

Effects of Phototherapy on the Serum Magnesium Level in Neonates with Indirect Hyperbilirubinemia: A Prospective Cohort Study

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Abstract

Aim: The aim of the present study was to determine the effect of phototherapy on serum magnesium level in term neonates with hyperbilirubinemia.

Material & Methods: A prospective hospital-based comparative study was conducted on 100 eligible neonates admitted in Department of Pediatrics, AIIMS, New Delhi, receiving phototherapy from January 2019 to December 2019. After approval of the ethical committee, informed consent was obtained from the parents of the selected neonates. This study included 100 full-term neonates who were subjected to phototherapy for treating neonatal hyperbilirubinemia according to the guidelines of the American Academy of Pediatrics.

Results: Our study included 100 full-term neonates with jaundice who received phototherapy for treating neonatal indirect hyperbilirubinemia, comprising 60 (60%) males, and 40 (40%) females, with the mean gestational age of 38 ± 0.7 weeks and mean postnatal age of 5.4 ± 1.3 days. There were 32 (32%) neonates delivered by normal vaginal delivery and 68 (68%) neonates delivered by cesarean section. Mean birth weight was 3.1 kg. The mean difference of jaundice onset age, intrauterine age, admission weight and mother's age were not significant. The amount of total serum bilirubin decreases in all groups. The serum total magnesium level and its changes were reported in three groups before and after phototherapy.

Conclusion: In the present study, the serum magnesium level showed a significant reduction only in the double phototherapy method and remained in the normal range in the other two groups. On the other hand, in all three treatment groups, the level of serum magnesium before the treatment was normal and did not increase significantly.

Keywords: Hyperbilirubinemia, Magnesium, Phototherapy

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Introduction

Hyperbilirubinemia is a substantial clinical problem that is the most common cause of newborn hospitalization. Neonatal jaundice is defined as a total serum bilirubin level above 5 mg per dl ($86 \mu\text{mol/l}$) or total serum bilirubin more than 95th percentile. [1] Jaundice affects at least 60% of full-term

and 80% of preterm neonates. [2] There are two main types of jaundice in neonates, indirect hyperbilirubinemia (non-conjugated) and direct hyperbilirubinemia (conjugated). Direct hyperbilirubinemia does not lead to neurotoxicity, while indirect hyperbilirubinemia is toxic and

harmful for the brain. When indirect bilirubin reaches a toxic level for neuronal cells, it deposits in the nerve membrane and causes permanent neurological damage to the central nervous system. [3-6] The most commonly used treatment for hyperbilirubinemia is phototherapy. Phototherapy has minor complications including hyperthermia, fever, diarrhea effects on blood cells, cytokines, and vitamins, as well as ocular and dermatological complication. Magnesium plays a role in protecting the neural system against hypoxia and neurotoxic effects of bilirubin, through blocking N-methyl-D-aspartate (NMDA) receptor. Bilirubin leads to hyperactivity of the NMDA receptor and exerts neurotoxic effects through binding to NMDA, which has a key role in synaptic physiologic functions and memory. [7] There was a positive relation between serum magnesium and bilirubin levels, and it was propounded that rising of magnesium in hyperbilirubinemia might be a compensatory mechanism against toxic effects of bilirubin. Magnesium protects the nervous system against hypoxia and neurotoxic effects of bilirubin. It seems to apply these protective effects by blocking the NMDA receptor. [8] Deposition of bilirubin in neurons causes permanent neuronal injury. Magnesium is an NMDA antagonist, and it acts against the neurotoxic effects of bilirubin. Several adverse effects have been reported for phototherapy in the treatment of neonatal hyperbilirubinemia but less has been reported regarding the effect of phototherapy on serum magnesium levels. [8]

Therefore, this study was carried out to determine the effect of phototherapy on serum magnesium level in term neonates with hyperbilirubinemia.

Materials & Methods

A prospective hospital-based comparative study was conducted on 100 eligible

neonates admitted in Department of Pediatrics, AIIMS, New Delhi, receiving phototherapy from January 2019 to December 2019. After approval of the ethical committee, informed consent was obtained from the parents of the selected neonates. This study included 100 full-term neonates who were subjected to phototherapy for treating neonatal hyperbilirubinemia according to the guidelines of the American Academy of Pediatrics. [9]

Exclusion Criteria

- Neonates who had direct bilirubin more than 20%, exchange transfusion cases.
- Neonates with Cephalhematoma, congenital malformation.
- Inborn errors of metabolism and sepsis.
- Neonates whose mothers received magnesium sulphate or oxytocin at any time during gestation,
- Intrauterine growth retardation,
- Infants of diabetic mothers,
- Neonates on intravenous fluid,
- Hypocalcemia
- Hypomagnesemia before starting phototherapy
- Hemolytic hyperbilirubinemia.

