Electrolyte Imbalances Resulting from Phototherapy Use in Neonatal Hyperbilirubinemia in Suez Canal University Hospital's Neonatal Intensive Care Unit.

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Abstract

***Background*: Neonatal hyperbilirubinemia is a very common clinical problem during the neonatal period. It occurs due to excessive formation of unconjugated bilirubin and limited ability of neonatal liver to rapidly clear it from the blood. Phototherapy is one of the most effective ways available in preventing the neurotoxic complications of indirect hyperbilirubinemia, but it can cause unwanted side effects including electrolyte abnormalities. *Aim:* To estimate serum electrolyte levels in neonates before and after phototherapy and to detect electrolyte imbalances arising due to phototherapy if they ever occurred. *Patients and methods:* This prospective hospital based observational comparative study was conducted on forty eligible neonates admitted to Suez Canal University Hospital's Neonatal Intensive Care Unit with unconjugated hyperbilirubinemia not associated with any co-morbidity. *Results:* Differences in serum electrolytes (sodium, potassium, ionized calcium, magnesium) and creatinine levels after different intervals of phototherapy were statistically significant (P value for all electrolytes were <0.001) ; all cases had normal serum electrolyte levels on admission, 45% of them developed hyponatremia, 30% had hypokalemia, 65% encountered hypocalcemia, 32.5% developed hypomagnesemia and 25% of cases had elevated serum creatinine level more than normal after 48 hours or more of phototherapy. There was a statistically significant relationship between gestational age and changes that occurred in serum sodium level after 48 hours or more of phototherapy (P value 0.001). *Conclusion:* Phototherapy results in remarkable decline in serum bilirubin level together with different effects on serum electrolytes (sodium, potassium, ionized calcium, magnesium) and creatinine.**

***Keywords*:** Light therapy; Jaundice; electrolyte disturbance.

Introduction

Neonatal hyperbilirubinemia is a very common clinical problem occurring during the neonatal period. [1,2] Due to their shorter lifespans and greater turnover rates of red blood cells, infants-especially preterm-produce more bilirubin than adults[3,4]. Because bilirubin inhibits mitochondrial enzymes, interferes with DNA and protein synthesis; high serum bilirubin levels can be harmful[5]. Untreated severe hyperbilirubinemia can lead to a number

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of health issues, including cerebral palsy, acute bilirubin encephalopathy, behavioral and neurological dysfunction even in full-term babies[(6)]. Treatment options for jaundice include exchange transfusion, pharmacological treatment and phototherapy (which is further divided into conventional and intense forms)[(7,8)]. One of the best methods for avoiding the neurotoxic side effects of indirect hyperbilirubinemia is phototherapy. Additionally, it lessens the necessity of exchange transfusions and the associated risks[(9,10)]. The body can eliminate bilirubin molecules by converting them into water-soluble isomers by the help of light. Normal bilirubin absorbs light and is transformed into two isomeric forms: configurational and structural isomers[(11, 12)]. Loose stools, heat, dehydration, skin burn, retinal damage, low platelet count, increased red cell osmotic fragility, bronze baby syndrome, riboflavin insufficiency and DNA damage are among the side effects of phototherapy that are frequently observed[(13)]. Electrolyte imbalance, particularly hypocalcemia, is a lesser-known side effect of phototherapy that can potentially become catastrophic[(14, 15)]. Phototherapy causes hypocalcemia, which is more in preterm than term infants [(16,17)]. The cause of hypocalcemia is due to phototherapy's suppression of melatonin secretion from the spinal cord, which prevents cortisol's impact on calcium levels in the bone. In addition to its direct hypocalcemic impact, cortisol also promotes calcium absorption by the bone[(18, 19)]. Phototherapy also causes hyponatremia[(20,21)], hypokalemia[(21)], and hypomagnesemia[(22, 23)]. We aimed to reduce morbidity and mortality arising due to neonatal jaundice and its complications.

