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Original Research Article

Magnitude of Hypocalcemia in Hypoxic Ischemic Encephalopathy in Term Neonates

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Abstract: *Hypoxic ischemic encephalopathy has continued to be a global problem for term neonates and the leading cause of hypocalcemia.* ***Objective:*** *The aim of this study was to find out the magnitude of hypocalcemia in hypoxic ischemic encephalopathy in term neonates.* ***Method:*** *The current study was carried out in neonatal intensive care unit Bacha Khan Medical Complex Gajju Khan Medical College Swabi from August 2023 to January 2024 after taking approval from the ethical committee of the institute. All neonates (from birth to 3 days of age) presented to NICU with hypoxic ischemic encephalopathy were screened for hypocalcaemia. 5 ml venous blood sample was drawn from each participant for serum calcium (total ionized). Cobas Roche analyzer was used to measure total calcium, and an apparatus known as Easylyte was used to measure ionized calcium. Data was analyzed through SPSS. Mean & SD had been derived for age. Post stratification chi square analysis was done and relationship of hypocalcaemia was evaluated with factors such as: ages, weight, sex, gestational age & mother's educational status. P-value ≤0.05 was deemed as significant.* ***Results:*** *In the current study a total of 120 neonates with hypoxic ischemic encephalopathy were included out of which 80 (66.6%) were male and 40 (33.3%) were females. The mean age of the study population was 1.0-0.7 days. Based on the medical records, the neonate's mean birth weight was 2.85 + 0.6 kg. Serum ionized calcium levels were 4.2 + 0.8 mg/dl on average. The operational definition of hypocalcemia states that it was observed in 41 (34.1%) of participants. The prevalence of hypocalcemia varied significantly among these factors according to the neonate's age at birth, weight at birth, and mothers' educational status (p-value <0.05).* ***Conclusion:*** *Our study concluded that one of the major causes of hypocalcemia (34%) in term neonates is hypoxic ischemic encephalopathy.*

Keywords: Magnitude; Hypocalcemia; Hypoxic ischemic encephalopathy; Term neonates

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Introduction

Neonatal encephalopathy is the leading cause of long term illness and newborn mortality .It affects 2–5 newborns out of every 1000 live births. Cerebral ischemia is defined as "decreased quantity of blood that gets to the brain," whereas hypoxemia is defined as a decline in oxygenated blood flow. Both kinds of oxygen deficiency are significant, however cerebral ischemia is of greater importance as it also results in glucose deprivation, which contributes to the formation of damaging neurons. (1) Hypoxic ischemic encephalopathy (HIE), sometimes referred to as hypoxic ischemic cerebral injury, has continued to be a global problem for term and near-term newborns. Despite significant improvements in maternal health over the past few decades, hypoxic ischemic encephalopathy—the primary reason of encephalopathy in newborns—is still considered a dangerous condition that can result in significant illness and death. (2, 3) HIE, sometimes referred to as newborn asphyxia or hypoxia, is distinguished from other forms of asphyxia by clinical and biochemical evidence of sub-acute brain damage. Following prompt vitals stabilization and restoration, Hypoxic ischemic encephalopathy therapy is primarily supportive and should focus on the following: blood pressure control, adequate breathing, fluid management, preventing hyperglycemia and hypoglycemia, treating seizures, preventing hyperthermia, and adequate perfusion. Additionally, research indicates that therapeutic hypothermia (33–33.5°C for 72 hours) and gradual, regulated rewarming are required for newborns with mild to severe HIE. Additionally, to prevent reduced cerebral perfusion, the average blood pressure must be maintained above 35–40 mm Hg. (4, 5) Worldwide, prenatal hypoxia accounts for around 23% of newborn fatalities. (6) The majority of therapy now provided to an infant with encephalopathy focuses on supportive interventions to manage seizures, maintain proper gas exchange, and enhance and maintain cerebral perfusion. (7-9) Furthermore, perinatal hypoxia is recognized to be the cause of hypocalcaemia in infants less than three days. Hypocalcemia-induced neuromuscular irritability might show up as twitches, jitters, convulsions, and/or discomfort. Additionally, it may result in general symptoms including vomiting, lethargy, and irregular eating habits. Often, hypocalcemia occurs in infants who have asphyxiated. For babies with moderate to severe Hypoxic ischemic encephalopathy, hypothermia for therapeutic purposes is still considered the gold standard of care, despite the fact that hyperthermia is known to be associated with more dangerous consequences. (10) Hypothermia improves neuron protection by lowering the amount of calcium (Ca) that enters the cells during the return period. Therapeutic hyperthermia may be able to reverse the effects of HIE's hypocalcemia by increasing blood calcium levels. (11) Through several mechanisms, therapeutic hypothermia promotes neuroprotection by preventing intracellular calcium influx, which may increase levels of calcium in the blood and preserve homeostasis. (12) Inducing hypothermia as a therapy for asphyxiated babies has shown encouraging outcomes in reducing neurodevelopmental deficits in those who survive. (13) Therefore the current study was carried out to determine the Magnitude of hypocalcemia in hypoxic ischemic enchapalopahty in term neonates.

