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ORIGINAL ARTICLE

Metabolic Derangement in Birth Asphyxia due to Cellular Injury with Reference to Mineral Metabolism in Different Stages of Hypoxic-ischemic Encephalopathy in Central India

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ABSTRACT

Introduction: Perinatal asphyxia is one of the major causes of neonatal mortality and long-term morbidity. Although neonates with severe birth asphyxia are known to be at increased risk of early-onset hypocalcemia, the magnitude of the problem is not well documented. Magnesium plays a role in neuroprotection for neonates with hypoxic-ischemic encephalopathy (HIE). The objective of this study was to determine the prevalence of early-onset hypocalcemia and hypomagnesemia in severely asphyxiated neonates.

Materials and methods: This study was carried out on 75 newborns distributed as group I (50 asphyxiated neonates) and group II (25 healthy neonates). Serum calcium and serum magnesium was estimated within 24 hours after birth, followed by third and fifth day postbirth.

Results: Maximum number of cases (81.3%) were born by vaginal delivery. The mean value of serum calcium on days 1, 3, and 5 for group I was 7.004 ± 0.691, 7.482 ± 0.760, 8.184 ± 0.811 in contrast to group II: 8.788 ± 0.399, 9.476 ± 0.250, 9.992 ± 0.277 respectively. Whereas the mean value of serum magnesium for group I is reported as 1.545 ± 0.045, 1.496 ± 0.067, 1.556 ± 0.057 on days 1, 3, and 5, while that of group II was 1.518 ± 0.053, 1.597 ± 0.049, 1.66 ± 0.065 respectively. On HIE stage-wise comparison, abnormal calcium metabolism percentage increases with severity of asphyxia (46.6% abnormal in stage I, while 71.4% abnormal in stage III). Abnormal magnesium metabolism percentage also increases with severity of asphyxia (26.6% abnormal in stage I, while 71.4% abnormal in stage III) and this abnormality persists up to fifth day in stage III.

Conclusion: Birth asphyxia is the most common and important cause of preventable cerebral injury occurring in the neonatal period. Serum calcium and magnesium level plays exceptionally imperative role for escaping HIE and other induced complications.

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INTRODUCTION

Asphyxia is defined as the failure to breathe well within 1 minute after delivery.[1] Hypoxia may cause a baby to have a decreased heart rate, decreased blood flow out of the heart, and low blood pressure. This may limit the blood flow to organ and tissue, leading to improper cell function or damage.

The most frequent abnormalities involve kidneys (50%) followed by central nervous system (CNS; 28%), cardiovascular (25%), and pulmonary system (23%).[2] Thus, there is evidence of multiorgan system dysfunction in the immediate neonatal period, CNS, pulmonary, metabolic, gastrointestinal tract, hematologic, renal, and death.[3] Perinatal mortality rate in India has remained almost static at appealingly high figure of around 65 per 1000 for nearly three decades.[4]

Calcium is an important second messenger in our body and also helps out muscle function and acts as a cofactor for several enzymatic activities. During pregnancy, calcium is transferred actively from the maternal circulation to the fetus by a transplacental calcium-pump regulated by the parathyroid hormone-related peptide. The majority of fetal calcium accretion occurs in the third trimester. This process results in higher plasma calcium concentration in fetus than in the mother and leads to fetal hypocalcemia with total and ionized calcium concentration of 10 to 11 and 6 mg/dL in umbilical cord blood at term. According to latest estimates by the World Health Organization,[5] approximately 4 million babies die each year before they reach the age of 1 month. Actually, 98% of these neonatal deaths take place in developing countries.

Perinatal asphyxia and birth injuries together contribute to almost 29% of these deaths.

After birth, due to the abrupt cessation of placental transfer, calcium levels start falling to 8 to 9 mg/dL and ionized calcium to 4.4 to 5.4 mg/dL at 24 hours of age. Serum calcium then starts rising to reach levels comparable to older children and adults by 2 weeks of age. Magnesium, the second most common intracellular cation, plays an important role in protein synthesis, bone formation, and regulation of potassium and calcium channels in the cell membrane. In addition, magnesium may play a role in neuroprotection for neonates with HIE. Magnesium also plays important roles in many physiologic functions, including protein synthesis, bone development, and cell membrane function.