Each neonate was subjected to detailed history taking (gestational age, mode of delivery, detailed prenatal, natal history, age on admission, and day of onset of jaundice, family history of neonatal jaundice) and clinical examination.

The basic characteristic and demographic data of the neonates including the age of the jaundice onset (day), intrauterine age (week), weight at admission time (g), delivery type (cesarean section or vaginal delivery), mother's age, total serum bilirubin, and magnesium levels were collected before phototherapy. The method of serum bilirubin and magnesium measuring was photometry and atomic absorption spectrophotometry, respectively. For phototherapy, fluorescence lamps are placed above the head of the neonates with full coverage of

the eyes and genitalia. The treatment criterion was the total serum bilirubin levels below 12 mg/dl. Immediately after the completion of the phototherapy treatment period, the total serum bilirubin and magnesium levels of the newborns were measured again.

Statistical Analysis

The collected data were revised, coded, tabulated, and introduced to a computer software using (IBM Corp. Released 2017.

IBM SPSS Statistics for Windows, Version 25.0. Armonk, New York: IBM Corp.). Shapiro test was done to test the normality of data distribution. Paired sample t test was used to assess changes over time. The correlation coefficient defines the strength and direction of the linear relationship between two variables. P value is significant if less than 0.05 at confidence interval 95%.

Results

Table 1: Demographic details

Gender	N%
Male	60 (60)
Female	40 (40)
Mode of delivery	
NVD	32 (32)
LSCS	68 (68)
Neonatal age (days) Mean±SD	5.4±1.3
Gestational days (weeks) Mean±SD	38±0.7
Birth weight (kg) Mean±SD	3.1±0.2

Our study included 100 full-term neonates with jaundice who received phototherapy for treating neonatal indirect hyperbilirubinemia, comprising 60 (60%) males, and 40 (40%) females, with the mean gestational age of 38 ± 0.7 weeks and

mean postnatal age of 5.4 ± 1.3 days. There were 32 (32%) neonates delivered by normal vaginal delivery and 68 (68%) neonates delivered by cesarean section. Mean birth weight was 3.1 kg.

Table 2: Characteristics of neonates for the treatment groups

Variable	Single		Double			Intensive	
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	P value
Jaundice onset age (day)	3.60 ± 1.75	2-12	3.16 ± 1.40	2-9	3.14 ± 1.52	2-10	0.420
Intrauterine age (week)	38:45 ± 0.50	38-40	38:42 ± 0.85	38-41	38.72 ± 0.72	38-41	0.456
Admission weight (gr)	2684 ± 320	2500-3900	3246 ± 340	2500-4150	3165 ± 356	2500-4000	0.160
Mother’s age (year)	27.46 ± 4.32	17-39	28.47 ± 5.30	16-40	29:32 ± 5.25	16-42	0.120

The mean difference of jaundice onset age, intrauterine age, admission weight and mother’s age were not significant.

Table 3:

Table 3: Total serum bilirubin levels before and after single, double, and intensive phototherapy

Phototherapy types	Before	After	Differences (mg/dl)	
	Mean±SD			
Single	16.32 ± 0.6	8.40 ± 1:40	-7:92 ± 1:56	<0.001
Double	18.36 ± 0.70	8.75 ± 1:42	-9:61 ± 1:65	<0.001
Intensive	20.60 ± 2.40	9.20 ± 1.22	-11.4 ± 2:73	<0.001

The amount of total serum bilirubin decreases in all groups.

Table 4: Serum magnesium levels before and after single, double, and intensive phototherapy

Phototherapy types	Before	After	Differences (mg/dl)	
	Mean±SD			
Single	2.05 ±0.30	2.00 ± 0.30	-005 ± 0.25	0.550
Double	2.18 ±0.36	2.08 ± 0.32	-0.1 ±0.42	0.020
Intensive	2.02 ± 0.35	2.05 ± 0.28	0.03 ± 0.30	0.565

Serum total magnesium level in single and double phototherapy decreases after treatment, but this decrease is significant only in the double phototherapy group (P = 0.020). In the intensive group, this parameter has slightly increased, which is not statistically significant (P = 0.565). The serum total magnesium level and its changes were reported in three groups before and after phototherapy.

