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Original Research Article

How serum magnesium level is related to severity of asphyxia

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ABSTRACT

Background: Perinatal asphyxia is a most common cause of neonatal death. Magnesium, the second most common intracellular cation, may play a role in neuroprotection.
Methods: This observational study was undertaken in the Department of Gynecology and Pediatrics in GMC, Shahdol from January 2021 to June 2023. The term babies were included with congenital anomaly, diabetic mother, IUGR, and mother receiving magnesium therapy during labour were excluded. Data analysis was conducted using IBM SPSS statistical software (version 22.0).
Results: Out of 46 newborns, mild to moderated asphyxia and severe asphyxia were presenting 32 (69.6%) and 14 (30.4%) cases respectively. HIE-I were 20 (43.5%), HIE II-16 (34.8%) and HIE III-10 (21.7%). The mean serum magnesium level in neonates with mild to moderate asphyxia was 2.1±0.3 and with severe asphyxia 1.5±0.5 respectively (p=0.001). Serum magnesium was significantly low in severe birth asphyxia as compared to mild to moderate (p=0.001) and level was significantly low in HIE stage 3. The difference in serum magnesium between HIE 1 and 3 and HIE 2 and HIE 3 was statistically significant (p=0.003 and p=0.009, respectively). A significant correlation between serum magnesium and Apgar score at 1 minute (Pearson's correlation coefficient, r=0.518, p=0.001) and score at 5 minutes was also statistically significant (Pearson's correlation coefficient, r=0.379, p=0.009).
Conclusions: Neonates with severe asphyxia and HIE- grade III have significant hypomagnesemia. Asphyxia can lead to hypomagnesemia, and it is recommended to evaluate levels of magnesium in neonates with asphyxia as a routine test.

Keywords: Perinatal asphyxia, Neonates, Moderated asphyxia

INTRODUCTION

Perinatal asphyxia is a condition during the first and second stages of labor, that leads to fetal hypoxemia and hypercarbia due to impaired gas exchange.[1] It is the third most common cause of neonatal death (11%) after preterm birth (24%) and severe infections (12%). It is an end result of a significant degree of global hypoxic ischemia during the time of birth. Hypoxic-ischemic encephalopathy (HIE) is defined as an abnormal neurobehavioral state in which, a decreased level of consciousness and usually other signs of brain stem and/or motor dysfunction were found.[2]

Perinatal asphyxia is an end result of a significant degree of global hypoxic ischemia during the time of birth, which leads to multiorgan failure, so multisystem approach to management of perinatal asphyxia will help to minimize high mortality and morbidity associated with devastating condition.[3]

American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG)6 proposed the criteria for birth asphyxia as: profound metabolic or mixed acidemia; persistence of Apgar scores 0-3 for longer than 5 minutes; neonatal neurologic HIE (e.g., seizures,

coma, hypotonia) and multiple organ (e.g., kidney, lungs, liver, heart, intestine) involvement.[6]

In India, as per the NNPD (National Neonatal Perinatal Database), the incidence of perinatal asphyxia defined as Apgar score of <7 at 1 minute of life-was 8.4% of all live births. The incidence in India is 14 per 1000 live births with birth asphyxia causing 30% of neonatal and 50% of perinatal deaths.[7] Among the neonates with HIE, 10-15% may die, 10-15% may develop cerebral palsy, and upto 40% are likely to develop other disabilities, severe and permanent neuropsychological sequelae, including mental retardation, visual motor or visual perceptive dysfunction, increased hyperactivity, cerebral palsy, and epilepsy.[8]

A variety of markers have been examined to identify perinatal hypoxia but studies for early determination of tissue damage due to birth asphyxia are still lacking.[9] Magnesium, the second most common intracellular cation, may play a role in neuroprotection for neonates with perinatal asphyxia. The initial event resulting in fetal hypoxia leading to decreased cardiac output and subsequent decreased cerebral blood flow sets off a cascade of events resulting in brain injury. During HIE, an excessive amount of the excitatory amino acid glutamate is released from the presynaptic terminals of nerve cells.[10]

