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Alterations in Serum Magnesium Levels in Hyperbilirubinemic Neonates Before and After Phototherapy

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ABSTRACT

Background: Bilirubin binds to cell membrane phospholipids, including N-methyl D-aspartate receptor, and causes excessive activation that can lead to neurotoxic effects. Since magnesium is an important inhibitor of this receptor, a comparison can be made between the physiological effects of magnesium and the neurological effects of bilirubin. This study aimed to compare changes in serum magnesium levels before and after phototherapy in hyperbilirubinemic newborns.

Methods: This retrospective cross-sectional study examined full-term newborns with hyperbilirubinemia. These newborns were admitted between 2012 and 2014 to the Neonatal Unit of Children's Medical Center in Tehran, Iran. Based on the amount of bilirubin upon admission, participants were divided into three groups of mild (<18 mg/dl), moderate (18-20 mg/dl), and high (>20 mg/dl). The total serum magnesium levels were measured before and 12-24 h after phototherapy.

Results: A total of 143 newborns were included in this study. A significant difference was observed between serum magnesium levels before (2.42±0.46 mg/dl) and after (2.07±0.32 mg/dl) phototherapy (P<0.001). This difference was observed in all etiologies of icterus.

Conclusion: The magnesium level decreased significantly after the completion of jaundice treatment for all causes of the condition. These findings raise the hypothesis that an increase in the level of extracellular magnesium is a defense mechanism that reduces the neurotoxic effects of bilirubin.

Keywords: Hyperbilirubinemia, Magnesium, Neonate, Phototherapy

Introduction

Hyperbilirubinemia is found in about 60% of term neonates and 80% of preterm infants in the first week of birth (1). An increase in the level of indirect bilirubin has neurotoxic effects on the blood-brain barrier and cell membrane (2). This increases the sensitivity of the neuronal cells to damage induced by factors, such as asphyxia, prematurity, hyperosmolality, and infection (2, 3). Breastfeeding, dehydration, and delay in meconium passage will raise the level of serum bilirubin (4-6).

Bilirubin binds to cell membrane phospholipids, including the N-methyl D-aspartate (NMDA) receptor, which is an ion-exchange channel (7). By binding to the NMDA receptor in the neural synapses, bilirubin causes excessive activation of the receptor, destruction of the ion channel complex in the membrane, and promotion of its neurotoxic effects. Long-term stimulation of the NMDA receptor has also been observed in nerve damage caused by prenatal asphyxia (8).

Magnesium is a cofactor for enzymatic systems (9) and an important inhibitor of the NMDA receptor (3). The NMDA channel is normally closed by Mg^{2+} ions in a voltage-dependent manner (3). It appears that many of the physiological effects of magnesium can be related to the neurological effects of bilirubin (3).

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An increase in magnesium levels has been shown in patients with hyperbilirubinemia (3), and several studies have found a significant relationship between serum magnesium levels and the severity of hyperbilirubinemia (3, 10). This increase in magnesium may be due to the destruction of cells, particularly neurons and erythrocytes that causes the release of secondary intracellular magnesium. Moreover, an increase in magnesium level may act as a compensatory mechanism, play a protective role, and provide magnesium with beneficial effects that will improve the neurological outcomes (11). This study aimed to measure the serum magnesium levels in neonates with hyperbilirubinemia before and after phototherapy to investigate the possible protective effect of magnesium in neonatal hyperbilirubinemia.

Methods

This retrospective cross-sectional study was performed at the Neonatal Unit of Children's Medical Center, a pediatric specialty hospital under the auspices of Tehran University of Medical Sciences, Tehran, Iran. Neonates diagnosed with hyperbilirubinemia that required phototherapy and/or exchange transfusions were enrolled between December 2012 and April 2014 and followed until treatment completion. The inclusion criteria were being full-term neonates of appropriate gestational age that had been admitted for evaluation and treatment of jaundice. On the other hand, newborns diagnosed with any type of congenital malformation, an inborn error of metabolism, proven sepsis, infection or jaundice in the first 24 h of life or those whose mothers had a history of diabetes or had been treated with magnesium sulfate during pregnancy were excluded from the study.

The study protocol was approved as a student thesis by the research and medical Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran, under the Helsinki declaration. It is worth mentioning that informed consent was obtained from the parents.

