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Magnesium Changes in Neonatal Hyperbilirubinemia Treated with Phototherapy

Conflict of interest: nothing to declare.
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Abstract

Introduction. Increased levels of unconjugated bilirubin cause neonatal jaundice, which can have a neurological aftereffect such as encephalopathy. Magnesium is high in hyperbilirubinemia and plays a neuroprotective role. One of the many side effects of phototherapy, which is still the predominant treatment for newborn jaundice, is hypomagnesemia.
Purpose. Examine the serum magnesium level in full-term neonates treated with phototherapy for hyperbilirubinemia both before and after the procedure, and investigate its association with specific neonatal, maternal, and labor factors.
Materials and methods. A prospective study has been carried out in Basrah Maternity and Children Hospital, 2nd neonatal care unit from 1st of May till 1st of December 2017. 25 of whom were female and 23 of whom were male. The neonates were aged 14 days or younger and were receiving phototherapy for unconjugated hyperbilirubinemia. Neonates with asphyxia, respiratory distress, prematurity, low for gestational age, congenital deformities, infant of diabetic mother, sepsis, exchange transfusion, sodium bicarbonate or magnesium therapy, neonates of mothers on magnesium sulphate prenatally were excluded. Serum magnesium levels were measured before and after phototherapy; the normal range is 1.6–2.8 mg/dl. Nennatal and maternal data were gathered, and hypomagneseia was examined in connection to particular variables.
Results. Following phototherapy, it was discovered that total serum bilirubin had decreased. In 20% of the newborns, hypomagnesemia was discovered. It was greater in late neonatal phase (>7 days) and female with statistically significant outcome. Neonates who receive more than 3 days phototherapy had lower magnesium level ($p=0.002$). Serum Magnesium was related to bilirubin level before phototherapy. Magnesium was not related to gestational age, weight, maternal age, parity, or mode of delivery.
Conclusion. Serum magnesium is elevated in hyperbilirubinemia. Hypomagnesemia is significant among neonates treated with phototherapy; magnesium is lower in extensive and prolonged phototherapy, late neonatal period, female neonates.
Keywords: phototherapy, hypomagnesaemia, hyperbilirubinemia, full term, total serum bilirubin

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Изменения магния при неонатальной гипербилирубинемии после фототерапии

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Резюме

Введение. Повышенный уровень неконъюгированного билирубина вызывает желтуху новорожденных, которая может иметь неврологические последствия, такие как энцефалопатия. Магний повышен при гипербилирубинемии и играет нейропротекторную роль. Одним из многочисленных побочных эффектов фототерапии, которая по-прежнему является основным методом лечения желтухи новорожденных, является гипомагниемия.
Цель. Изучить уровень магния в сыворотке у доношенных новорожденных, прошедших фототерапию при гипербилирубинемии, как до, так и после процедуры и изучить его связь со специфическими неонатальными, материнскими и родовыми факторами.
Материалы и методы. Проспективное исследование проводилось в родильном и детском госпитале Басры, 2-м отделении неонатальной помощи с 1 мая по 1 декабря 2017 г.; 25 пациентов – женского пола, 23 – мужского. Новорожденные были в возрасте 14 дней или младше и получали фототерапию при неконъюгированной гипербилирубинемии. Новорожденные с асфиксией, респираторным дистрессом, недоношенные, с низкой для гестационного возраста степенью, врожденными уродствами, дети от матерей с диабетом, сепсисом, обменным переливанием, терапией бикарбонатом натрия или магнием, новорожденные от матерей, получавших пренатально сульфат магния, были исключены. Уровень магния в сыворотке измерялся до и после фототерапии; нормальный диапазон составляет 1,6–2,8 мг/дл. Были собраны данные о неонатальном и материнском периоде, и гипомагниемия была исследована в связи с определенными переменными.
Результаты. После фототерапии было обнаружено, что общий уровень билирубина в сыворотке снизился. У 20% новорожденных обнаружена гипомагниемия. Она была выше в поздней неонатальной фазе (>7 дней) и у женщин со статистически значимым результатом. У новорожденных, которые получали фототерапию более 3 дней, наблюдался более низкий уровень магния (p=0,002). Уровень магния в сыворотке был связан с уровнем билирубина до фототерапии. Магний не был связан с гестационным возрастом, весом, возрастом матери, количеством родов или способом родоразрешения.

