Role of Magnesium ion in neonatal jaundice

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Abstract: Magnesium is found almost entirely in the intracellular compartment. The small serum component gives a poor representation of the active, physiologic state of the metal. This state is assessed much better by measuring ionized magnesium in the serum, This study was undertaken to investigate the plasma levels of ionized Mg in neonatal nonhemolytic hyperbilirubinemia by comparing the newborns with and without significant hyperbilirubinemia, Forty full term neonates their gestational ages ranged from 37 to 42 weeks were presented with jaundice(study group) and another 40 full term neonates without jaundice (control group) were included in the study both groups were subjected to complete clinical examination , laboratory investigations, CBC ,serum calcium ,phosphorus , serum bilirubin and ionized Magnesium . The results showed that Serum bilirubin was significantly higher in study group compared to control group (*P* value <0.001). Also Serum ionized Mg was significantly higher in study group compared to control group (*P* value = 0.04). Positive correlation between the mean serum bilirubin and the plasma ionized Mg levels .Conclusion; increase in plasma IMg may be due to extracellular movement of Mg, a principally intracellular ion, resulting from generalized cellular injury including neurons and erythrocytes. This increase has neuroprotective role against emerging toxicity risk of increasing serum bilirubin levels.

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1. Introduction

Deposition of unbound bilirubin or its acid form in the neuron membrane causes permanent neuronal injury with a distinctive regional topography throughout the CNS.(1-2) the sequence of membrane events initiated by bilirubin molecules damages all adjacent membrane-bound enzymes and receptors. However, distant plasma membrane structures such as N-methyl-d-aspartate (NMDA) receptor/ion channel complex located within neuronal membranes on the synaptic surface of neurons are disrupted as well. Increased and prolonged activation of NMDA receptor as in perinatal asphyxia and hypoxic ischemic encephalopathy (HIE) results in brain cell injury despite its physiologic roles in brain plasticity; neuronal growth; synaptogenesis; and development of learning, memory, and vision. However, it has been shown in newborn piglets that bilirubin also increases activation of the NMDA receptor by modifying its binding characteristics, increases the receptor's affinity for NMDA receptor antagonists, and thus results in neuronal injury [(3)]. Magnesium (Mg) ion, is one of the most important antagonistic regulators of the NMDA receptor/ion channel complex (8-,9). It protects the CNS against hypoxia and exerts its neuroprotective effects by blocking excitotoxic and NMDA receptor–mediated neuronal injury mechanisms [(10–11)]. Many physiologic functions of Mg ions seem to act against or compensate for the neurotoxic effects of bilirubin molecules [(12, 13)]. Plasma levels of ionized Mg (IMg), which is thought to reflect the metabolic status of the physiologically active fraction of Mg truly and accurately [(14)], and its relationship to serum bilirubin levels in neonatal hyperbilirubinemia have not been investigated previously. In this study, we aimed to investigate the plasma levels of IMg in neonatal nonhemolytic hyperbilirubinemia by comparing the newborns with and without significant hyperbilirubinemia.

2. Subjects and Methods

This a case control study was performed at Pediatrics department of El Minia University Hospital during the period from June 2011 to February 2012, forty newborns were presented with jaundice, they were full-term, appropriate-for-gestational-age, and healthy newborns were enrolled in the study. Also another 40 healthy full term matched neonates without jaundice was taken as control group Newborns that had cephalohematoma, any congenital malformation, inborn errors of metabolism, or proven sepsis or infection or whose mother was antenatally administered Mg sulfate at any time during gestation were not included. Newborns with anemia or with hemolytic hyperbilirubinemia were excluded from the study. Written informed consent was obtained from the parents of the patients and controls

Both study group and control group were subjected to the followings:

1-History taking: Birth weight, mode of delivery, sex, gestational age, Apgar score, and postnatal age of the cases were recorded , Antenatal medications, Maternal illness, day of onset of jaundice, Frequency of breast

feeding, time of initiation of breast feeding, Symptoms suggesting neonatal infection (poor suckling, fever, diminished activity), and bleeding anywhere