Patients & methods

This prospective hospital based observational comparative study was conducted on forty eligible neonates admitted to Suez Canal University Hospital's Neonatal Intensive Care Unit, Ismailia from August 2021 to April 2022 with unconjugated hyperbilirubinemia not associated with any co-morbidity.

Inclusion criteria

Neonates of both genders, delivered at or referred to Suez Canal University NICU with unconjugated hyperbilirubinemia, not associated with any co-morbidity and received phototherapy for at least 24 hours including those with physiological jaundice, jaundice due to RH or ABO incompatibility, breast-feeding jaundice, breast-milk jaundice and idiopathic jaundice.

Exclusion criteria

Neonates with conjugated hyperbilirubinemia, major or life-threatening congenital malformations, infants of diabetic mothers, history suggestive of birth asphyxia or obstructed labor, infants undergoing exchange transfusion, history of hyperthyroidism in the mother, neonates with co-morbidities like neonatal septicemia, respiratory distress syndrome and renal failure.

Data collection

All data of neonates who were receiving phototherapy for unconjugated hyperbilirubinemia was recorded on a predesigned proforma. Recording a detailed history (as given by the patient's mother).

Measurement of anthropometric indicators: weight, length and head circumference.

A head-to-toe examination was performed to identify any apparent congenital anomaly and icterus extent.

All enrolled neonates were subjected to testing levels of: hemoglobin (g/dl), reticulocyte count, blood group, Rh typing, blood glucose (mg/dl), serum bilirubin (mg/dl), serum calcium (mg/dl), serum sodium (mmol/L), serum potassium (mEq/L), Serum magnesium (mg/dl), Serum creatinine (mg/dl) before the start of phototherapy (first sample) and at intervals of 24 hours, 48 hours, or at the discontinuation of phototherapy whenever earlier.

A comparative study was made between these samples to determine the changes in serum electrolytes before and after phototherapy.

Ethical committee approval

The study was initiated and carried out after explaining the procedures in detail and getting informed consent from the patient's guardian. An approval from the Research Ethics Committee in the Faculty of Medicine at Suez Canal University was obtained.

Statistical Analysis

Data was analyzed using IBM SPSS software package version 20.0 **(Armonk, NY: IBM Corp).** Normality of the data was tested by applying the Kolmogorov-Smirnov test. The tests used were:

Friedman test (Fr): for abnormally distributed quantitative variables, to compare between more than two periods or stages.

Post Hoc Test (Dunn's): for pairwise comparisons.

Significance was considered in cases where the p-value was found to be ≤ 0.05.

Results

Total number of cases was 40 neonates; 62.5% were female, about half of them (19 cases) were treated by 360'dimensional phototherapy unit and all cases included in the study were free of symptoms of kernicterus (ex; irritability-jitteriness-convulsions-high-pitched cry) on admission. The difference in serum bilirubin level after different intervals of phototherapy (after 24 hours, at 48 hours, or more than 48 hours) was statistically significant (P value < 0.001**)**. The differences in serum electrolytes (sodium, potassium, ionized calcium, magnesium and creatinine) levels after different intervals of phototherapy (before phototherapy, after 24 hours, after 48 hours, or more than 48 hours) were statistically significant (p value < 0.001). Only 22% of the study group had symptomatic hypocalcemia (ex; irritability / jitteriness). Regarding the relation between differences that occurred in serum electrolyte levels & the duration of phototherapy, only the differences in serum creatinine level were significant (p value 0.002), but others were insignificant. The relationship between different types of phototherapies used and changes that occurred in serum electrolyte levels were insignificant. Regarding the relation between gestational age and changes that occurred in serum electrolyte levels after 48 hours or more of phototherapy, only changes that occurred in serum sodium level were statistically significant (p value 0.001). Regarding the relation between changes that occurred in serum electrolyte level and weight for gestational age; all changes were insignificant.