Glutamate is an important neurotransmitter that plays a major role in the development of the central nervous system and is likely involved in normal brain functions including cognition, learning, and memory.[11] However, the release of excessive quantities of glutamate in HIE results in over stimulation of glutamate receptors, opens the calcium channels in the cell membrane of the postsynaptic neurons, resulting in an influx of calcium ions. Excessive intracellular calcium sets several reactions that result in programmed cell death or apoptosis.[12] Increased intracellular calcium induces events leading to secondary cell death, such as the synthesis of oxygen free radicals, protease activation, nuclear enzyme activation, and DNA fragmentation.[17]

Hence magnesium is an NMDA-receptor antagonist that may block the influx of calcium, therefore minimizing brain injury.[18]

The aim of our study was to find out the correlation of serum magnesium with severity of perinatal asphyxia.

METHODS

Study type

It was an observational cross-sectional study.

Study place

The study was conducted in the Department of Gynecology and Pediatrics in Birsa Munda GMC, Shahdol.

Period of study

The study was conducted from January 2021 to June 2023.

Sample size

The sample size for the study was 46.

Inclusion criteria

All the term neonates with birth asphyxia (≥37 weeks of gestation) were included in the study.

Exclusion criteria

Small for date babies (IUGR), Newborns with congenital malformations, mother receiving magnesium therapy during labour and newborns with diabetic mother are excluded.

Methodology

Birth asphyxia can be assessed in neonates by Apgar scoring system.

Persistence of APGAR scores 0-3 for longer than 5 min leads to neonatal neurological sequelae (e.g., seizures, coma, hypotonic) and multiple organ involvement (kidney, lungs, liver, heart, intestine). Intramural birth asphyxia is categorized on the basis of APGAR score as severe when Apgar score is 0-3 at 1 min and mild to moderate when Apgar score is 4-6 at 1 min.

Neonates born with Apgar score <7 at one minute of birth will be enrolled in the study. Newborns requiring resuscitation will be resuscitated as per NRP guidelines. After stabilization a pre-structured proforma was used to record the information from the parents. After obtaining the written consent from the parent's, clinical data thus obtained was entered in the prescribed proforma which included age, sex, religion, presenting complaints, type and duration of seizure, (if any) and maternal details like any risk factors for perinatal asphyxia, age, weight, Height, educational status, any H/O preeclampsia, eclampsia, diabetes, maternal infections, multiple gestation and complete physical and neurological examination of the newborn at admission will be noted according to the specified methodology in the proforma. Serum magnesium levels will be sent for all the term asphyxiated newborn along with other electrolytes. All the information thus obtained will be recorded in a pre-designed proforma. Detailed antenatal history, i.e., maternal age, past medical history, parity, gestational age, history of illness during pregnancy, any medication taken during pregnancy, antenatal history evidence of fetal distress, Apgar score, type of delivery, medication given to mother during delivery was noted and recorded in the prescribed proforma. Venous blood (2 ml) was collected within 24 hrs of life with due aseptic precautions and the serum

magnesium levels were quantitatively determined by fully automatic analyzer (XL 1000).

Magnesium meets with Xylidyl blue from a coloured compound in alkaline solution the intensity of the colour formed in proportional to the magnesium concentration, in the sample interfere with calcium is prevented by use of Ca-EDTA.

The results thus obtained will be analysed. Hypomagnesemia will be treated according to the protocol. An intravenous correction of hypomagnesemia (<1.6 mg/dl) with 50 mg/kg of magnesium sulfate given over 1 to 2 hours will be done. During the infusion period, the heart rate and respiratory rate will be monitored simultaneously, and blood pressure will be measured every 15 minutes to detect the development of respiratory depression or hypotension, which are the theoretically possible complications of magnesium infusion. If there is hypermagnesemia, removal of the source of any exogenous magnesium will be done.