2-Physical examination: Complete systematic examination for all cases was done with stress on: Weight, Length, Head circumference, Site of jaundice (head and neck, upper trunk, lower trunk, thigh, palms, soles), pallor. Organomegally (hepatosplenomegally, lymphadenopathy) bleeding and associated congenital anomalies

3-Laboratory investigations**:**

Under complete aseptic conditions, a venous blood sample was taken during the period (3^{rd} to 5^{th} day) of age from each subject and used for the determination of the followings: Complete blood count (CBC), using Sysmex KX-21 N, Japan ,Serum ca level, serum phosphorus level , Liver function tests (SGOT, SGPT), Blood urea nitrogen and serum creatinine levels, CRP (C- reactive protein), using semi quantitative latex agglutination test, Serum bilirubin levels

Plasma ionized magnesium levels; was measured spectrophotometrically using ready for use kit supplied by QUIMICA CLINICA APLICADA S.A. company-Spain.

Statistical Methods:

After collection of data, they were added and entered into a personal computer. Analysis of the data was done using SPSS (Statistical Package for the Social Sciences). The following statistical tests were used:

1. Mean and standard deviation (SD) to describe quantitative data.
2. Student t test was used to compare between two groups as regards parametric data.
3. Chi-square test was used to compare between two groups as regards non-parametric data.
4. Pearson correlation was used to correlate two quantitative variables.

For all tests, a probability (p) of less than 0.05 was considered significant.

Graphical presentation of the results was also done.

3. Results

Results of the study are presented in the following tables and figure.

Table (1) shows clinicolaboratory characteristics of the studied groups. There was no significant difference between both groups as regard, sex distribution, gestational age, Apgar score and mode of delivery. In Group I: 19 of the newborn babies had jaundice in head and neck (mild jaundice) and 21 newborns had jaundice in head, neck and upper trunk (moderate jaundice), Cases with severe jaundice were excluded from the study.

Also there was no significant difference between the two groups as regard, white blood cells count, hemoglobin level, platelets count, reticulocytic count, C-reactive protein, .renal function, serum calcium and phosphorus

Table (2); Serum bilirubin was significantly higher in group (I), (P value <0.001).and Serum ionized Mg was significantly higher in group I (P value = 0.043). The mean ± SD of plasma ionized Mg was (0.54 ± 0.06 mmol/L) in group (I) compared to (0.50 ± 0.06 mmol/L) in group (II).

Table (1): Clinical and laboratory manifestations of the studied groups

Datum	**Group I (Hyperbilirubinemia)** (n=40)	**Group II (Control)** (n=40)	***P* value**
Sex Female	21 (52.5%)	12 (60%)	0.69
Male	19 (47.5%)	8 (40%)	0.42
Mode of delivery Vaginal	24 (60%)	13 (65%)	0.67
Cesarean	16 (40%)	7 (35%)	0.21
Gestational age (weeks)	39.8 ±1.4	39.85 ±1.38	0.57
Age of onset of jaundice (days)	4.1±0.9	----	----
Site of jaundice Head and neck	19 (47.5%)	-------	-------
Head , neck &Upper trunk	21 (52.5%)	-------	
WBCs×10^3/mm^3	6.9± 1.8	7.1 ± 2.2	0.69
Haemoglobin (gm/dl)	14.6±2.48	14.9±3.3	0.67
Platelets ×10^3/mm^3	296±54	310±74	0.42
C-reactive protein	Negative	Negative	NS
SGOT (I.U./ l)	**45±17**	**47±21**	0.57
SGPT (I.U./ l)	**34±13**	**31±15**	0.52
Blood urea (mg/dl)	**12±1.2**	**11±2.3**	0.46
Serum creatinine (mg/dl)	**0.49±0.13**	**0.48±0.10**	0.54
Serum calcium (mg/dl)	8.87± 0.65	8.55± 0.73	0.26
Serum phosphorus (mg/dl)	5.4± 1	5.6±0.8	0.59