Заключение. Уровень магния в сыворотке повышается при гипербилирубинемии. Гипомагниемия значительна среди новорожденных, получавших фототерапию; уровень магния ниже при экстенсивной и длительной фототерапии, позднем неонатальном периоде, у новорожденных женского пола.
Ключевые слова: фототерапия, гипомагниемия, гипербилирубинемия, доношенный срок, общий сывороточный билирубин

INTRODUCTION

Jaundice is a common benign problem in neonates, in approximately 60% of term infants and 80% of preterm infants [1]. When the total serum bilirubin rises above the 95th percentile for age during the 1st week of life, it will be considered as hyperbilirubinemia [2].

Neonatal jaundice occurs due to the elevated levels of unconjugated bilirubin and may induce neurological sequel, such as encephalopathy [1]. It may occur due to the affinity of bilirubin molecules to the phospholipids of the plasma membrane or through activated oxidative stress and different pathways. Disruption of N-methyl-D-aspartate (NMDA) (distant plasma membrane structures) ion channel/receptor complex found in the membranes of neurons has occurred which result in neuronal injury [3].

Five to ten percent of newborns develop jaundice required the management of hyperbilirubinemia [2]. When it comes to treating newborn jaundice, phototherapy is still the mainstay [4].

It plays a significant role in prevention and treatment of hyperbilirubinemia. It has negative consequences like hyperthermia, feeding intolerance, loose stools, skin rashes, bronze baby syndrome, retinal changes, dehydration, and redistribution of blood flow, genotoxicity, hypocalcaemia [5] and hypomagnesaemia [4–7].

Haypocalcemia have been reported for phototherapy but less have been reported regarding the effect of phototherapy on serum magnesium level [6].

Transcranial illumination caused by phototherapy depresses the pineal gland, which lowers melatonin levels. Melatonin promotes release of cortisone, which lowers calcium and magnesium absorption resulting to hypocalcemia and hypomagnesemia [4, 6].

One of the most significant antagonistic regulators of the NMDA receptor/ion channel complex is the magnesium (Mg) ion. It prevents brain damage mechanisms mediated by NMDA receptors to produce its neuroprotective effects [3]. Magnesium is necessary for over 300 biochemical reactions in the body and plays a role in bone health, energy transport, blood pressure regulation, muscle contraction, and cytoprotection. A magnesium deficiency can lead to a number of disorders, including hypokalaemia, hypocalcaemia, cardiac and neurological manifestations [8] and some signs like nausea, vomiting, weakness, decreased feeding, seizures, arrhythmia [9]. It is concerned with transport of calcium and sodium [10, 11]. About 40% of cases with hypokalaemia have hypomagnesemia [12].

PURPOSE

Determine the magnesium level in full-term patients with hyperbilirubinemia who require phototherapy and to investigate its relationship to the severity of the condition as well as to specific neonatal, maternal, and labor variables.

MATERIALS AND METHODS

Design and setting

A prospective study has been carried out in Basrah Maternity and Children Hospital, 2nd neonatal care unit (out-born neonates) from 1st of May till 1st of December 2017 to assess serum magnesium on 54 term neonates with unconjugated hyperbilirubinemia treated by phototherapy.

Inclusion criteria

Term healthy neonates (gestational age 37–42 weeks) with indirect hyperbilirubinemia and managed with phototherapy, their serum bilirubin was more than 13 mg/dl. Born to healthy mothers who had no chronic medical illnesses or obstetric complications before and after delivery.

Exclusion criteria

Neonates who carry risk of hypomagnesemia such as neonatal asphyxia, respiratory distress, premature neonates, and small for gestational age, sepsis, infant of diabetic mother, those who had exchange transfusion, congenital malformations, sodium bicarbonate or magnesium therapy, neonates of mothers on magnesium sulphate prenatally were excluded.

Data collection

A unique questionnaire was created specifically for the study in order to evaluate the following information:

Neonatal data

Name, sex, date of birth, age, gestational age, weight, date of admission to hospital, type and duration of phototherapy, type of feeding, Family history of neonatal jaundice, or hemolytic anemia. Comprehensive newborn exams were performed, encompassing a general and systemic assessment, as well as the recording of growth metrics.

Maternal data

Name, blood group, parity, and age last menstrual cycle, long-term maternal illnesses (diabetes mellitus, hypertension, hemolytic anemia). Pregnancy complications include prolonged rupture of the membranes, fever, anemia, antepartum hemorrhage, and urinary tract infections.

Labor and delivery

Place of delivery: hospital or at home. Mode of delivery: vaginal or cesarean.