Table 1: Sarnat and Sarnat staging of hypoxic-ischemic encephalopathy.

Stages	Stage1 (mild)	Stage 2 (moderate)	Stage 3 (severe)
Level of consciousness	Hyperalert, Irritable	Lethargic or obtunded	Stuporous, comatose
Neuromuscular control	Uninhibited overreactive,	Diminished spontaneous movement	Diminished or absent spontaneous movement
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive, disinhibited	Decreased or absent
Segmental myoclonus	Present or absent	Present	Absent
Complex reflexes	Normal	Suppressed	Absent
Suck	Weak	Weak or absent	Absent
Moro	Strong, low Threshold	Weak, incomplete, High threshold	Absent
Oculo-vestibular	Normal	Over active	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both system depressed
Pupils	Mydriasis	Miosis	Mid position, often unequal, poor light reflex
Respirations	Spontaneous	Spontaneous, Occasional apnea	Periodic, apnea
HR	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
GIT motility	Normal or Decreased	Increased, diarrhoea	Variable
Seizures	None	Common focal or multifocal (6-24hrs of age)	Uncommon (excluding decerebration)
EEG finding	Normal (awake)	Early: generalizedlow voltage, slowing (continuous delta and thea) Later: periodic pattern (awake, seizures focal or multifocal, 1.0-1.5 Hz spike and wave	Early: periodic pattern with isopotential phases Later: totally isopotential
Duration of symptoms	< 24 hrs	2-14 days	Hours to weeks
Outcome	About 100% normal	80% normal, abnormal if symptoms more than 5-7 days	About 50% die, remainder withsevere sequelae

Statistical analysis

The statistical analysis was carried out using IBM SPSS (Statistical Package for Social Sciences) statistical version 20. The analysis includes frequency table, bar, pie chart, association of variables based on Chi square test and if any cell frequency was <5, then Yates corrections was used for 2×2 contingency table or method pooling and Fisher exact test was used (for higher order than 2×2 table) and proportion compare using the z proportion test. All quantitative variables were estimated using measures of central location (mean and median) and measures of dispersion (standard deviation). Normality of data was checked by Kolmogorov-Smirnov tests of normality. For normality distributed data, mean was compared in with respect to independent t test (for two groups) and one way ANOVA (for more than two groups). For not normality distributed data, median was compared using Mann Whitney U test (for two groups) and Kruskal Wallis (for more than two groups). Pearson's correlation was used for relationship. Reliability using the Cronbach's alpha. All statistical tests were seen at two-tailed level of significance ($p \leq 0.01$ and $p \leq 0.05$).

Ethical justification

The study was conducted in asphyxiated newborns admitted in Birsa Munda Government Medical College Shahdol after ethical clearance of department. All the investigations will be done free of cost as per the existing JSSK programme.

RESULTS

The present study evaluated serum magnesium in 46 neonates with perinatal asphyxia.

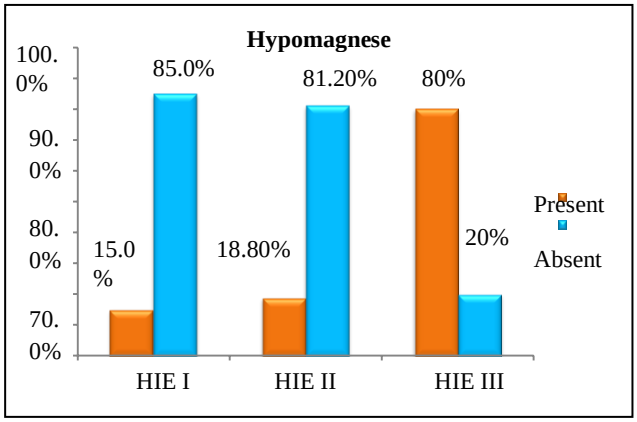

Figure 1: Hypomagnesemia according to HIE staging.

There were 28 males and male to female ratio 1.5/1.