Methodology

The current study was carried out in neonatal intensive care unit Bacha Khan Medical Complex Gajju Khan Medical College Swabi from August 2023 to January 2024 after taking approval from the ethical committee of

the institute. All neonates (from birth to 3 days of age) presented to NICU with neurological impairment, a 1-minute APGAR score of 3 or below, and more than one minute of delayed crying were screened for hypocalcaemia while individuals with tracheo-esophageal atresia, preterm neonates, and other congenital abnormalities such as hydrocephaly or micro or macrocephaly were excluded. The sample size was calculated using WHO calculator and the sample size was 120. In this study, hypocalcaemia was defined as an ionized calcium level of less than 4 mg/dl. After being informed about the goal and advantages of the study, the careers or parents gave their consent. 5 ml venous blood sample was drawn from each participant for serum calcium (total ionized). Cobas Roche analyzer was used to measure total calcium, and an apparatus known as Easylyte was used to measure ionized calcium. After being collected, each sample was processed in a day. Iv calcium gluconate was given to the infant with hypocalcaemia; no treatment was given prior to the determination of the blood calcium level. Data was analyzed through SPSS. For categorical variables, such as hypocalcemia, age (categorized), gestational age (categorized), and neonatal weight (categorized), we computed frequencies and proportions. Mean & SD had been derived for age. Post stratification chi square analysis was done and relationship of hypocalcaemia was evaluated with factors such as: ages, weight, sex, gestational age & mother's educational status. P-value ≤0.05 was deemed as significant. The primary results are displayed in tables.

In the current study a total of 120 neonates with hypoxic ischemic encephalopathy were included out of which 80 (66.6%) were male and 40 (33.3%) were females. The mean age of the study population was 1.0-0.7 days. We classified the age group into 3 separate categories. The most predominant age group was 1 day 48(40%)(Table 1). A mean of 37.7 + 2.2 weeks was the gestational age at birth. Term neonates made up over fifty percent of the sample, which we classified as pre-term (less than 37 weeks), term (between 37 and 42 weeks), and post-term (greater than 42 weeks). Based on the records, the newborn's mean weight at birth was 2.95 + 0.5 kg. Table 1 lists three weight groups for newborns: underweight (less than 2.5 kg), normal weight (between 2.5 and 3.5 kg), and overweight (greater than 3.5 kg). Of these, almost 60% of newborns with HIE were in the normal weight category. Based on the medical records, the neonate's mean birth weight was 2.85 + 0.6 kg. Underweight (less than 2.5 kg), normal weight (between 2.5 and 3.5 kg), and overweight (greater than 3.5 kg). Of these, almost 60% of newborns with Hypoxic ischemic encephalopathy were in the normal weight category. The majority of the neonates in the research had mothers who were either completely illiterate or just had matriculation-level literacy. Demographic features of the study population is presented in table 1. Serum ionized calcium levels were 4.2 + 0.8 mg/dl on average. The operational definition of hypocalcemia states that it was observed in 41 (34.1%) of participants.(table 2.) Table 3 outlines the significance of the differences in hypocalcemia across a number of aspects, such as the neonate's gender, age at birth, pregnancy age at birth, bodyweight at birth, and the mothers' educational status. The prevalence of hypocalcemia varied significantly among these factors according to the neonate's age at birth, weight at birth, and mothers' educational status (p-value <0.05) as presented in table 3.