With this background, it was deemed worthwhile to investigate the incidence of birth asphyxia in the hospital delivery, and biochemical changes especially serum calcium and serum magnesium during blood asphyxia.

MATERIALS AND METHODS

This study was carried out in neonatal intensive care unit of Department of Pediatrics, in collaboration with the Department of Biochemistry and Department of Obstetrics and Gynecology at a tertiary care center in Bhopal.

For the study, 75 newborns admitted to neonatal unit of the Department of Pediatrics were enrolled. The enrolled babies were further divided into group I (50 asphyxiated neonates) and group II (25 healthy neonates).

The study group comprised 50 asphyxiated term neonates. A baby was considered full term with complete gestational age of 37 weeks. The assessment of gestational age was done by the modified Dubowitz criteria and the staging of asphyxia was done by Sarnat and Sarnat staging.

Inclusion Criteria

- The documentation of intrapartum fetal distress through recognition of abnormal fetal heart rate patterns with or without passage of meconium.
- The presence of immediate neonatal distress as evidenced by a low (<7) Apgar score.
- The need for immediate neonatal resuscitation including bag and mask ventilation.
- An abnormal neurologic examination during the first 24 hours of life as judged by application of Sarnat and Sarnat staging.

A full-term newborn fulfilling any two of the abovementioned criteria was included in the study.

Exclusion Criteria

All neonates with evidence of septicemia, intrauterine infection, congenital anomalies, necrotizing enterocolitis, and marked respiratory distress were excluded from the study.

Control Group

The control group had 25 healthy term neonates delivered in the Department of Gynecology and Obstetrics of a tertiary care center in Bhopal. The control group was selected by random sampling and screened for any health problem. The control group comprised healthy and gestational age-matched neonates only.

Laboratory Examination

Following investigations has been carried out in the newborns that were included in our study, immediately after the admission to hospital followed by first day, third day and fifth day of life:

- Serum calcium by O Cresolphthalein Complexone method[6,7]
- Serum magnesium by Calmagite method [Bagainski ES (1973). Clin Chem Acta 46:46][6,7]

Criteria adopted for labeling as asphyxiated neonate is having serum calcium 8 to 11 mg/dL, serum magnesium 1.5 to 2 mEq/dL.[6,7] These criteria were applied on 24, 72, and 120 hours of life.

All the values reported have been assessed by statistical analysis; $p < 0.001$ is considered significant.

RESULTS

Majority of babies were delivered by normal vaginal route (80%; n = 40); and 20% (n = 10) were delivered by LSCS route among the study group

Very significant ($p \leq 0.001$) hypocalcemia was reported in hypoxic children from day of birth, which persisted up to the study period ($p \leq 0.01$) on the first, third, and fifth day

The observation depicts that abnormal calcium metabolism percentage increases with severity of asphyxia (46.6% abnormal in stage I, while 71.4% abnormal in stage III) and this abnormality persists up to fifth day in stage III, but it gets improved in stages I and II by fifth day of life

No change in serum magnesium levels in both asphyxiated and nonasphyxiated neonates have been reported. Thus, there is no significant impact of asphyxia on magnesium metabolism

Abnormal magnesium metabolism percentage increases with severity of asphyxia (26.6% abnormal in stage I, while 71.4% abnormal in stage III) and this abnormality persists up to fifth day in stage III, but it gets improved in stages I and II by the fifth day of life

Table 1: Distribution of cases based on the place and mode of delivery

	Total cases	*Hospital*	*Private*	*Home*
Normal vaginal	40 (80%)	26 (65%)	11 (27.5%)	3 (7.5%)
LSCS	10 (20%)	4 (10%)	6 (15%)	–(0%)
Total	50	30 (60%)	17 (34%)	3 (6%)

Table 2: Serum calcium level on days 1, 3, and 5 in study and control groups

Days	*Cases (n = 50)*	*Controls (n = 25)*	*p-value*
First day	7.004 ± 0.691	8.788 ± 0.399	≤0.001
Third day	7.482 ± 0.760	9.476 ± 0.250	≤0.01
Fifth day	8.184 ± 0.811	9.992 ± 0.277	≤0.01