The mode of delivery in study participants is 21 (45.7%) neonates had normal vaginal delivery, 24 (52.2%) had LSCS and 1 (2.2%) had assisted delivery.

Most common risk factors are fetal distress (37%), meconium-stained liquor (30.4%) and leaking PV (19.6%).

Fetal distress was most common indication for LSCS followed by MSL. Fetal distress indicated in 10 (41.7%), MSL in (33.3%), leaking PV and previous LSCS in 2 (8.3%) and breech presentation and cord around neck in 1 (4.2%) patient.

Bag-mask ventilation and intubation were needed in 34.78% and 17.39% of cases respectively, 47.83% of cases resuscitated with tactile stimulation.

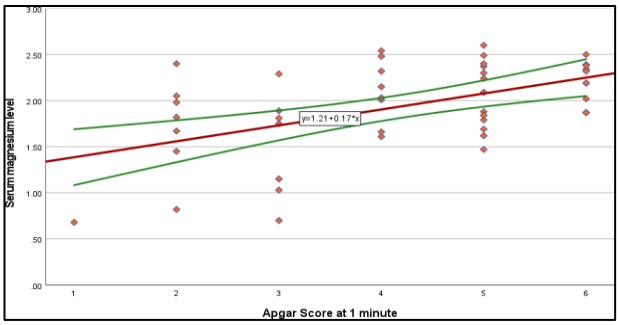

Figure 2: Correlation of serum magnesium with Apgar score at 1 minute.

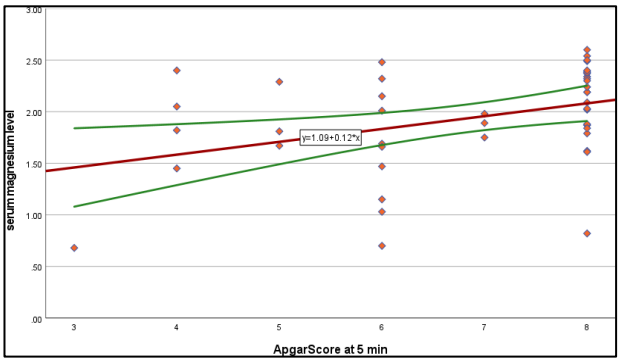

Figure 3: Correlation of serum magnesium with Apgar score at 5 minutes.

Table 2. Risk factors

Risk factors	N (%)
Meconium-stained liquor	14 (30.4)
Leaking PV	9 (19.6)
Fetal distress	17 (37)
Cord around neck	2 (4.3)
Previous LSCS	1 (2.2)
Preeclampsia	1 (2.2)
Breech presentation	2 (4.3)
Total	46 (100)

The mean Apgar score at 1 min was 4.2±1.4 (range 1-6) and at 5 minutes was 6.85±1.47 (range 3-8). The mean

gestational age was 38.2±1.1 weeks. The mean birth weight was 2.8±0.3 kg.

Mild to moderate and severe asphyxia was presenting 69.6% and 30.4% cases respectively.

There were 20 (43.5%) HIE I, 16 (34.8%) HIE II and 10 (21.7%) HIE III respectively out of 46 asphyxiated neonates.

In our study mean serum magnesium were 1.9±0.5 mg/dl, random blood sugar (RBS) was 76.8±24mg/dl, serum sodium were 136±2.8 mEq/l, serum potassium were 5.1±0.9 mEq/l and serum urea were 24.6±9.3 mg/dl.

The mean serum magnesium level in neonate with mild to moderate asphyxia was 2.1±0.3 and in neonate with severe asphyxia was 1.5±0.5 respectively (independent, t test, p=0.001). Serum magnesium was significantly low in severe birth asphyxia as compare to mild to moderate birth asphyxia (p=0.001).

Table 3: Baseline characteristics.

Characteristics	N	Minimum	Maximum	Mean	Std. deviation
Apgar score 1 min	46	1	6	4.20	1.455
Apgar score 5 min	46	3	8	6.85	1.475
Gestational age (weeks)	46	37	41	38.26	1.104
Birth weight (kg)	46	2.50	3.50	2.8667	0.33233

Table 4: Hypomagnesemia in relation to birth asphyxia.