Results

Table 1.Demographic features of the study population

Features	Frequency / percentage
Sex	
Female	40(33.3%)
Male	80(66.6%)
Age in days	
One day	48(40%)
1-2 days	38(31.6%)
> 2 to 3 days	34(28.33%)
Gestational age	
Term	66(55%)
Preterm	36((30%)
Post term	18(15%)
Birth weight	
Normal	72(60%)
Over weight	19(15.8%)
Under weight	29(24.1%)
Mothers Education status	
Intermediate	16(13.3%)
Matric	36(30%)
Middle	23(19.1%)
Illiterate	45(37.5%)

Table 2. Hypocalcemia in the participants with hypoxic ischemic encephalopathy

Hypocalcemia	**Frequency /percentage**
No	79(65.8%)
Yes	41 (34.1%)
Total	120(100%)

Table 3. Hypocalcemia's relationship to multiple factors

Features	Hypocalcemia		
	Yes	**No**	**P value**
Sex			
Female	9 (22.5%)	31(77.5%)	0.066
Male	32(40%)	48(60%)	
Age in days			
One day	23(47.9%)	25(52.0%)	0.256
1-2 days	10(26.3%)	28(73.6%)	`
> 2 to 3 days	9 (26.4%)	25(73.5%)``	
Gestational age			
Term	19(28.7%)	47(71.2%)	0.256
Preterm	15(41.6%)	21(58.3%)	
Post term	10(55.5%)	8(44.4%)	
Birth weight			0.001
Normal	33(45.8%)	39(54.1%)	
Over weight	0	19(100%)	
Under weight	8(75.5%)	21(72.4%)	
Mothers Education status			
Intermediate	7(43.7%)	9(56.2%)	Less than 0.001
Matric	9(25%)	27(75%)	
Middle	0	23(100%)	
Illiterate	26(57.7%)	19(42.2%)	

Discussion

Hypocalcemia is a major concern for neonates with hypoxia ischemic encephalopathy. This study set out to determine the prevalence of hypocalcemia in babies suffering from hypoxia ischemic encephalopathy as well as any potential contributing factors. The study's key findings indicate that 41 (34.1%) of the neonates with hypoxic ischemic encephalopathy had hypocalcemia. The incidence of hypocalcemia among the newborns who were admitted to the NICU with HIE and included in this study was significantly correlated with the neonates' weight, age, and mothers' educational attainment. The average gestational age at delivery in the present research was 37.7 + 2.2 weeks on average, which was comparable to the 39-week gestational age found in a related study carried out in Kenya. (14) In our study, hypocalcemia was found in 34.1% of the newborns. According to an Indian research, newborns with hypoxia or HIE may have hypocalcemia. (15) Perinatal hypoxia is the primary cause of stillbirths (45.1%) and the most common cause of newborn mortality (28.8%) and morbidity in India. (16) A study carried out in Nigeria found that 22.6 percent of newborns with severe Hypoxic ischemic encephalopathy had hypocalcemia, which is less than what the current study found. (17) The findings of our investigation closely resemble those of a 2016 study that discovered neonatal hypocalcemia in 31.6% of full-term newborns. (18) The hypocalcemia in newborns with HIE was significantly correlated with the neonates' birth weight ($p<0.001$), according to our study's findings.

These results were confirmed by the research showing that hypocalcemia occurs in newborns with lower birthweights. (19) Seizures, shock, and other metabolic problems can arise from alterations in the normal blood levels of sodium, potassium, and calcium, the three primary electrolytes in the human body. Calcium is an essential second messenger in our bodies, helping muscles contract and acting as a cofactor for many enzyme-related functions. (20)

Discussions concerning the causes of hypocalcemia in birth asphyxia are still going on. (21)

prenatal hypoxia, delayed meal introduction, elevated calcitonin production, elevated natural phosphate load, renal insufficiency, and reduced parathyroid hormone secretion are some of the causes of hypocalcemia. (19) A similar research (12) that found 21% hypocalcemia in babies with HIE in the non-therapeutic hypothermia group was comparable to the current study in terms of sample size. However, the included sample was not used to research Thyroid hormone as part of our study domain. Similar results were seen in another investigation that found pre-TH fetuses with HIE had decreased calcium levels. (13) In order to assess calcium levels, we looked at the first three days of life. Lowe et al. found that the mean overall and ionized calcium in the blood concentration was significantly lower in HIE, which differed from findings from numerous studies, including large RCTs. The study also found that the albumin level was low. (22) It is also thought that various maternal factors, such as the use of calcium supplements during pregnancy, the method of delivery, and the delivery facility, are linked to hypocalcemia in HIE neonates. Further studies can better understand the relationship between these factors and hypocalcemia.

Conclusion

Our study concluded that one of the major causes of hypocalcemia (34%) in term neonates is hypoxic ischemic encephalopathy.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (IRBEC-BKMC-011-22)

Consent for publication

Approved

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Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

NUHK (Trainee Medical officer)
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Study Design, manuscript review, critical input.

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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