Table (1): Comparison between the three studied periods according to serum bilirubin level after different intervals of phototherapy

Bilirubin (mg/dl)	Admission		24 hrs.		≥ 48 hrs.		Fr	P
	No.	%	**No.**	%	**No.**	%		
Less than 5	0	0.0	0	0.0	21	52.5	74.340*	<0.001*
5 – 10	0	0.0	2	5.0	16	40.0		
10 – 15	4	10.0	8	20.0	3	7.5		
15 – 20	22	55.0	29	72.5	0	0.0		
More than 20	14	35.0	1	2.5	0	0.0		
Sig. bet. groups	p_1=0.019*, p_2<0.001*, p_3<0.001*							

Fr: Friedman test, *Sig. bet. periods were done using* ***Post Hoc Test (Dunn's)***
p: p value for comparing between the studied periods in each group
p_1: p value for comparing between ***Admission and 24 hrs.***
p_2: p value for comparing between ***Admission and 48 hrs.***
p_3: p value for comparing between ***24 hrs. and 48 hrs.***
**: Statistically significant at p ≤ 0.05*

Table (2): Comparison between the three studied periods according to serum electrolyte levels

	on admission		after 24 hrs.		after 48 hrs. or more		Fr	P
	No.	%	No.	%	No.	%		
Na (mmol/L)								
Less than 135	0	0.0	3	7.5	18	45.0	31.0*	<0.001*
135 – 145	40	100.0	37	92.5	22	55.0		
Sig. bet. Groups	p_1=0.615, p_2=0.003*, p_3=0.012*							
K (mEq/L)								
Less than 3.50	0	0.0	0	0.0	12	30.0	24.0*	<0.001*
3.50 – 5.50	40	100.0	40	100.0	28	70.0		
Sig. bet. Groups	p_1=1.000, p_2=0.044*, p_3=0.044*							
Calcium (ionized) (mg/dl)								
Less than 4.2	0	0.0	2	5.0	26	65.0	48.308*	<0.001*
4.2 – 5.58	40	100.0	38	95.0	14	35.0		
Sig. bet. Groups	p_1=0.737, p_2<0.001*, p_3<0.001*							
Mg (mg/dl)								
Less than 1.6	0	0.0	0	0.0	13	32.5	26.0*	<0.001*
1.6 – 2.6	40	100.0	40	100.0	27	67.5		
Sig. bet. Groups	p_1=1.000, p_2=0.029*, p_3=0.029*							
Creatinine (mg/dl)								
0.3 – 1.2	40	100.0	40	100.0	30	75.0	20.0*	<0.001*
More than 1.2	0	0.0	0	0.0	10	25.0		
Sig. bet. Groups	p_1=1.000, p_2=0.094, p_3=0.094							

Fr: **Friedman test**, Sig. bet. periods were done using **Post Hoc Test** (**Dunn's**)
p: p value for comparing between the studied periods in each group
p_1: p value for comparing between **Admission and 24 hrs.**
p_2: p value for comparing between **Admission and 48 hrs.**
p_3: p value for comparing between **24 hrs. and 48 hrs.**
*: Statistically significant at p ≤ 0.05

Table (3): Relation between duration of phototherapy and serum electrolytes

	Duration of phototherapy						Fr	P	total (40)
	Less than 48 hrs. (n= 1)		48 hrs. (n= 22)		More than 48 hrs. (n= 17)				
	No	%	No.	%	No.	%			
Na (mmol/L)									
Less than 135	0	0.0	9	40.9	9	52.9	1.358	0.625	18
135 – 145	1	100.0	13	59.1	8	47.1			22
K (mEq/L)									
Less than 3.50	0	0.0	4	18.2	8	47.1	4.105	0.102	12
3.50 – 5.50	1	100.0	18	81.8	9	52.9			28
Calcium (ionized) (mg/dl)									
Less than 4.2	0	100.0	12	54.4	14	82.4	2.477	0.296	26
4.2 – 5.58	1	0.0	10	45.5	3	17.6			14
Mg (mg/dl)									
Less than 1.6	0	0.0	4	18.2	9	52.9	5.552	0.051	13
1.6 – 2.6	1	100.0	18	81.8	8	47.1			27
Creatinine (mg/dl)									
0.3 – 1.2	1	100.0	21	95.5	8	47.1	12.173*	0.002*	30
More than 1.2	0	0.0	1	4.5	9	52.9			10