Asphyxia	Hypomagnesemia		P value
	Yes, N (%)	No, N (%)	
Mild to moderate (n=32)	5 (15.6)	27 (84.4)	0.002
Severe (n=14)	9 (64.3)	5 (35.7)	
Total (n=46)	14 (30.4)	32 (69.6)	-

Table 5: Serum magnesium in relation to HIE staging.

HIE staging	N (%)	Mean±SD	P value (ANOVA)
HIE1	20 (43.5)	2.2±0.3	0.001
HIE2	16 (34.8)	2.0±0.3	
HIE3	10 (21.7)	1.3±0.6	
Total	46 (100)	-	-

Mean serum magnesium in relation to stages of hypoxic ischemic encephalopathy. There was a significant difference in serum magnesium between the HIE stages (ANOVA, p=0.001). Serum magnesium level was significantly low in HIE stage 3. On post-hoc test, the difference in serum magnesium between HIE 1 and HIE 2 was not statistically significant (p=0.398), The difference in serum magnesium between HIE 1 and 3 and HIE 2 and HIE 3 was however statistically significant (p=0.003 and p=0.009, respectively).

The hypomagnesemia was observed in 14 (30.4%) neonates out of 46 neonates. Hypomagnesemia was found in 3 (15%) neonates in HIE stage I, 3 (18.8%) neonates in HIE stage II, 8 (80%) neonates in HIE stage III. Hypomagnesemia was significant in all stages of HIE (ANOVA, p=0.001). Hypomagnesemia was significantly more in HIE stage III as compared to HIE stage I and II (Chi-square test, p=0.001).

It shows the correlation of serum magnesium with Apgar score. There was a significant correlation between serum magnesium and Apgar score at 1 minute (Pearson's correlation coefficient, r=0.518, p=0.001). The correlation between serum magnesium and Apgar score at 5 minutes was also statistically significant (Pearson's correlation coefficient, r=0.379, p=0.009).

A total 87% patients improved, 10.8% patients referred and only 2.2% cases death found.

DISCUSSION

An observational cross-sectional study was conducted at a district hospital in the northern part of the Indian subcontinent. In our study, serum magnesium levels were evaluated and correlated with asphyxia severity in newborns with perinatal asphyxia. The results of our study suggest that serum magnesium levels were significantly (independent t test, p=0.001) lower in neonates with severe asphyxia as compared to neonates with mild to moderate asphyxia. Our results also suggested that serum magnesium levels were significantly lower (ANOVA,

p=0.001) in hypoxic-ischemic encephalopathy stage 3 as compared to stages 1 and 2.

Several studies have reported metabolic abnormalities in asphyxiated neonates like hypocalcemia, hypoglycemia, hyperammonemia, including hypomagnesemia. Some of these abnormalities result in hypoxic damage in neonates in organs like kidneys, lungs, and liver, including the central nervous system.[26]

Romero et al conducted a prospective, observational, and descriptive study in hospitalized newborns with hypoxic ischemic neuropathy. Serial measurements of blood magnesium revealed hypomagnesemia in 81.3% subjects.[27] In our study, 30.4% of neonates with HIE had hypomagnesemia. Small sample size (n=46) and hence type 2 error (underestimation) could account for the differences in observations.

