium value of 0.261mmol/L between babies with normocalcemia and hypocalcemia irrespective of

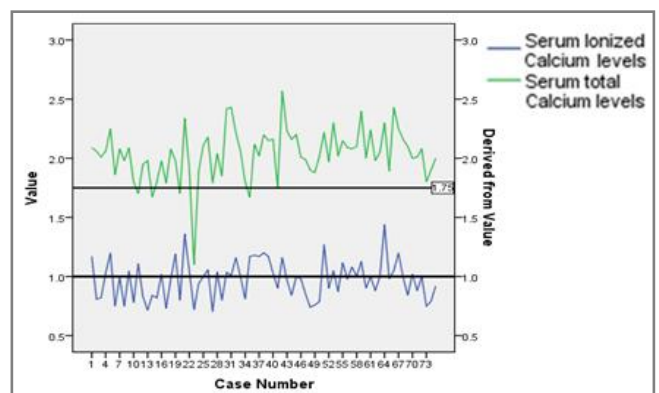


Figure: Proportionate relationship between total calcium values and ionized calcium values.

gestational age or birth weights.

According to bivariate correlation between the two gestational age groups, there was no significant relationship between incidence of hypocalcemia in late preterm and very preterm

babies or in very low birth weight and extremely low birth weight babies.

According to linear regression analysis, ionized calcium level were not linearly related with gestational age and birth weight. However, a significant proportionate relation was found between plasma total calcium levels and plasma ionized calcium levels when means were compared.

DISCUSSION

Early onset neonatal hypocalcemia has been documented more evidently in preterm and small for gestational age neonates⁵. During third trimester of intrauterine life, calcium is actively transported through a transplacental pump. This uptake is promoted by parathyroid hormone related peptide (PTHrP), substantiated by comparison of calcium levels in maternal blood and cord blood;

which are high in the later⁵. This active transport leads to higher plasma calcium concentrations in fetal blood. Thus a high serum total calcium level of 2.5-2.75mmol/L and ionized calcium level of 1.5mmol/L. After abruptio of maternal supply, the total calcium levels fall to 2.0-2.25mmol/L and ionized calcium levels reach 1.1-1.35mmol/L.

Out of the 1% calcium in extracellular fluid, 50% is present as free ionized form and it is actually the biologically active form⁷. In this context, a number of studies have been performed to record hypocalcemia using ionized calcium or albumin corrected total calcium in past⁶. Very recently, newer studies have been directed to assess the importance of calcium supplementation and prophylaxis in premature neonates with symptomatic and asymptomatic hypocalcemia⁴. According to a research conducted on 1200 patients with calcium disorders, a comparison of efficacy of three different laboratory methods; serum total calcium, albumin-corrected total calcium and ionized calcium levels; was made which showed that albumin corrected total calcium and ionized calcium levels had the lesser discordance of up to 17.9%⁶. So, our study was

performed on preterm and very low birth weight newborn babies to validate the relationship between prematurity and hypocalcemia by measuring ionized calcium levels only. The results of our study, however, did not relate the fact that birth weight also had an impact on the levels of calcium apart from gestational age. According to an earlier study performed on total calcium in low birth weight neonates, a significant positive correlation was established between hypocalcemia and low birth weight. About 20.2% of the babies had hypocalcemia⁸.

Another study performed on extremely low birth weight babies before 24 hours of life also showed marked hypocalcemia with mean calcium values of 6.90 mg/dl and a 95% confidence interval⁹. This previous study emphasized that the current reference range used to define hypocalcemia may not be actually true. Similarly, in a research trial conducted at a hospital in Brooklyn, calcium levels were measured on first day of life in term and premature infants. A significant positive correlation was found between weight of neonates and calcium levels¹⁰.

A study performed on 53 newborn babies under 72hrs of life, at Minnesota University, by measuring ionized calcium levels did not show a significant positive correlation between weight or gestational age and hypocalcemia incidence¹¹.

Hypocalcemia should be promptly treated as it can lead to certain serious implications. Oral calcium therapy is usually indicated in neonates with asymptomatic hypocalcemia and intravenous (IV) therapy is given to those with symptoms of seizures and in planned surgeries¹². For IV therapy injectable calcium gluconate can be given via peripheral line or calcium chloride can be given via umbilical vein. A study was conducted on extremely preterm neonates in which calcium levels were recorded after certain hours of birth; 37% developed hypocalcemia at 12 hours, 83% by 24 hours and 89% by 36 hours. In our study, 50.7% of babies were hypocalcemic between 24-72 hours of life. The former study also inferred that hypocalcemia in extremely

preterm babies was resistant to even higher than physiologic doses of calcitriol¹³. For management of asymptomatic hypocalcemia; 3mmol/kg/day of intravenous calcium gluconate can be added to fluids until establishment of enteral feeding. In patients with symptomatic hypocalcemia, 0.15 mmol/kg of intravenous calcium gluconate can be given as a stat slow correction¹².

In a study carried out at neonatology department of Slovenia, various risk factors such as prematurity, Vitamin D deficiency, neonatal sepsis, exchange transfusion, perinatal asphyxia and maternal gestational diabetes were found to be associated with hypocalcemia¹⁴. Amongst them 28% of the neonates with hypocalcemia were premature making it a predominant risk factor.

In another study, conducted retrospectively; without any preference for gestational age, to determine the clinical features and risks of hypocalcemia; serum ionized calcium levels were found to be low in 13.2% of the babies with low birth weight¹⁵. This current study also did not show a significant linear relation between hypocalcemia and birth weight.

Transient neonatal hypocalcemia is usually observed in babies presenting with late onset symptomatic hypocalcemia and it is mainly attributed to vitamin D deficiency and hypoparathyroidism¹⁶. In the 8th international conference of child's bone health, transient neonatal hypoparathyroidism was reported as an important cause of neonatal hypocalcemia¹⁷.

In an Iranian study, the frequency of early and late onset neonatal hypocalcemia was determined retrospectively over 796 neonates¹⁸. Two hundred sixty seven of neonates were found to be hypocalcemic showing a statistically significant relation between prematurity and early onset hypocalcemia. Our study showed that 38 out of 75 neonates had early onset hypocalcemia which was statistically significant.

Prematurity leads to an increased risk of bone related metabolic disorders. Evidence shows that premature babies are more prone to hypocalcemia likely due to lesser trans-placental

mineral delivery, rapid loss and increased calcitonin. Serum calcium and phosphorous levels were found to be significantly decreased in babies <30 weeks of gestation as compared to controls in a research conducted on premature babies to assess bone mineralization^{19,20}. Thus supporting the significant incidence of early onset hypocalcemia of 50.7%.

A study conducted over an 8 month duration showed hypocalcemia in 29.8% of low birth weight neonates²¹. According to another study conducted on 900 mother-neonate pairs, to measure calcium levels, a significant percentage (79.09%) of hypocalcemia was found in premature neonates²². In comparison our study sample and duration was small. Amongst other limitations, difficulty in sampling of premature and very low birth weight neonates also contributed as a drawback.

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CONCLUSION

Hypocalcemia has an increased frequency in early preterm neonates within 72 hours due to immature hormonal responses and poor calcium reserves. However, a significant direct proportionate relationship between prematurity and low birth weight with early onset neonatal hypocalcemia could not be established through our study.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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