Neonates with Jaundice who were admitted to second neonatal care unit are kept on single, double or extensive phototherapy unit using of fluorescent blue light lamps which supplies spectral irradiance of ≥5 $mw/cm^2/nm$ with wave-length (420–470) nm/cm^2.

Naked neonates were placed while covering eyes and genitalia at a distance of (30) cm from phototherapy unit. The position of the neonate was changed from time to time.

Procedures

1. To ass's serum magnesium, venous blood samples were drawn from the neonates at arrival and 48 hours after phototherapy into plain tubes, were either analyzed within 2 h or centrifuged, and the separated plasma was stored at –20 °C in a refrigerator for further analysis. The specimens were analyzed with ISE method in conjunction with an AVL 988-4 ISE Analyzer (AVL List GmbH Medizintechnik, Graz, Austria) [11]. Neonates are divided into 2 groups according to serum magnesium level after phototherapy: Normomagnesemic group when total serum magnesium level range (1.6–2.8 mg/dl), hypomagnesemic group when total serum magnesium concentration less than 1.6 mg/dl [13].
2. Total serum bilirubin (T.S.B): was estimated by (BIL READ) Bilirubin meter using special standardized solution put in capillary tube, while both direct and indirect bilirubin estimated by spectrophotometer.
3. Other investigations done included complete blood count using hematological analyzer (Sysmex KX-21 N, 2006). Blood group and Rh for the mothers and neonates, Blood film morphology.

Statistical analysis

Statistical analysis was done using (SPSS program V.21). Data were expressed by mean±SD. A comparison of proportion was performed using Chi-Square test-test and ANOVA test. For the purpose of analyzing various indicators, logistic regression analysis (Binary Logistic) was performed utilizing the Odd Ratio (OR) and 95% Confidence Interval (CI). A statistically significant P value was defined as <0.05.

■ RESULTS

It was found that TSB was lower after phototherapy with statistically significant result. The mean serum magnesium after phototherapy was lower than before phototherapy with statistical significant result (Table 1).

Hypomagnesemia was found in 20.4% of neonates (Table 2).

It was more in late neonatal period and female with statistically significant result (Table 3).

It was more in extensive phototherapy than double or single p value 0.05. Neonates who receive more than 3 days phototherapy had lower magnesium level (p=0.002) (Table 4).

Serum magnesium was related to TSB level before phototherapy, hypomagnesemia was more in high level of bilirubin (>300 mmol/l) with a high significant difference (p=0.027) (Table 5, 6).

Table 1
Serum magnesium and bilirubin level in neonates before phototherapy and 48 hours after it

Variable	Before phototherapy, Mean±SD	48 hours after phototherapy, Mean±SD	P value
T.S.B. mmol/l	310.56±48.463	193.81±22.984	0.0001
S. Mg^{+2} mg/dl	2.2689±0.356	1.915±0.299	0.0001

Table 2
Frequency of neonatal hypomagnesemia after phototherapy

Variable	No. (%)	Serum magnesium range	Serum Magnesium Mean±SD	P value
Normomagnesemic group (1.6–2.8 mg/dL)	43 (79.6)	1.6–2.45	2.01±0.238	0.0001
Hypomagnesemic group (<1.6 mg/dl)	11 (20.4)	1.3–1.55	1.5±0.091	0.0001

Table 3
Serum magnesium (after phototherapy) in relation to neonatal age and sex

Variable		Normomagnesemic group, No. (%)	Hypomagnesemic group, No. (%)	P value
Age (days)	<7	33 (89.2)	4 (10.8)	0.016
	>7	10 (58.8)	7 (41.2)	
Sex	Male	23 (92.0)	2 (8.0)	0.024
	Female	20 (71.4)	8 (28.6)	
Total		43 (79.6)	11 (20.4)	

Table 4
Serum magnesium (after phototherapy) in relation to type and duration of phototherapy

Variable		Normomagnesemic group, No. (%)	Hypomagnesemic group, No. (%)	P value
Type of phototherapy	Single	21 (91.3)	2 (8.7)	0.053
	Double	8 (88.9)	1 (11.1)	
	Extensive	14 (63.6)	8 (36.4)	
Duration of phototherapy (days)	<3	27 (96.4)	1 (3.6)	0.002
	≥3	16 (61.5)	10 (38.5)	

Table 5
Serum magnesium in relation to total serum bilirubin level before phototherapy

Variable		Normomagnesemic group		Hypomagnesemic group		P value
		No.	%	No.	%	
T.S.B.	<300 mmol/l	24	92.3	2	7.7	0.027
	≥300 mmol/l	19	67.9	9	32.1	

Table 6
Serum magnesium in relation to total serum bilirubin level after phototherapy

Variable		Normomagnesemic group		Hypomagnesemic group		P value
		No.	%	No.	%	
T.S.B.	<200 mmol/l	31	77.5	9	22.5	0.408
	>200 mmol/l	12	85.7	2	14.3	

Serum magnesium was not related to gestational age, weight, maternal age, parity, or mode of delivery (Table 7–9).