Khalessi et al compared serum magnesium levels in newborns (asphyxia grade 2) with normal controls. The authors found that asphyxiated newborns have significantly lower (p=0.01) serum magnesium as compared to normal newborns. The authors also found a significant correlation between asphyxia and hypomagnesemia (OR=2.1). Our study found a significant correlation (p=0.002) between hypomagnesemia and severity of asphyxia. The odds ratio could not be calculated in our study as all new-borns evaluated had asphyxia (mild to moderate/severe).[28]|

Ilves et al evaluated serum magnesium in mixed umbilical cord blood and venous blood serum in 46 asphyxiated and 35 healthy term infants at a median age of 33 hours. The authors found that asphyxiated infants with severe HIE had a significantly lower (p<0.05) umbilical cord blood total magnesium (0.64, 95% CI, 0.47-0.87) mmol/l as compared to normal infants or those with mild to moderate HIE (0.81, 95% CI, 0.75-0.87) mmol/l.[24] Our study also observed significantly lower serum magnesium in HIE 3 (1.9, 95% CI, 1.8-2) mg/dl as compared to HIE 2 (2, 95% CI, 1.9-2.2) mg/dl and HIE 1 (2.2, 95% CI, 2.0-2.3) mg/dl.

These observations were further substantiated in a study by Foley et al. The authors found that neonates with hypoxic ischemic encephalopathy (n=30) had a significantly higher levels of serum zinc and copper and lower serum magnesium, calcium, and potassium levels compared to healthy non-asphyxiated neonates (n=30).[29]

Zaman et al conducted a study to evaluate hypomagnesemia in asphyxiated babies (n=102) with moderate to severe HIE; the frequency of HIE II and HIE III was 65.68% and 34.31%, respectively. The authors reported that the prevalence of hypomagnesemia was 27.4% and 45.7% in HIE II and HIE III.[19] Mia et al reported that the prevalence of hypomagnesemia was 26.7%, 36.3%, and 37% in HIE stage I, II and III, respectively.[30] In our study, the prevalence of hypomagnesemia was 15%, 18.8% and 80% in HIE I, II, and III stages, respectively.

Pius et al conducted a study to determine the effect of magnesium sulphate in hypoxic ischemic encephalopathy resulting from severe perinatal asphyxia. Severely asphyxiated new-borns (n=52) with hypoxic ischemic encephalopathy were administered magnesium sulphate at <6 hours after birth (n=29), 6-24 hours (n=16) and greater than 24 hours (n=7), respectively. The authors found that hypoxic ischemic neuropathy resolved better when magnesium sulphate therapy was commenced earlier.[23] This study had several limitations as the trial was not randomized or placebo controlled leading to selection bias. In contrast, our study was observational and non-interventional.

Hossain et al conducted a randomized, single blind, controlled, trial to see the effect of magnesium sulfate infusion in perinatal asphyxia. Term neonates (n=50) having postnatal age less than 12 hours with perinatal asphyxia and mild to moderate hypoxic ischemic encephalopathy were included. Patients were randomized to receive either magnesium sulphate infusion or normal saline (placebo group). Baseline characteristics (age, birth weight, gender, mode and place of delivery, parity, ANC, liquor colour and hypoxic-ischemic encephalopathy (HIE) staging and mean age of intervention) were comparable between experimental and control groups. The authors reported that 26% neonate in the experimental group had neurological deficit, compared with 61% of infants in the control group at discharge. This study substantiated the role of postnatal magnesium sulfate infusion in improving short-term outcomes in neonates with perinatal asphyxia.[31]

Bhat et al conducted a longitudinal randomized, placebo-controlled trial to evaluate whether magnesium sulfate treatment could improve neurologic outcomes at discharge among term neonates with severe perinatal asphyxia (n=40). Their findings demonstrated that postnatal treatment with magnesium sulfate improves neurologic outcomes at discharge for term neonates with hypoxic ischemic neuropathy.[25]

Strengths

The strength of this study was that neonates enrolled as per study protocol and there was no dropout of neonate till discharge from the hospital.

Limitations

The limitations of the study were that the study design was cross-sectional, observational and there was no control group to compare results. Second, the sample size was small (n=46). Also, there was no intervention done regarding hypomagnesemia in our study in neonate with perinatal asphyxia.

CONCLUSION

Neonates with severe asphyxia and HIE grade III have significant hypomagnesemia. Asphyxia can lead to hypomagnesemia, and it is recommended to evaluate levels of magnesium in neonates with asphyxia as a routine test.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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