Table (2) Serum bilirubin and plasma ionized magnesium

Parameters	Group I (study) (n=40)	**Group II (Control)** (n=40)	***P* value**
Serum bilirubin (mg/dl)	8.3 ±2.6	0.62 ±0.17	<0.001**
Plasma ionized magnesium (mmol/l)	0.54 ± 0.06	0.5 ± 0.067	0.04*

***=Significant ** Highly significant**

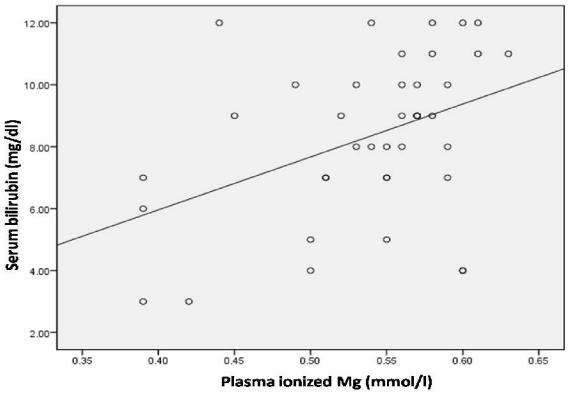

Figure (1): Correlation between plasma ionized Mg and serum bilirubin level

It shows the positive correlation between the mean serum bilirubin and the plasma ionized Mg levels in the newborns included in our study (group 1).

4. Discussion

The exposure of astrocytes to UCB (unconjugated bilirubin) decreases the uptake of glutamate and thus prolongs the presence of glutamate in the synaptic cleft [(15)]. This leads to overstimulation of NMDA receptors (excitotoxicity), both *in vitro* (developing rat brain neurons) and *in vivo* (the jaundiced Gunn rat) [(16-17)]. Although the blocking and modulating effects of Mg ions on NMDA receptor/ion channel complex have been well demonstrated [(18)] and its neuroprotective effects in the pathophysiology of HIE (hypoxic ischemic encephalopathy) have been investigated [(19-21),] the relationship between Mg and neonatal hyperbilirubinemia has not been investigated in details.

Measurement of ionized magnesium (IMg) provides an accurate assessment of the free form of Mg, which is the physiologically active form and is most reflective of the biologically active and not easily measurable intracellular Mg fraction[(22)].

The aim of the study was to evaluate the plasma level of ionized Mg and correlate it with serum bilirubin level in neonatal jaundice. Sixty full term neonates included in the study and classified into two groups: **Group I (study group)**: included 40 full term newborn infants with neonatal jaundice (21 females and 19 males) and their gestational age ranges from 37 to 42 weeks. Apart from neonatal jaundice they were clinically free; no evidence of sepsis, hemolysis or inborn error of metabolism. **Group II (control)**: included 20 full term healthy neonates without jaundice cross matched with age and sex (12 females and 8 males), their gestational age ranges from 37 to 42 weeks.

The study revealed no significant difference between both groups as regard sex, mode of delivery, gestational age and Apgar score Also there was no significant difference between the two groups as regard, white blood cells count, hemoglobin level, platelets count, reticulocytic count, C-reactive protein, renal function, serum calcium and phosphorus

There was a significant difference as regard jaundice in group 1 compared to group II, because in **group I**, 19 of the newborn babies had jaundice in head and neck (mild jaundice) and 21 newborns have jaundice in head and neck & upper trunk (moderate jaundice) [(23- 24)]. In this study we found that there was a significant increase in serum bilirubin in **group 1** compared to **group 2** (p=< .0001).