Measurements

The accepted minimum sample size was calculated to be 100 cases at a significance level of 95% ($P<0.05$) and a power of 90%. Serum bilirubin was measured using the spectrophotometric method with a Selectra-2 autoanalyzer (Vital Scientific; the Netherlands). Neonates requiring phototherapy were divided into three groups of mild (<18 mg/dl), moderate (18-20 mg/dl), and high (>20 mg/dl) based on the amount of bilirubin upon admission. Management of the hyperbilirubinemia was primarily based on the American Academy of Pediatrics guidelines (12). Phototherapy was continued until the total serum bilirubin decreased to below 12 mg/dl.

The magnesium level was measured using the spectrophotometric method (Roche kit and Cobas spectrophotometry device; Roche Diagnostics; USA). Magnesium levels of less than 1.5 mg/dl were considered to be deficient and those greater than 3 mg/dl were considered to be excessive. The clinical symptoms of hypermagnesemia monitored in patients with high magnesium levels included apnea, lethargy, hypotonia, hyporeflexia, decreased intestinal motility, and delayed passage of meconium. A complete blood count and peripheral smear, blood group determination, Rh typing, Coombs test, G6PD activity test, and thyroid function tests (in prolonged jaundice) were performed for all subjects.

Statistical Analysis

The sample size was calculated by comparing two means of a quantitative variable in two dependent communities. According to the study conducted by Khosravi et al. (3), the sample size was obtained at 64 ($\mu1=0.270$, $\sigma1=2.24$, $\mu2=2.12$, confidence level=1.96). The data were analyzed in SPSS software (version 22) through the chi-square test, Fisher's exact test, and paired t-tests. Moreover, the Pearson test was employed for correlation analysis. A p-value less than 0.05 was considered statistically significant.

Results

This prospective cohort study was conducted on 143 full-term hyperbilirubinemic neonates who were admitted to the Children's Medical Center, Tehran, Iran. Tables 1 and 2 list the demographic characteristics of the neonates. None of the patients had clinical symptoms of hypermagnesemia. The neonates were divided into three groups of mild (<18 mg/dl), moderate (18-20 mg/dl), and high (>20 mg/dl) based on the amount of bilirubin measured upon admission. Mild, moderate, and severe groups included 61 (42.7%), 40 (28%), and 42 (29.4%) neonates, respectively. There was no significant relationship between mean bilirubin level and gender before phototherapy ($P=0.951$).

Correlations between bilirubin and magnesium levels were assessed using the Pearson correlation test, and no significant relationship was detected between the bilirubin level upon admission and

Table 1. Qualitative demographic characteristics of neonates

Variable		No. of subjects	Percentage
Gender	Female	71	49.7
	Male	72	50.3
Delivery type	Normal vaginal	54	37.8
	Cesarean section	89	62.2
Maternal age	<25	27	18.8
	≥25	116	81.2
Treatment	Phototherapy	133	93
	Phototherapy + exchange transfusion	10	7
Gravidity	1	86	60.1
	2	41	28.7
	3	15	10.5
	≥4	1	0.7
Feeding type	Breastfeeding only	118	82.5
	Formula only	4	2.8
	Breastfeeding+formula	21	14.7
Etiology of jaundice	ABO incompatibility	7	4.9
	RH incompatibility	1	0.7
	Breastfeeding failure	51	35.7
	Breast milk	18	12.6
	Idiopathic	64	44.8
	G6PD deficiency	2	1.3

Table 2. Quantitative demographic characteristics of neonates

Variable	Treatment	Mean ± SD	Min-Max
Birthweight (g)		3166.68±363.146	2500-4100
Weight at admission (g)		3018.04±375.788	2080-4180
Age at admission (day)		5.89±3.118	2-28
Maternal age (year)		28.34±4.729	18-42
Gestational age (week)		38.52±0.690	38-41
Phototherapy duration (day)		2.47±0.680	1-4
Admission hemoglobin (g/dl)		15.7 ±1.7	11.4-21
Serum bilirubin (mg/dl)	Phototherapy	18.46±2.84	11.3-25.8
	Phototherapy+exchange transfusion	19±3.43	11.3-31
Magnesium (mg/dl)	phototherapy	2.42±0.46	1-3.6
	Phototherapy+exchange transfusion	2.47±0.46	1-3.6

Table 3. Magnesium level in neonatal hyperbilirubinemia before and after phototherapy