Table (4): Relation between different types of phototherapies used and serum electrolytes (after 48 hrs)

After 48 hrs.	Type of phototherapy used						Fr	P
	LED (n= 15)		Fluorescent tube (n= 6)		360'dimension al unit. (n= 19)			
	No.	%	No.	%	No.	%		
Na (mmol/L)								
Less than 135	7	46.7	1	16.7	10	52.6	2.280	0.358
135 – 145	8	53.3	5	83.3	9	47.4		
K (mEq/L)								
Less than 3.50	4	26.7	1	16.7	7	36.8	0.901	0.724
3.50 – 5.50	11	73.3	5	83.3	12	63.2		
Calcium (ionized) (mg/dl)								
Less than 4.2	9	60.0	2	33.3	15	78.9	4.288	0.111
4.2 – 5.58	6	40.0	4	66.7	4	21.1		
Mg (mg/dl)								
Less than 1.6	7	46.7	0	0.0	6	31.6	4.069	0.146
1.6 – 2.6	8	53.3	6	100.0	13	68.4		
Creatinine (mg/dl)								
0.3 – 1.2	11	73.3	6	100.0	13	68.4	2.178	0.430
More than 1.2	4	26.7	0	0.0	6	31.6		

Table (5): Relation between gestational age and serum electrolyte changes after phototherapy (after 48 hrs)								
After 48 hrs.	Gestational age						Fr	P
	Pre-term (n= 16)		Full term (n= 18)		Post-term (n= 6)			
	No.	%	No.	%	No.	%		
Na (mmol/L)								
Less than 135	13	81.3	4	22.2	1	16.7	13.967*	0.001*
135 – 145	3	18.8	14	77.8	5	83.3		
K (mEq/L)								
Less than 3.50	8	50.0	3	16.7	1	16.7	6.649	0.082
3.50 – 5.50	8	50.0	15	83.3	5	83.3		
Calcium (ionized) (mg/dl)								
Less than 4.2	13	81.3	11	61.1	2	33.3	4.447	0.113
4.2 – 5.58	3	18.8	7	38.9	4	66.7		
Mg (mg/dl)								
Less than 1.6	8	50.0	5	27.8	0	0.0	4.977	0.080
1.6 – 2.6	8	50.0	13	72.2	6	100.0		
Creatinine (mg/dL)								
0.3 – 1.2	10	62.5	14	77.8	6	100.0	2.994	0.228
More than 1.2	6	37.5	4	22.2	0	0.0		

Table (6): Relation between weight for gestational age and electrolyte disturbances after phototherapy (after 48 hrs)								
After 48 hrs.	Weight for gestational age						Fr	P
	Appropriate (n= 29)		Small (n= 8)		Large (n= 3)			
	No.	%	No.	%	No.	%		
Na (mmol/L)								
Less than 135	15	51.7	3	37.5	0	0.0	2.785	0.273
135 – 145	14	48.3	5	62.5	3	100.0		
K (mEq/L)								
Less than 3.50	10	34.5	2	25.0	0	0.0	1.187	0.722
3.50 – 5.50	19	65.5	6	75.0	3	100.0		
Calcium (ionized) (mg/dl)								
Less than 4.2	21	72.4	4	50.0	1	33.3	2.926	0.235
4.2 – 5.58	8	27.6	4	50.0	2	66.7		
Mg (mg/dl)								
Less than 1.6	10	34.5	3	37.5	0	0.0	1.247	0.713
1.6 – 2.6	19	65.5	5	62.5	3	100.0		
Creatinine (mg/dl)								
0.3 – 1.2	22	75.9	6	62.5	3	100.0	1.360	0.581
More than 1.2	7	24.1	3	37.5	0	0.0		