Also the study showed that plasma ionized Mg level was significantly higher in **group 1** compared to **group 2** (P=0.03). The increased Mg level may be due to mild hemolysis not detectable by the ordinary investigations Also the increase in Mg level may be due to extracellular movement of intracellular Mg because of cellular injury by high bilirubin level that may cause neuronal and generalized cellular injury **Sarici *et al.*** [(24)]. These results are in agreement with **Misra *et al.* (25)** who reported increased serum Mg in neonatal physiological jaundice and also in agreement with **Huseyin *et al.* (26)** who found higher serum Mg and manganese in newborn infant with physiological jaundice and their mothers compared to newborn without jaundice **.**

Different from our results are **Tuncer *et al.* (27)** as they reported that lower serum total mg concentrations in both umbilical cord and maternal blood of newborns with hyperbilirubinemia when compared with normal newborns, and they postulated that hypomagnesemia results from intracellular shift of Mg ions **.**

In their next study, **Tuncer *et al.* (28)** investigated the serum levels of zinc, copper and total mg in umbilical cord blood and peripheral venous blood of newborns with nonhemolytic hyperbilirubinemia and they reported lower umbilical and neonatal serum zinc and total mg concentrations in both newborns with moderate hyperbilirubinemia and

newborns with severe hyperbilirubinemia undergoing exchange transfusion in comparison with newborns without hyperbilirubinemia. They speculated that maternal gestational malnutrition may have caused maternal and neonatal hypomagnesemia by negatively affecting enzymes in bilirubin metabolism and antioxidant enzyme in erythrocytes, thus leading to significant neonatal indirect hyperbilirubinemia .

The differences in Mg levels (decreased versus increased) between these two studies and our study may be due to either the differences in the method used or to the differences in serum bilirubin levels and ages of the newborns among these studies. Also the differences may be due to that in our study we measured ionized Mg.

In another study, **Pintov *et al.* (29)** investigated the value of umbilical cord zinc, copper and total Mg measurements in predicting the future (48^{th} hour) development of hyperbilirubinemia and they reported no differences in the levels of these trace elements and Mg between 29 newborns with a serum bilirubin level of ≥136.8 μM (mean, 186.4±41 μM) and 61 newborns with a serum bilirubin level of ≤ 136.8μM (mean, 106±17.1μM) at the 48^{th} hour of life. They regarded the measurement of these elements in cord blood of no value in predicting the development of significant hyperbilirubinemia. However, the mean serum bilirubin levels in that study were in the range of physiolgic hyperbilirubinemia, and these serum bilirubin levels may not be high enough to reveal the relationship between Mg and hyperbilirubinemia .

In this study we found that there was no correlation between plasma ionized Mg level and gestational age, these results was not in agreement with **Mehta and Petrova, [30]** as they found that plasma ionized magnesium level varies with gestational age this may because we include in the study full term neonates but their study include preterm neonates. In our study we found that there was a significant positive correlation between serm bilirubin level and ionized Mg level (correlation coefficient, r = 0.27& p=0.01). This finding suggests the possibility of a neuroprotective role or a compensatory machanism in plasma ionized Mg increase against emerging toxicity risk of increasing serum bilirubin values. These results are in agreement with **Sarici *et al.* [24]** who found a positive correlation between ionized Mg and the severity of hyperbilirubinemia in full term newborns with neonatal jaundice .

Supporting our suggestion regarding the neuroprotective role of magnesium, **Gathwala *et al.* (20)** in an earlier study, had reported that a dose of 250 mg/kg and 125 mg/kg of magnesium sulfate given as an infusion is safe and well tolerated by asphyxiated neonates. He found that EEG abnormalities occurred in 43.75% of the cases in the control group .

Also **Bhat *et al.* (19)** in a recent study concluded that postnatal magnesium sulfate treatment improves neurologic outcomes at discharge for term neonates with severe perinatal asphyxia . On the other side, **Broner *et al.* (31)** in a study performed on pediatric intensive care patients, concluded that hypermagnesemia and hypocalcaemia were both associated with poor outcome as measured by either survival or length of ICU stay.

5. Conclusion

In conclusion, presence of significantly higher plasma IMg levels in newborns with hyperbilirubinemia suggest that increase in plasma IMg may be due to extracellular movement of Mg, resulting from generalized cellular injury including neurons and erythrocytes., we also may conclude the possibility of a neuroprotective role or a compensatory mechanism of increased IMg levels to reduce bilirubin toxicity. And to question the future value of Mg treatment in the therapy of neonatal hyperbilirubinemia.

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