The logistic regression analysis of risk factors for hypomagnesemia after phototherapy listed in Table 10. Although, no significant found among sex, gestational age, type of delivery and duration of phototherapy.

Table 7
Serum magnesium in relation to neonatal age and weight

Variable		Normomagnesemic group (1.6–2.8 mg/dl), No. (%)	Hypomagnesemic group (<1.6mg/dl), No. (%)	P value
Gestational age (Weeks)	37–39	42 (80.8)	10 (19.2)	0.369
	40–42	1 (50.0)	1 (50.0)	
Weight (KG)	2.5–3.5	35 (79.5)	9 (20.5)	0.673
	3.5–4	8 (80.0)	2 (20.0)	
Total		43 (79.6)	11 (20.4)	

Table 8
Serum magnesium (after phototherapy) in relation to maternal age and parity

Variable		Normomagnesemic group, No. (%)	Hypomagnesemic group, No. (%)	P value
Maternal age	<18	1 (100)	0 (0.0)	0.754
	18–35	37 (80.4)	9 (19.6)	
	>35	5 (71.4)	2 (28.6)	
Parity	1	7 (87.5)	1 (12.5)	0.121
	2–5	36 (80.0)	9 (20.0)	
	>5	0 (0.0)	1 (100.0)	
Total		43 (79.6)	11 (20.4)	

Table 9
Serum magnesium (after phototherapy) in relation to mode of delivery

Variable		Normomagnesemic group, No. %	Hypomagnesemic group, No. %	P value
Mode of delivery	Vaginal	30 (76.9)	9 (23.1)	0.350
	Cesarean section	13 (86.7)	2 (13.3)	
Total		43 (79.6)	11 (20.4)	

Table 10
A logistic regression analysis of risk factors for hypomagnesemia after phototherapy

Variables	B	Significant	Confidence interval (95%)	
			Lower	Upper
Sex	2.262	1	0.0001	–
Gestational age	1.703	0.16	0.017	1.958
Type of delivery	3.047	0.076	0.726	610.698
Duration of phototherapy	22.811	0.997	0.0001	–

■ DISCUSSION

The human body possesses a competitive method for preserving the maturity that of the brain. Changes in magnesium play a role in proper brain function after cellular damage caused by hyperbilirubine, its level in neonatal hyperbilirubinemia before and after phototherapy [4].

The study revealed a significant decrease in total serum bilirubin (TSB) following phototherapy. This is because light energy absorbed by bilirubin in the skin triggers multiple photochemical reactions that transform the toxic unconjugated bilirubin into unconjugated (which can be eliminated in bile without conjugation) and lumirubin (which can be eliminated by the kidneys in its unconjugated form) [1].

Serum magnesium was found to be higher before phototherapy than after it and was related to TSB, this result was also found in other studies [2–4, 14]. This was suggested by the possibility of extracellular movement of intracellular magnesium to exert it`s neuroprotective role and plasma magnesium increases as a protective mechanism against the possibility of elevated serum bilirubin levels [4]. Magnesium also blocks excitotoxic and NMAD receptor – mediated neuronal injury, to act against neurotoxic effect of bilirubin molecules [3].

It was demonstrated that phototherapy was associated with decrease level of serum magnesium, it`s mean value was significantly lower after phototherapy as decrease level of TSB. This is in agreement with other studies [6, 7]. This is explained by the fact that phototherapy causes transcranial illumination to cause a depression in the pineal gland leading to decrease in magnesium absorption and then hypomagnesemia [4, 6].

Hypomagnesemia was found in 20% of neonates with hyperbilirubinemia treated with phototherapy, the low magnesium was more in late neonatal period where those exposed to phototherapy and more in female than male for unknown reason, may be clearer with including more cases.

CONCLUSION

Hypomagnesemia was found more with extensive and prolonged duration of phototherapy (more than 3 days) due to more intensity of phototherapy. It was not related to gestational age, weight as all neonates is full term; it was not related to maternal age, parity, or mode of delivery.

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