ISSN: 0975-3583,0976-2833 VOL13,ISSUE08,2022

Level of serum magnesium in newborns with hypoxic ischemic encephalopathy: A cross-sectional study

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ABSTRACT

Objective- To study the correlation of serum magnesium with hypoxic ischemic encephalopathy in newborn.

Methods- In this hospital based observational cross sectional study we included 46 full term neonates with birth asphyxia. Sarnat and Sarnat staging done for hypoxic ischemic encephalopathy and serum magnesium level evaluated for all stages of HIE.

Results- 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 significantly more in HIE stage III as compared to HIE stage I and II(P=0.001)

Conclusion- We found statistically significant lower serum magnesium level in neonates with severe birth asphyxia(HIE stage III) as compared to mild to moderate asphyxia (HIE stage II & III) which may have treatment implications.

Keywords: Asphyxia, Hypoxic Ischemic Encephalopathy, hypomagnesemia.

BACKGROUND

Data from National Neonatal Perinatal database (NNPD) suggests that the incidence of birth asphyxia in India is 14 per 1000 live births with asphyxia causing 30% of neonatal and 50% of perinatal deaths [1]. 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[2]. 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[3].

Magnesium, the second most common intracellular cation, may play a role in neuroprotection for neonate with perinatal asphyxia. 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[4]. 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 [5]. The NMDA-operated channel permits the entry of ionized calcium and sodium and the exit the potassium ions.[6]. The channel is normally closed by magnesium ions in

ISSN: 0975-3583,0976-2833 VOL13,ISSUE08,2022

a voltage-dependent manner. [7,8]. Hence Magnesium is an NMDA- receptor antagonist that may block the influx in calcium, therefore minimizing brain injury [9].

METHODS

This cross-sectional observational study was done in tertiary care hospital from 1 January, 2021 to 30 June, 2021 in neonates admitted with perinatal asphyxia after permission from institutional ethics core committee. All the term neonates with birth asphyxia (≥37 weeks of gestation) were enrolled in the study after consent from parents. Sample size was calculated as per Zaman R et al. (2012) study[10] in which mean serum magnesium level in HIE-2 and HIE-3 were 1.36 and 1.16 respectively. The sample size calculated was 46 with power of study 85%, alpha error of 5% and difference of power 20%.

Neonates born with APGAR score<7 at one minute of birth were enrolled in the study and those with small for date (IUGR), newborns with congenital malformations, whose mother were receiving magnesium therapy during labor, and newborns of diabetic mother were excluded from the study. Newborns requiring resuscitation were managed as per NRP guidelines. After stabilization of newborns 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 history of preeclampsia, eclampsia, diabetes, maternal infections, multiple gestation and complete physical and neurological examination of the newborn at admission were noted. Apgar score, type of delivery, medication given to mother during delivery was noted. According to Sarnat and Sarnat staging (Table 1) HIE grading of newborn were done. Venous blood (2ml) was collected within 24 hours of life with due aseptic precautions and the Serum Magnesium levels were quantitatively determined by fully automatic analyzer (i.e XL 1000).

Table 1: Sarnat and Sarnat staging for HIE in term neonates

SIGNS	STAGE I	STAGE II	STAGE III
Level of consciousness	Hyperalert	Lethargic	Stuporous, Coma
Muscle tone	Normal	Hypotonic	Flaccid
Posture	Normal	Flexion	Decerebrate
Tendon reflexes/Clonus	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriasis	Myosis	Unequal, Poor light reflex
Seizures	None	Common	Decerebration
EEG findings	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	< 24 hrs if	24 hrs to 14	Days to

ISSN: 0975-3583,0976-2833 VOL13,ISSUE08,2022

	progresses, otherwise may remain normal	days	weeks
Outcome	Good	Variable	Death, Severe deficits

Statistical analysis- The statistical analysis was carried out using IBM SPSS (Statistical Package for Social Sciences) statistical version 20. Mean was compared with respect to independent t-test (for two groups) and One way ANOVA (for more than two groups). Normality of data was checked by Kolmogorov–Smirnov tests. 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 was checked using the Cronbach's Alpha. All statistical tests were seen at two-tailed level of significance ($P \leq 0.01$ and $P \leq 0.05$).

RESULTS

There were 46 neonates with perinatal asphyxia included in the study. After Sarnat and Sarnat staging there were 20(43.5%) neonates in HIE I, 16(34.8%) in HIE II and 10(21.7%) in HIE III respectively. Mean serum magnesium levels in HIE stage I , II, and III were 2.2 ± 0.3, 2.0 ± 0.3 and 1.3 ± 0.6 respectively[Table 2]. The difference in serum magnesium between HIE I and HIE II was not statistically significant (p=0.398). However the difference in serum magnesium between HIE I & III and HIE II & HIE III were statistically significant (p=0.003 and p=0.009 respectively). 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[Table 3]. Hypomagnesemia was significantly more in HIE stage III as compared to HIE stage I and II (Chi-square test, P=0.001).

Table 2 : Serum magnesium in relation to HIE staging

HIE staging	N	Mean±SD	P Value (ANOVA)
HIE I	20(43.5%)	2.2±0.3	0.001
HIE II	16(34.8%)	2.0±0.3	
HIE III	10(21.7%)	1.3±0.6	

Table 3 : Hypomagnesemia according to HIE staging

HIE Staging	N	Hypomagnesemia		P value (ANOVA)
		Yes	**No**	
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%)	

ISSN: 0975-3583,0976-2833 VOL13,ISSUE08,2022

DISCUSSION

In our observational cross sectional study we found a relationship of magnesium levels with degree of asphyxia. Mean serum magnesium levels were low in all stages of HIE but the hypomagnesemia was significantly more in cases of HIE III as compared to HIE I and II. We also found that number of neonates in HIE III with hypomagnesemia were also significantly more when compared to neonates in HIE I and II.

In many studies low serum magnesium was observed in neonates with birth asphyxia [10-13]. In a study it was observed that degree of hypomagnesemia was significantly correlating with the decreased survival rate. [14] In a pilot study it was found that hypoxic ischemic neuropathy resolved better when magnesium sulphate therapy was commenced earlier [15]. A randomized, single blind, controlled trial was conducted in the term neonates (n=50) having postnatal age less than 12 hours with perinatal asphyxia and mild to moderate hypoxic ischemic encephalopathy to see the effect of magnesium sulfate infusion, which found that there was significantly lower incidence of neurological deficit in neonates receiving magnesium sulfate infusion (26%) when compared to the control group not receiving the same (61%). This study substantiates the role of postnatal magnesium sulfate infusion in improving short-term outcomes in neonates with perinatal asphyxia [16]. A longitudinal randomized, placebo-controlled trial demonstrated that postnatal treatment with magnesium sulfate improves neurologic outcomes at discharge for term neonates with hypoxic ischemic neuropathy [17].

WHAT THIS STUDY ADDS

Hypomagnesemia can be a prognostic marker in birth asphyxia and the degree of hypomagnesemia directly correlates with the degree of Hypoxic Ichaemic Encephalopathy.

The limitations in our study were cross-sectional, observational study with no control group to compare the results; the sample size was small and no intervention done regarding hypomagnesmia in neonates with perinatal asphyxia.

To conclude, in neonates with hypoxic ischemic encephalopathy, as the severity increases serum magnesium level decreases, so our study gives scope to further explore that serum magnesium can be used as early marker to define severity and supplementation of magnesium either prophylactically or as treatment can improve the outcome.

ISSN: 0975-3583,0976-2833 VOL13,ISSUE08,2022

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