MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.59218/makrjms.2023.512.520

Correlation of Serum Magnesium with Severity of Asphyxia

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ABSTRACT

Perinatal asphyxia refers to a condition during the first and second stage of labour in which impaired gas exchange leads to fetal hypoxemia and hypercarbia. Asphyxia has been shown to be the third most common cause of neonatal death (11%) after preterm birth (24%) and severe infections (12%). Perinatal asphyxia is an end result of significant degree of global hypoxic ischemia during the time of birth. Lack of oxygen delivery from this episode often leads to multiorgan failure. A variety of markers have been examined to identify perinatal hypoxia but studies for early determination of tissue damages due to birth asphyxia are still lacking. Magnesium, the second most common intracellular cation, may play a role in neuroprotection for neonate 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. This observational cross-sectional study was undertaken in Department of Pediatrics in GMSH-16 in Chandigarh from January, 2021 to June, 2021. The term babies (37-41 weeks of gestation) were included in the study. Newborn with congenital anomaly, diabetic mother, small for date babies (IUGR) and mother receiving magnesium therapy during labour were excluded from the study. Sample size was justified with 46 cases. Analysis of data were conducted using IBM SPSS statistical software (version 22.0). With due consideration of all inclusion and exclusion criteria total 46 cases were included in the study. Out of 46 newborns, mild to moderated asphyxia and severe asphyxia were presenting 32 (69.6%) and 14 (30.4%) cases respectively and HIE I were 20 (43.5%), HIE II were 16 (34.8%) and HIE III were 10 (21.7%). 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). 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). Hypomagnesaemia 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. Hypomagnesaemia 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). 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). Neonates with severe asphyxia and Hypoxic ischemic encephalopathy (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.

OPEN ACCESS

Key Words
Magnesium, Asphyxia, labour, hypercarbia

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Received: 5 July 2023
Accepted: 13 July 2023
Published: 15 July 2023

Citation: Brijesh Kumar Patel, Mohit Sharma, Amit Kumar Singh and Shreya Shrivastava, 2023. Correlation of Serum Magnesium with Severity of Asphyxia. Res. J. Med. Sci., 17: 512-520, doi: 10.59218/makrjms.2023.512.520

INTRODUCTION

Perinatal asphyxia refers to a condition during the first and second stage of labour in which impaired gas exchange leads to fetal hypoxemia and hypercarbia[1]. Asphyxia has been shown to be the third most common cause of neonatal death (11%) after preterm birth (24%) and severe infections (12%). Hypoxic-ischemic encephalopathy (HIE) is defined as abnormal neurobehavioral state consisting of decreased level of consciousness and usually other signs of brain stem and/or motor dysfunction[2]. Perinatal asphyxia is an end result of significant degree of global hypoxic ischemia during the time of birth. Lack of oxygen delivery from this episode often leads to multiorgan failure. A multisystem approach to management of perinatal asphyxia will help to minimize high mortality and morbidity associated with devastating condition as stated by Sexson in 1976[3]. In same year Scott outlined the outcomes of severe birth asphyxia[4]. Robertson et al defined HIE as "an acute non-static encephalopathy caused by intrapartum or late antepartum brain hypoxia and ischemia[5]. American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) proposed the criteria for birth asphyxia as[6]:

- Profound metabolic or mixed acidemia
- Persistence of Apgar scores 0-3 for longer than 5 min
- Neonatal neurologic HIE (e.g., seizures, coma, hypotonia) and multiple organ (e.g kidney, lungs, liver, heart, intestine) involvement

In India, as per the NNPD (National neonatal perinatal database), the incidence of perinatal asphyxia-defined as Apgar score of <7 at 1 min of life-was 8.4% of all live births. Oxygen was the most commonly used resuscitative measure in 9.5%, bag and mask ventilation in 6.3%, chest compressions in 0.8% and medications in 0.5%. PA was responsible for 28.8% of all neonatal deaths. Data from National Neonatal Perinatal database (NNPD) suggests that the incidence of 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 damages due to birth asphyxia are still lacking[9].