Discussion

Neonatal hyperbilirubinemia (NH) is the commonest clinical problem occurring during the first week of life, as more than two thirds of newborns develop clinical jaundice [10,11] that can be treated by phototherapy, exchange transfusion, or by pharmacologic agents. Phototherapy is the most common intervention in therapy used

as it is relatively safe and non-invasive. [3,12] The conventionally used light sources in phototherapy are fluorescent tubes and halogen spotlights. However, they cannot be placed close to the infant as they produce considerable amount of heat. Due to this limitation, light-emitting diodes (LEDs) have been used as alternatives as they produce low heat rendering them safe to be placed very close to the infant. [13,14] Jaundice is the most common condition that requires medical attention and hospital readmission in newborns. The yellowish coloration of the skin and sclera in newborns with jaundice is the result of the accumulation of unconjugated bilirubin. [15]

Our study included 100 full-term neonates with jaundice who received phototherapy

for treating neonatal indirect hyperbilirubinemia, comprising 60 (60%) males, and 40 (40%) females, with the mean gestational age of 38 ± 0.7 weeks and mean postnatal age of 5.4 ± 1.3 days. There were 32 (32%) neonates delivered by normal vaginal delivery and 68 (68%) neonates delivered by cesarean section. Mean birth weight was 3.1 kg. Subjects have a mean intrauterine age of 38.2 weeks and a jaundice onset age of 3.60 days. The mean difference of jaundice onset age, intrauterine age, admission weight and mother's age were not significant. The amount of total serum bilirubin decreases in all groups. Our study showed that there was a statistically significant positive correlation between total bilirubin and magnesium (total and ionized) in all studied neonates. This agreed with the study done by Sapkota. [16]

Serum total magnesium level in single and double phototherapy decreases after treatment, but this decrease is significant only in the double phototherapy group ($P = 0.020$). In the intensive group, this parameter has slightly increased, which is not statistically significant ($P = 0.565$). The serum total magnesium level and its changes were reported in three groups before and after phototherapy. The serum magnesium level in newborns before treatment was normal in all three treatment groups. The study by Meghana [17] concluded that average magnesium value noted before phototherapy was 2.8 mg/dl and after phototherapy was 1.7 mg/dl, showing a significant difference. Subhashini et al [18] observed that serum magnesium levels before phototherapy in newborns were increased. There was a significant decrease in the level of magnesium after phototherapy, but none reached hypomagnesemia. Bezboruah and Majumder [19] discovered only a significant reduction of mean serum magnesium value following phototherapy.

The status of each patient showed that single, double, and intensive phototherapy

groups have magnesium content of more than 2.2 mg/dl, respectively. In our study, serum magnesium level showed a significant reduction after phototherapy in double phototherapy, but this difference did not show significant changes in both single and intensive phototherapy methods. The reason for insignificant findings in single and intensive phototherapy methods may be a delay in blood sampling due to ethical issues because in our study, no additional blood sampling was performed. Reduced serum magnesium levels after double phototherapy are probably due to increased levels of plasma magnesium in association with hyperbilirubinemia, in which after phototherapy, the magnesium level decreases in association with bilirubin reduction. Since only 1% of the body's magnesium is extracellular, most of these changes are due to the displacement of magnesium between the inside and outside of the cell. Therefore, with increasing bilirubin, plasma levels of magnesium also increase as a result of cellular degradation or as a defense mechanism. In Khosravi et al.'s study, the total serum magnesium levels decreased significantly after phototherapy; it is similar to our results in double phototherapy methods. [20]

In a study, Sarici et al.'s reported that in the severe hyperbilirubinemia group, serum ionized magnesium levels were significantly higher in comparison to the moderate hyperbilirubinemia group. [21] But our results revealed that the serum magnesium level was normal in all three groups before the treatment, and there was no increase in serum magnesium level. In Sarici et al.'s study, the increase in magnesium levels in severe hyperbilirubinemia was caused by magnesium leakage from damaged neurons and red blood cells to exert its protective effect on the nervous system. Shahriarpanah et al [22] found that the serum level of magnesium decreased through relieving hyperbilirubinemia, and the increase in the plasma level of

magnesium might be owing to synchronization with hyperbilirubinemia too.

Conclusion

Bilirubin exerts its neurotoxicity effect by binding to the NMDA receptor in the neural synapse. Magnesium is one of the most important inhibitors of the NMDA receptor. The body increases the level of extracellular magnesium to reduce the neurotoxicity effects of bilirubin as a defense mechanism. In the present study, the serum magnesium level showed a significant reduction only in the double phototherapy method and remained in the normal range in the other two groups. On the other hand, in all three treatment groups, the level of serum magnesium before the treatment was normal and did not increase significantly.