Table 3: Serum calcium in different stages of HIE on days 1, 3, and 5

	Day 1		*Day 3*		*Day 5*	
Stages	*Normal*	*Abnormal*	*Normal*	*Abnormal*	*Normal*	*Abnormal*
I	8 (53.3%)	7 (46.6%)	9 (60%)	6 (40%)	10 (66.6%)	5 (33.3%)
II	9 (32.14%)	19 (67.85%)	10 (35.71%)	18 (64.28%)	12 (42.85%)	16 (57.1%)
III	2 (28.57%)	5 (71.42%)	3 (42.85%)	4 (57.14%)	2 (28.57%)	5 (71.42%)
Total	19 (38%)	31 (62%)	22 (44%)	28 (56%)	24 (48%)	26 (52%)

Abnormal calcium metabolism percentage increases with severity of asphyxia (46.6% abnormal in stage I, while 71.4% abnormal in stage III) and this abnormality persists up to fifth day in stage III, but it gets improved in stages I and II by fifth day of life

DISCUSSION

Birth asphyxia is very commonly seen in newborn babies. It has extremely serious immediate and long term adverse effects. The present study has been intended to evaluate the incidence and effect of birth asphyxia on certain biochemical parameters like serum calcium and serum magnesium among different categories of neonates. In India about one million babies suffer from birth asphyxia every year and it is the leading cause of neonatal mortality in our country, accounting for nearly 28.8% of the neonatal deaths and major subsequent squalid causing physical and mental handicap (1.5%).

In the present study, 40 (80%) were born by vaginal delivery and 10 (20%) were born by lower segment cesarean section (LSCS) (Table 1). Prasan et al[8] have also reported male preponderance. Maximum number of cases (81.3%) were born by vaginal delivery. Similar observations were made by Finner et al,[9] who have reported 65% vaginal delivery and 35% LSCS delivery in their study.

The mean value of serum calcium (Table 2) on days 1, 3, and 5 (groups I–II) were 7.004 ± 0.691, 8.788 ± 0.399, 7.482 ± 0.760, 9.476 ± 0.250, 8.184 ± 0.811, 9.992 ± 0.277 respectively.

It shows a very significant ($p \leq 0.001$) hypocalcemia in hypoxic children from day of birth, which persisted up to the study period ($p \leq 0.01$): First, third, and fifth day.

When the serum calcium was compared according to stages of HIE, abnormal calcium metabolism percentage increases with severity of asphyxia (46.6% abnormal in stage I, while 71.4% abnormal in stage III), and this abnormality persists up to fifth day in stage III, but it gets improved in stages I and II by fifth day of life (Table 3). Ilves et al[10] studied 46 asphyxiated and 35 healthy term infants. Between 24 and 48 hours, hypocalcemia was discovered in 23% of asphyxiated infants.

The pathogenetic mechanism by which birth asphyxia causes hypocalcemia is poorly understood. However, it has been speculated that delayed introduction of feeds, increased calcitonin production, increased endogenous phosphate load, transient functional hypoparathyroidism, target organ unresponsiveness, and sodium bicarbonate therapy may play a role. Of the total serum calcium, 40% is protein-bound, 10% is complexed with anions, such as citrate, sulfate, bicarbonate, phosphate, and lactate, and 50% is in the free or ionized physiologically active form.

In the present study, it was found that there was a significant decrease in the extracellular calcium levels in the asphyxiated babies, and the decrease was directly proportional to the degree of asphyxia.

Jajoo et al[11] studied 35 term infants with asphyxia. Asphyxiated infants had significantly lower serum calcium levels than control infant during each of the time period studied.

Schultz and Soltész[12] in their study on serum calcium levels in birth anoxic neonates found 26.76% incidence of hypocalcemia in full-term infants and 58.3% in premature infants. Hypocalcemia was associated with acidosis in the first 24 hours of life.

Tsang et al[13] in their study found that 37.6% of premature infants had serum calcium of <7 mg% and they also found that Apgar score was associated with low serum calcium values from 12 to 72 hours of age ($p < 0.01$). Birth asphyxia therefore, appears to play a separate role in neonatal calcium homeostasis apart from role of gestational age.