Normal serum magnesium levels in preterm and term infants range from 1.80-2.60 mg dL^{-1}. Magnesium, the second most common intracellular cation, may play a role in neuroprotection for neonate 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, 2-aminomethylphenylacetic acid(AMPA), kainite (KA) and N-methyl-d- aspartate (NMDA), located on the postsynaptic membrane of nerve cells this results in excitotoxicity[11]. For the purpose of this discussion, the NMDA receptor is the receptor of interest. Overstimulation of the NMDA receptor 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].

The magnesium cation is important in the regulation of a large of intracellular processes and may act to stabilize membrane components. Magnesium is one of the most important regulaters of N-methyl-D-aspartate (NMDA) channel function[13]. The NMDA-operated channel permits the entry of ionized calcium and sodium and the exit the potassium ions[14]. The channel is normally closed by magnesium ions in a voltage-dependent manner[15,16]. The hypoxia induced modification of the NMDA receptor-ion channel complex decreases the blocking effect of magnesium and leads to increased intracellular calcium concentrations. 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 in calcium, therefore minimizing brain injury[18].

Aims and objectives: This observational cross-sectional study was undertaken in Department of Pediatrics in GMSH-16 in Chandigarh from January, 2021 to June, 2021 in 46 patients. The aim of our study is-''Correlation of serum magnesium with severity of asphyxia''.

MATERIAL AND METHODS

Study population: Neonates admitted in our hospital with perinatal asphyxia

sample size: Sample size (46) have been calculated as per Zaman *et al*.[19] study in which mean serum magnesium level in HIE-2 and HIE-3 were 1.36 and 1.16, respectively.

Power and sample size

Sample Z test: Testing mean = null (versus not = null) Calculating power for mean = null+difference Alpha = 0.05 Assumed standard deviation = 0.315.

Difference	Sample Size	Power	Actual
Power 0.20	46	0.85	0.853683

- Inclusion criteria
  - All the term neonates with birth asphyxia (>37 weeks of gestation)
- Exclusion criteria
  - Small for date babies (IUGR)
  - Newborns with congenital malformations
  - Mother receiving magnesium therapy during labour
  - Newborns with diabetic mother

MATERIALS AND METHODS

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 (Table 1)

Neonates born with APGAR score <7 at 1 min of birth will be enrolled in the study. Newborns requiring resuscitation will be resuscitated as per NRP guidelines. After stabilization a pre-structured proforma will be used to record the information from the parents. After obtaining the written consent from the parent's, clinical data thus obtained will be entered in the prescribed proforma which includes 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 methology 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 viz. evidence of fetal distress, Apgar score, type of delivery, medication given to mother during delivery will be noted and recorded in the prescribed proforma. Venous blood (2 mL) will be collected within 24 hrs of life with due aseptic precautions and the Serum Magnesium levels will be quantitatively determined by fully automatic analyzer (i.e., XL 1000).

Table 1: 2-Sarnat and Sarnat Staging of hypoxic-ischemic encephalopathy

Stage	Stage1 (mild)	Stage 2 (moderate)	Stage 3 (severe)
Level of consciousness	Hyperalert, irritable	Lethargic or obtunded	Stuporous, comatose
Neuromuscular control	Uninhibited overreactive,	Diminished spontaneousmovement	Diminished or absent spontaneous movement
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong disal 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 systemdepressed
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 (6-24 Hrs of age)	Uncommon (Excluding decerebration)
EEG Finding	Normal (awake)	Early: Generalized low 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 with severe sequelae

Xylidyl blue: 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[18-20].

The results thus obtained will be analysed. Hypomagnesemia will be treated according to the protocol. An intravenous correction of hypomagnesemia (<1.6 mg dL^{-1}) with 50 mg kg^{-1} of magnesium sulfate given over 1-2 hrs 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 min 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.

Statistical methods: The statistical analysis will be 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 is <5, than Yates corrections is used for 2×2 contingency table or method pooling and Fisher exact test is used (for higher order than 2×2 table) and proportion compare using the z-proportion test. All quantitative variables will be estimated using measures of central location (mean and median) and measures of dispersion (standard deviation). Normality of data will be checked by Kolmogorov-Smirnov tests of normality. For normality distributed data, Mean will be 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 will be compared using Mann Whitney U test (for two groups) and Kruskal Wallis (for more than two groups). Pearson's Correlation using for relationship. Reliability using the Cronbach's Alpha. All statistical tests will be seen at two-tailed level of significance ($p \leq 0.01$ and $p \leq 0.05$).