Discussion

This study demonstrated that the decrease in total serum bilirubin level after different intervals of phototherapy (after 24 hours – after 48 hours or more than 48 hours) was statistically significant (P value < 0.001). This result is similar to findings in many studies such as: Shahriarpanah et al. (2018) [23], Bezboruah & Majumder (2019) [14] and Amneenah (2022) [24] in addition to AboHussein et al. (2022). [25] This effect is mostly due to bilirubin's structure changing as a result of phototherapy. These structural and configurational isomers of bilirubin become less lipophilic than normal bilirubin, so, can be easily excreted in urine and bile without being glucuronidated in the liver. [11,12] The present study showed that all changes that occurred in serum electrolytes (sodium, potassium, ionized calcium, magnesium) and creatinine levels after different intervals of phototherapy were statistically significant (P value < 0.001).

Serum Sodium:

All cases in this study had normal serum sodium levels on admission, 45% of them developed hyponatremia after 48 hours or more of phototherapy. This result is similar to other studies including Suneja et al. (2018) [26], Ghosh et al. (2020) [27] and Amneenah (2022) [24] in which significant decrease in serum sodium levels after phototherapy occurred. Unlike AboHussein et al. (2022) [25] in which there was a decrease in mean (± SD) serum sodium level from 136.5 ± 12.85 before phototherapy to 135.8 ± 2.75 after phototherapy but the difference was not statistically significant, which was explained by the small size of the studied group. Hyponatremia mostly occurs because phototherapy may result in diarrhea with transient impairments in water and sodium absorption. [20] [21]

Serum potassium:

Regarding serum potassium in this study, all enrolled neonates had normal serum potassium levels on admission, 30% of them developed hypokalemia after 48 hours or more of phototherapy (a statistically significant decrease in serum potassium levels had occurred; P value < 0.001).This finding has similarity to some studies such as AboHussein et al. (2022) [25] in which significant difference in serum potassium level after phototherapy occurred (p value < 0.001) where mean (± SD) level of serum potassium decreased from 4.48 ± 1.19 before phototherapy to 3.85 ± 0.53 after phototherapy. Also, a statistically significant decrease in serum potassium level occurred in other studies like Bezboruah & Majumder (2019) [14] and Jena et al. (2019) [28]. The decrease in serum potassium level most probably occurs in a way similar to that of hyponatremia as a consequence of impaired water and potassium absorption in neonates receiving phototherapy. [21]

Serum Ionized calcium:

All cases in this study had normal serum ionized calcium levels ranging from 4.2-5.58 mg/dl on admission, 65% of them were less than 4.2 mg/dl after 48 hours or more of phototherapy (P value <0.001). Similar statistically significant decrease in serum calcium levels also occurred in many studies, such as those by: Suneja et al. (2018) [26], Bezboruah & Majumder (2019) [14], Jena et al. (2019) [28], Amneenah (2022) [24] and AboHussein et al. (2022) [25].

Asl et al. (2016) [29] reported a decrease in serum calcium levels, but the changes did not lead to hypocalcemia, and they recommended further complementary studies with larger sample size. Light entering the skull can have an inhibi tory impact on pineal gland, causing a decrease in melatonin secretion and perhaps contributing to hypocalcaemia.[17] [18] It may also occur as a result of the decrease in parathormone production that may occur in jaundiced newborns treated with phototherapy.[19] [20] Regarding the occurrence of symptomatic hypocalcemia after phototherapy, 22% of this study group had symptomatic hypocalcemia (jitteriness- irritability), which has similarities to a study done by Jain et al. (1998) [30] in which 30% of full-term newborns and 55% of preterms had phototherapy-induced hypocalcaemia; 63.6% of the affected preterm infants with hypocalcemia became jittery, and 27.3% were irritable. In addition, 50% of the full-term newborns with hypocalcemia were jittery, and 16.7% developed irritability. Accordingly, they advised giving infants receiving phototherapy calcium supplements to prevent hypocalcemia.