References

1. Olusanya BO, Osibanjo FB, Slusher TM. Risk factors for severe neonatal hyperbilirubinemia in low and middle-income countries: a systematic review and meta-analysis. *PloS one*. 2015 Feb 12;10(2):e0117229.
2. Bhutani VK, Zipursky A, Blencowe H, Khanna R, Sgro M, Ebbesen F, Bell J, Mori R, Slusher TM, Fahmy N, Paul VK. Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. *Pediatric research*. 2013 Dec;74(1):86-100.
3. Xiong T, Qu Y, Cambier S, Mu D. The side effects of phototherapy for neonatal jaundice: what do we know? What should we do?. *European journal of pediatrics*. 2011 Oct;170:1247-55.
4. Eghbalian F, Monsef A. Phototherapy-induced hypocalcemia in icteric newborns. *Iranian Journal of Medical Sciences*. 2015 Nov 30;27(4):169-71.
5. Monsef A, Eghbalian F. Does conventional phototherapy have any effect on platelet count in full term neonates with indirect hyperbilirubinemia. *Health*. 2011 Dec 8;3(12): 70 9-11.
6. Eghbalian F, Pourhossein A, Zandevakili H. Effect of clofibrate in non-hemolytic indirect hyperbilirubinemia in full term neonates. *The Indian Journal of Pediatrics*. 2007 Nov;74:1003-6.
7. Imani M, Rezaee-pour M, Mohamdi M, Shiri M, Noroozifar M, Mahmodi N. Study of relationship between total Magnesium and total bilirubin levels in neonates' sera before and after phototherapy. *Razi Journal of Medical Sciences*. 2012 Oct 10;19(100):54-61.
8. Sapkota NK. Effect of phototherapy on serum bilirubin and ionized magnesium level in hyperbilirubinemic neonates. *Innovare J Med Sci*. 2017; 5(1):10-1.
9. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004 Jul; 114 (1):297-316.
10. Ullah S, Rahman K, Hedayati M. Hyperbilirubinemia in neonates: types, causes, clinical examinations, preventive measures and treatments: a narrative review article. *Iranian journal of public health*. 2016 May;45(5):558.
11. Venaktamurthy M, Balaji MD, Reddy KT. A study on effect of phototherapy on platelet count in neonates with neonatal hyperbilirubinemia in a tertiary care rural hospital. *Int J Contemp Pediatr*. 2016 Feb;3:253-5.
12. Mreihil K, Benth JS, Stensvold HJ, Nakstad B, Hansen TW. Norwegian Neonatal Network. Phototherapy is commonly used for neonatal jaundice but greater control is needed to avoid toxicity in the most vulnerable infants. *Acta Paediatr*. 2018;107(4):611-9.
13. Mohammadzadeh M, Eliadarani FK, Badiei Z. Is the light-emitting diode a better light source than fluorescent tube for phototherapy of neonatal jaundice in

- preterm infants?. *Advanced Biomedical Research*. 2012 Jan 1;1(1) :51.
14. Gutta S, Shenoy J, Kamath SP, Mithra P, Baliga BS, Sarpangala M, Srinivasan M. Light emitting diode (LED) phototherapy versus conventional phototherapy in neonatal hyperbilirubinemia: a single blinded randomized control trial from coastal India. *BioMed Research International*. 2019 Apr 11;2019.
 15. Mitra S, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment. *British Journal of Hospital Medicine*. 2017 Dec 2;78(12):699-704.
 16. Sapkota NK. Effect of phototherapy on serum bilirubin and ionized magnesium level in hyperbilirubinemic neonates. *Innovare J Med Sci*. 2017;5 (1):10-1.
 17. Khatab AA, Ashour NM, Shehata ML. Effect of phototherapy on serum magnesium level in newborn with hyperbilirubinemia. *Menoufia Medical Journal*. 2021 Jul 1;34(3):1004.
 18. Subhashini B, Vani SA, Das P, Niranjana R. Adverse effects of phototherapy on calcium, magnesium and electrolytes levels in neonatal jaundice. *Int J Clin Biochem Res*. 2019;6(3):275-8.
 19. Bezboruah G, Majumder AK. Electrolyte imbalances resulting from phototherapy in neonatal hyperbilirubinemia. *IOSRJDSM*. 2019; 18:51-8.
 20. Khosravi N, Aminian A, Taghipour R. Total serum magnesium level in icteric neonates before and after phototherapy. *Tehran University Medical Journal*. 2011 Oct 1;69(7).
 21. Sarici SU, Serdar MA, Erdem G, Alpay F. Evaluation of plasma ionized magnesium levels in neonatal hyperbilirubinemia. *Pediatric research*. 2004 Feb;55(2):243-7.
 22. Shahriarpanah S, Tehrani FH, Davati A, Ansari I. Effect of phototherapy on serum level of calcium, magnesium and vitamin D in infants with hyperbilirubinemia. *Iranian journal of pathology*. 2018;13(3):357.