Ethical justification: The study will be conducted in asphyxiated newborns admitted in Government Multi Speciality Hospital, Sector-16, Chandigarh. Blood sample for serum magnesium (2 mL) will be taken along with routine blood samples for evaluation of serum magnesium in asphyxiated term neonates. 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.

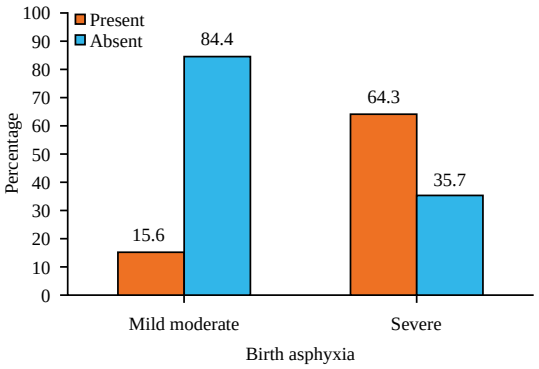

Fig. 1: Hypomagnesemia in relation to birth asphyxia

Table 2: Gender distribution

Gender	No.	Percentage
Male	28	60.9
Female	18	39.1
Total	46	100

Table 3: Mode of delivery

Mode	No.	Percentage
Normal Vaginal delivery	21	45.7
Lower segment Caesarean section	24	52.2
Assisted Delivery	1	2.2
Total	46	100

Table 4. Risk Factor

Risk factors	No.	Percentage
Meconium-stained liquor	14	30.4
Leaking PV	9	19.6
Fetal Distress	17	37.0
Cord around neck	2	4.3
Previous LSCS	1	2.2
Preeclampsia	1	2.2
Breech Presentation	2	4.3
Total	46	100.0

Table 5: Indication of LSCS

Indication of LSCS	No.	Percentage
MSL	8	33.30
Leaking PV	2	8.30
Foetal distress	10	41.70
Cord around neck	1	4.20
Previous LSCS	2	8.30
Breech presentation	1	4.20

Table 6: Mode of resuscitation

Mode of resuscitation	No.	Percentage
Tactile Stimulation	22	47.83
Bag and Mask ventilation	16	34.78
Intubation	08	17.39
Total	46	100

There were 28 males with a male to female ratio of 1.5:1. Table 1 and Fig. 1 shows the gender distribution of patients (Table 2).

Table 3-4 shows the mode of delivery in study participants. Twenty-one (45.7%) neonates had normal vaginal delivery.

Table 5 shows that Foetal distress was most common indication for LSCS with 41.7%.

Table 6 depicts the mode of resuscitation in neonates. Bag-mask ventilation and intubation was needed in 34.78 and 17.39% of cases respectively, 47.83% of cases resusciateted with tactile stimulation.

Table 7: Baseline Characteristics

	No.	Minimum	Maximum	Mean	Standard deviation
Apgar score 1min	46	1	6	4.2000	1.45500
Apgar score 5min	46	3	8	6.8500	1.47500
Gestational age (weeks)	46	37	41	38.2600	1.10400
Birth weight (kg)	46	2.50	3.50	2.8667	0.33233

Table 8: Distribution of cases according to birth asphyxia

Birth asphyxia	No.	Percentage
Mild to moderate	32	69.6
Severe	14	30.4
Total	46	100

Table 9: HIE staging

HIE stage	No.	Percentage
HIE I	20	43.5
HIE II	16	34.8
HIE III	10	21.7
Total	46	100.0

Table 10: Biochemical investigations

Investigation	Mean±SD	Minimum	Maximum
Serum magnesium (mg dL^{-1})	1.9 (0.5)	0.7	2.6
RBS (mg dL^{-1})	76.8 (24)	38	200
S. Sodium (mEq L^{-1})	136 (2.8)	129	145
B. Urea (mg dL^{-1})	24.6 (9.3)	12	59
S. Potassium (Eq L^{-1})	5.1 (0.9)	3.3	7.8

Table 11: Serum magnesium in relation to birth asphyxia

Asphyxia	Serum magnesium mean (SD)	p-value
Mild to moderate	2.13±0.30	0.001
Severe	1.50±0.54	
Total	1.93±0.46	-

Table 12: Hypomagnesemia in relation to birth asphyxia

	Hypomagnesemia		
Asphyxia	Yes	No	p-value
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 13: Serum magnesium in relation to HIE staging