The mean values of serum magnesium (Table 4) on days 1, 3, and 5 (groups I and II) were 1.545 ± 0.045, 1.518 ± 0.053, 1.496 ± 0.067, 1.597 ± 0.049, 1.556 ± 0.057, 1.66 ±

Table 4: Serum magnesium level (mean ± SD) on days 1, 3, and 5 in study and control groups

Days	*Cases (n = 50)*	*Control (n = 25)*	*p-value*
First day	1.545 ± 0.045	1.518 ± 0.053	NS
Third day	1.496 ± 0.067	1.597 ± 0.049	NS
Fifth day	1.556 ± 0.057	1.66 ± 0.065	NS

SD: Standard deviation; NS: Not significant

Table 5: Serum magnesium in different stages of HIE on days 1, 3, and 5

	Day 1		*Day 3*		*Day 5*	
Stages	*Normal*	*Abnormal*	*Normal*	*Abnormal*	*Normal*	*Abnormal*
I	11 (73.33%)	4 (26.6%)	13 (86.6%)	2 (13.33%)	14 (93.3%)	1 (6.66%)
II	18 (64.28%)	10 (35.71%)	20 (71.42%)	8 (28.57%)	21 (74%)	7 (25%)
III	2 (28.57%)	5 (71.42%)	3 (42.85%)	4 (57.14%)	4 (57.14%)	3 (42.85%)
Total	31 (62%)	19 (38%)	36 (72%)	14 (28%)	39 (78%)	11 (22%)

Table 6: Serum calcium in different stages of HIE on days 1, 3, and 5

	Day 1		*Day 3*		*Day 5*	
Stages	*Normal*	*Abnormal*	*Normal*	*Abnormal*	*Normal*	*Abnormal*
I	8 (53.3%)	7 (46.6%)	9 (60%)	6 (40%)	10 (66.6%)	5 (33.3%)
II	9 (32.14%)	19 (67.85%)	10 (35.71%)	18 (64.28%)	12 (42.85%)	16 (57.1%)
III	2 (28.57%)	5 (71.42%)	3 (42.85%)	4 (57.14%)	2 (28.57%)	5 (71.42%)
Total	19 (38%)	31 (62%)	22 (44%)	28 (56%)	24 (48%)	26 (52%)

0.065 respectively. There was no change in serum magnesium level in both asphyxiated and nonasphyxiated neonates. Thus, there is no significant impact of asphyxia on magnesium metabolism.

Abnormal magnesium metabolism percentage increases with severity of asphyxia (26.6% abnormal in stage I, while 71.4% abnormal in stage III) and this abnormality persists up to fifth day in stage III, but it gets improved in stages I and II by fifth day of life (Table 5). The mean value of serum magnesium in the cases were slightly lower in days 1, 3, and 5 in full-term babies < 2.5 kg as compared with full-term babies ≥ 2.5 kg, but this observation was not statistically significant (Table 6).

Asphyxiated infants whose serum magnesium level dipped only slightly at 12 hours and then rose to normal by 24 hours were compared with asphyxiated infants whose hypoxemia (starting at 12 hours) persisted through 48 to 72 hours.[14] Such infants, however, often exhibit hypomagnesemia within 12 hours after birth,[14] possibly reflecting inadequacy of tissue stores or the shift of extracellular magnesium to the intracellular phase with normal oxygenation. Serum calcium concentration should be determined in all neonates with encephalopathy.

Birth asphyxia is the most common and important cause of preventable cerebral injury occurring in the neonatal period. In India, about one million babies suffer from birth asphyxia every year, and it is the leading cause of neonatal mortality in our country, accounting for nearly 28.8% of the neonatal deaths and major subsequent sequelae causing physical and mental handicap (1.5%).[15]

In infants with HIE, hypomagnesemia may be the result of increased magnesium consumption during the ischemic insult or ongoing losses caused by ischemic damage to renal glomeruli and tubules. Glutamate is an important neurotransmitter that plays a major role in the development of the CNS. Magnesium plays some important roles in many physiologic functions, including protein synthesis, bone development, and cell membrane function. There is some evidence to suggest a role for magnesium sulfate as a therapeutic neuroprotective agent along with therapeutic hypothermia in infants with HIE, but studies are inconclusive. Both ischemic insult and hypothermia may play a role in altered magnesium levels in this population. Therapeutic hypothermia likely involved in normal brain functions, including cognition, learning, and memory.[8] However, the release of excessive quantities of glutamate in HIE results in overstimulation of glutamate receptors, 2-aminomethylphenylacetic acid, kainite, and N-methyl-D-aspartate, located on the postsynaptic membrane of nerve cells, resulting in excitotoxicity.

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