Cause of jaundice	Phototherapy magnesium level (mg/dl)		P-value	Phototherapy + exchange transfusion magnesium level (mg/dl)		P-value
	before	after		before	after	
Hemolytic	2.60±0.25	2.03±0.27	<0.001	2.42±0.41	1.94±0.30	<0.001
Breastfeeding and breast milk Jaundice	2.47±0.47	2.12±0.32	<0.001	2.48±0.48	2.12±0.32	<0.001
Idiopathic	2.35±0.45	2.03±32	<0.001	2.36±0.45	2.03±31	<0.001
Other	2.41±0.46	2.08±0.32	<0.001	2.42±0.46	2.07±0.32	<0.001

the levels of magnesium before and after phototherapy. Moreover, comparison of the mean magnesium levels before and after treatment with phototherapy or phototherapy plus exchange transfusion showed that the serum levels after phototherapy had decreased significantly in neonates treated with either phototherapy alone or in combination with exchange transfusion (P<0.001).

Table 3 tabulates the mean serum magnesium levels in the subjects with different etiologies and treatments. The mean serum magnesium decreased significantly for all causes of neonatal jaundice after treatment (P<0.001). Moreover, there was no significant correlation between hyperbilirubinemia severity and mean serum magnesium level upon admission (P=0.109) or between the mean concentration of magnesium before phototherapy and the hemolytic or non-hemolytic causes of jaundice (P=0.922).

Discussion

Prolonged NMDA stimulation by bilirubin has important neurotoxic effects. Magnesium is an inhibitor of the NMDA receptor; however, the relationship between magnesium and neonatal hyperbilirubinemia remains unclear. There has been disagreement between the results of previous studies and the findings in this study (13).

The results of the present study showed that the mean serum magnesium level decreased significantly after phototherapy, compared to before treatment (P<0.001). Khosravi et al. (3) found that the total serum magnesium levels decreased significantly after phototherapy, compared to before phototherapy. Furthermore, Karambin et al. (14) reported that the mean magnesium level was significantly higher before phototherapy than after phototherapy.

In the same vein, Afify et al. (15) revealed that serum magnesium levels were significantly higher in icteric neonates than in the controls. They stated that this might be related to mild hemolysis since the magnesium level was higher in the erythrocytes, especially reticulocytes, than in serum concentrations, and the serum levels increased after hemolysis. In addition, the increase in magnesium level could have resulted from the extracellular movement of intracellular magnesium secondary to cellular injury caused by high bilirubin levels, which can cause neuronal and generalized cellular injury.

In a study conducted by Afify et al. (15), there was a significant difference between the cause of jaundice and the magnesium level before and after phototherapy (P<0.001). However, the current study found no significant correlation between the mean magnesium concentration before phototherapy and the cause of jaundice (P=0.327). There was also no significant difference between the mean magnesium concentration before phototherapy and hemolytic or non-hemolytic causes of jaundice (P=0.922).

Similarly, Hasan (16) compared a group of healthy infants with a group of hyperbilirubinemic infants and reported a higher level of magnesium among the icteric neonates. In addition, Choudhury and Borkotoki (17) reported a positive correlation between the plasma magnesium level and serum bilirubin level, which was attributed to intracellular shifts in magnesium.

In the present study, there was no significant relationship between the mean serum magnesium level before phototherapy and the severity of hyperbilirubinemia (P=0.109). In line with these findings, Khosravi et al. (3) found no significant relationship between jaundice severity and plasma magnesium level. The present evaluation showed a significant decrease in magnesium levels for all causes of hyperbilirubinemia after phototherapy; nonetheless, Sarici et al. (11) reported a significant relationship between serum magnesium levels and hyperbilirubinemia severity only in neonates with non-hemolytic jaundice. Moreover, they reported remarkable neuroprotective effects of magnesium against the risk of toxicity associated with increased serum bilirubin.

Conclusion

The current study found a significant decrease in magnesium level after the completion of jaundice treatment. Moreover, there was no significant difference between the magnesium levels and the different causes of jaundice. These findings advance the hypothesis that an increase in the level of extracellular magnesium is a compensatory mechanism that reduces the neurotoxic effects of bilirubin. It was observed that the increased level of magnesium in hyperbilirubinemia leads to the release or withdrawal of magnesium from cells as a result of cellular degradation in order to reduce the toxic effects of bilirubin. Further studies are required to determine the value of magnesium treatment in the therapy of infants with high levels of bilirubin in order to reduce the toxic effects of bilirubin.

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Conflicts of interest

The authors declare no conflict of interest.

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