HIE staging	No.	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%)	-	-

Table 14: Hypomagnesemia according to HIE staging

		Hypomagnesemia		
HIE staging	No.	Yes	No.	p-value (ANOVA)
HIE I	20	3 (15%)	17 (85%)	0.001
HIE II	16	3 (18.8%)	13 (81.20%)	
HIE III	10	8 (80%)	2 (20%)	
Total	46	14 (30.4%)	32 (69.56%)	-

The mean Apgar score at 1 min was 4.2±1.4 (range 1-6) and at 5 min 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 (Table 7).

Table 8 shows the presence of birth asphyxia in study participants. Mild to moderate and severe asphyxia was presenting 69.6 and 30.4% cases respectively.

Table 9 shows the Hypoxic ischemic encephalopathy (HIE) staging in neonates. There were 20 (43.5%) HIE I, 16 (34.8%) HIE II and 10 (21.7%) HIE III respectively out of 46 asphyxiated neonate.

Table 10 depicts biochemical investigations in study participants. In our study mean serum magnesium were 1.9±0.5 mg dL^{-1}, random blood sugar (RBS) were 76.8±24 mg dL^{-1}, Serum sodium were 136±2.8 mEq L^{-1}, Serum potesium were 5.1±0.9 mEq L^{-1} and serum urea were 24.6±9.3 mg dL^{-1}.

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 11).

Table 12 and Figure 2 Shows the 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 stastistically 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).

Table 14 shows the hypomagnesiumia was observed in 14 (30.4%) neonates outoff 46 neonate. Hypomagnesiumia 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. Hypomagnesiumia 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).

Figure 3 and 4 shows correlation of serum magnesium with Apgar Score. There was a significant correlation between serum magnesium and Apgar score at 1 min (Pearson's correlation coefficient, r = 0.518, p = 0.001). The correlation between serum magnesium and Apgar score at 5 min was also statistically significant (Pearson's correlation coefficient, r = 0.379, p = 0.009).

DISCUSSIONS

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 new-born 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

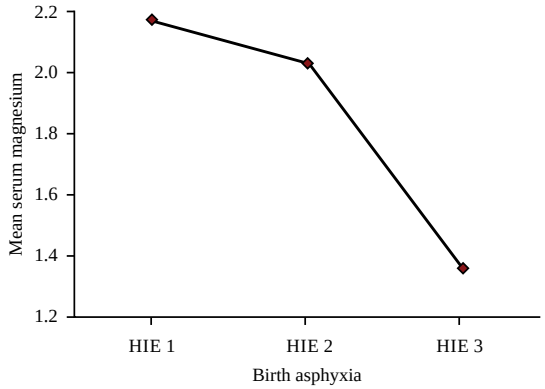

Fig. 2: Serum magnesium in relation to HIE staging

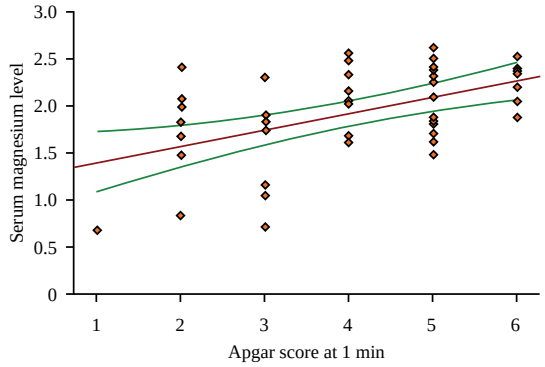

Fig. 3: Correlation of serum magnesium with APGAR Score at 1 mL

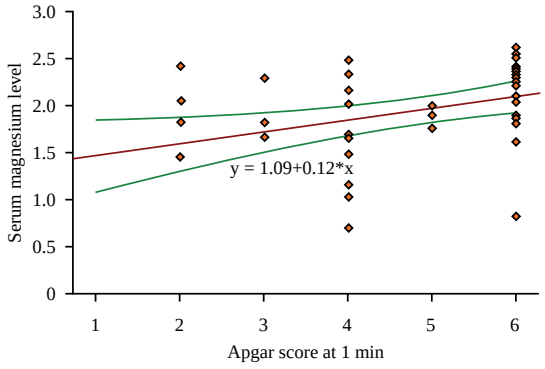

Fig. 4: Correlation of serum magnesium with APGAR Score at 5 min

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, liver, including the central nervous system (Table 15)[21-26].