Serum magnesium:

All cases in the present study had normal serum magnesium levels on admission, 32.5% of them were less than 1.6 mg/dl after 48 hours or more of phototherapy. A significant decline occurred in mean serum magnesium level in this study, which is similar to findings in the studies by Shahriarpanah et al. (2018) [23], Bezboruah & Majumder (2019) [14] and Amneenah (2022) [24]. Phototherapy affects serum magnesium in a way similar to that on serum calcium, through depression of pineal gland secretions. [23]

Serum creatinine:

Concerning serum creatinine level, in the present study, 25% of cases had elevated serum creatinine level more than 1.2 mg/dl (statistically significant), unlike the findings in other studies such as: AboHussein et al. (2022) [25] and Suneja et al. (2018) [26] in which there were significant decrease in serum creatinine level after phototherapy.Elevated serum creatinine levels in this study may be explained by dehydration caused by phototherapy if fluid support was not adequate.

This study considered the co-relation between the difference that occurred in serum electrolyte levels and the duration of phototherapy. All of them in the present study were insignificant except for the differences that occurred in serum creatinine level, which were statistically significant (P value = 0.002). Other studies also demonstrated the significance of the duration of phototherapy on the changes that occurred in different serum electrolytes: such as Bezboruah & Majumder (2019) [14] and Rangaswamy et al. (2019) [21] in which the duration of phototherapy proved to have a highly significant negative correlation with the serum levels of sodium, potassium, ionized calcium and creatinine. These findings regarding the duration of phototherapy are unsimilar to those of Ghosh et al. (2020) [27], in which the changes that occurred in serum electrolytes were not statistically significant with the duration of phototherapy. Concerning the relation between gestational age and changes that occurred in serum electrolyte levels in this study, only changes that occurred in serum sodium were statistically significant (P value 0.001), but other electrolyte changes were insignificant. This finding has similarities to a study by Bezboruah & Majumder (2019) [14] in which preterm neonates had higher rates of post-phototherapy hyponatremia and hypocalcemia (18.31% and 25.34%) than term (11.02% and 10.24%) and post-term (12.5% and 0%), respectively, but the incidence of hypokalemia and hypomagnesemia did not correlate with gestational age. Jena et al. (2019) [28] also illustrated gestational age co-relation with electrolyte imbalances after phototherapy; preterm infants had more changes than full term in each of serum sodium (29.4% and 5% respectively), calcium (52.9% and 15% respectively) and potassium (all cases who developed hypokalemia were pre-term).

Owing to their immature skin, which makes them more susceptible to insensible water loss, as well as their unstable acid-base balance and less developed renal system, which gets better with increasing gestational age, preterm neonates may be more susceptible to electrolyte imbalances than full-term neonates. [5] [10] This study observed the relationship between different types of phototherapies used and changes that occurred in serum electrolytes. Contrary to our expectations, all changes were insignificant. We had assumed that the 360-dimensional phototherapy unit would result in more electrolyte changes than fluorescent tubes and LED phototherapy. So, further studies with a larger sample size are recommended. Findings are similar to those of Ghosh et al. (2020) [27]. In the present study, no significant relationship was observed between birth weight and electrolyte changes, unlike Bezboruah & Majumder (2019) [14], in which the incidence of hyponatremia, hypokalemia and hypocalcemia was higher in low-birth-weight infants (18.75%, 10% and 26.25%, respectively) than in normal neonates (10.32%, 4.76% and 7.94%, respectively).

Conclusion

Phototherapy results in a remarkable decline in serum bilirubin level together with different effects on serum electrolytes: sodium, potassium, ionized calcium, magnesium and creatinine (hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia and elevated serum creatinine level). All changes were statistically significant, but none of the cases showed any clinical manifestation since only marginal changes were observed. Such effects were mostly positively correlated with the duration of phototherapy used (especially regarding serum creatinine and serum magnesium).

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