Table 15: Diagnosis of cases

Final diagnosis	No.	Percentage
T/AGA/BA	31	67.4
T/AGA/BA/MSL/RD	9	19.6
T/AGA/BA/MSL/MAS	4	8.7
T/AGA/BA/SHOCK	1	2.2
T/AGA/BA/MSL/PPHN/SHOCK	1	2.2
Total	46	100

Table 16: Outcome of cases

Final-outcome	No.	Percentage
Improved	40	87
Referral	5	10.8
Death	1	2.2
Total	46	100

Decreased total serum calcium and magnesium levels in neonates with HIE was observed on 1st day of life with significant correlation between decreased serum calcium and magnesium levels to HIE disease outcome. Hence serum calcium and magnesium levels can be of value as prognostic (Table 16).

Romero *et al*.[27] conducted a prospective, observational and descriptive study in hospitalized new-borns with hypoxic ischemic neuropathy. Serial measurements of blood magnesium revealed hypomagnesemia in 81.3% subjects. In our study, 30.4% neonates with HIE had hypomagnesemia. Small sample size (n = 46) and hence type 2 error (underestimation) could account for the differences in observations (Table 17).

Khalessi *et al*.[28] compared serum magnesium levels in new-borns (asphyxia grade 2) with normal controls. The authors found that asphyxiated new-borns have significantly lower (p = 0.01) serum magnesium as compared to normal new-borns. 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. Odds ratio could not be calculated in our study as all new-borns evaluated had asphyxia (mild to moderate/severe) (Table 18)[28].

Ilves *et al*.[24] 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 hrs. 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^{-1} 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^{-1} as compared to HIE 2 (2, 95% CI, 1.9-2.2) mg dL^{-1} and HIE 1 (2.2, 95% CI, 2.0-2.3) mg dL^{-1}.

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].

Table 17: Hypomagnesemia

Year	Study	No. of cases (N)	Severity of asphyxia	Hypomagnesemia	Conclusion
2021	Observational cross sectional study	46	HIE-I (20) HIE-II (16) HIE-III (10)	3(15%) 3(18.8%) 8(80%)	Neonate with severe asphyxia and HIE grade III have significant hypomagnesemia

Table 18: Hypomagnesemia

Year	Study	No. of cases (N)	Hypomagnesemia	Conclusion
2018	Damera *et al*.[20] cross sectional study	95	20 (21.05%)	Decreased total serum calcium and magnesium levels in neonates with HIE was observed on 1st day of life with significant correlation between decreased serum calcium and magnesium levels to HIE disease outcome. Hence serum calcium and magnesium levels can be of value as prognostic indicators in HIE

Year	Study	No. of cases (N)	Severity of asphyxia	Hypomagnesemia	Conclusion
2017	Zaman *et al*.[19] cross sectional study	102	HIE – II (67) HIE – III (35)	19 (28.36%) 16 (45.71%)	Hypomagnesemia are significantly associated with degree of severity of HIE

Year	Study	No. of cases (N-152)	Hypomagnesemia	Conclusion
2017	Khalessi *et al*.[21] case control study	76 (case) 76 (control)	12 (16%) 0 (0.0%)	This study showed that serum magnesium levels in neonates with asphyxia was significantly lower than normal neonates and asphyxia can lead to hypomagnesemia

Year	Study	No. of cases (N-60)	Hypomagnesemia	Conclusion
2015	Saha *et al*.[26] Cross sectional case control study	30 (case) 30 (control)	3 (10%) 0 (0.0%)	This study show isolated are combinedhypoglycaemia, hypocalcemia hypomagnesemia are frequently found in newborns with perinatal asphyxia

Zaman *et al*.[19] 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*.[30] 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*.[23] 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 hrs after birth (n = 29), 6-24 hrs (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*.[31] 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 hrs 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 substantiates 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 and limitations

Strengths:

- Neonates enrolled as per study protocol
- There was no dropout of neonate till discharge from the hospital

Limitations:

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

CONCLUSION

Neonates with severe asphyxia and Hypoxic ischemic encephalopathy (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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