CLINICAL STUDY

The Effect of Phototherapy on Various Biochemical Parameters in Neonatal Hyperbilirubinemia

SHASHI KANT MEENA*, JAGDISH SINGH†, DHAN RAJ BAGRI‡, NEHA AGRAWAL#

ABSTRACT

Phototherapy (PT) is the current modality of choice for treatment of unconjugated hyperbilirubinemia. The effects of PT on various biochemical parameters including serum calcium, bilirubin profile, serum total protein, albumin, urea, creatinine, serum electrolytes in neonates are a concern in current times. Like any other treatment, PT also has its own side effects. This hospital-based, prospective, comparative observational study was conducted with the objective to assess the level of various biochemical parameters like serum calcium, serum sodium, serum potassium, serum chloride, serum urea and serum creatinine, serum total protein and serum albumin in addition to serum bilirubin before PT and after completion of 48 hours of PT in full-term neonates with unconjugated hyperbilirubinemia at a tertiary care center. On comparing biochemical parameters, a statistically significant difference in parameters such as bilirubin, urea, creatinine, sodium, potassium, chloride, calcium, total protein and albumin was observed after PT. On the other hand, there was a statistically nonsignificant difference in corrected calcium (p = 0.945).

Keywords: Phototherapy, neonatal hyperbilirubinemia, neonatal hypocalcemia, biochemical parameters in neonates

Neonatal hyperbilirubinemia affects nearly 80% preterm and 60% term babies during initial weeks of life[1]. About 6.1% term babies have a serum bilirubin over 12.9 mg/dL and 3% of them have levels over 15 mg/dL at the time of admission. Untreated severe unconjugated hyperbilirubinemia is potentially neurotoxic[2]. Premature infants when compared to term neonates have higher frequency of hyperbilirubinemia necessitating intervention[3]. Phototherapy (PT) prevents rise of bilirubin to dangerous levels, which may cause neurological damage[4]. Phototherapy can produce adverse effects such as dehydration, temperature instability, skin rashes, loose stools, retinal damage, hypocalcemia, bronze baby syndrome, redistribution of blood flow and genitotoxicity. In addition, limited evidences are available that depict the effect of PT on various biochemical parameters including serum calcium, bilirubin profile, serum total protein, albumin, urea, creatinine, serum electrolytes in neonates. Bilirubin encephalopathy is the most serious complication of jaundice and PT is the current modality of choice for treatment of unconjugated hyperbilirubinemia. Like any other treatment PT also has its own side effects but they are not fatal and have no known long-term effects. One of its possible side effects is electrolyte imbalance. Hence, the present study was conducted with the objective to assess the level of various biochemical parameters like serum calcium, serum sodium, serum potassium, serum chloride, serum urea and serum creatinine, serum total protein and serum albumin in addition to serum bilirubin before PT and after completion of ≥48 hours of PT in full-term neonates with unconjugated hyperbilirubinemia.

MATERIAL AND METHODS

This hospital-based prospective comparative observational study was conducted in the Department of Pediatrics, SMS Medical College, Jaipur, from June 2019 to July 2020, after taking requisite clearance from the research board of the institute. Full-term neonates with unconjugated hyperbilirubinemia requiring PT for ≥48 hours were included in the study after getting written informed consent from the parents. Babies born

*Senior Registrar
†Senior Professor
‡Assistant Professor
#Associate Professor
Dept. of Pediatrics, SMS Medical College, Jaipur, Rajasthan, India
Address for correspondence
Dr Dhan Raj Bagri
Assistant Professor
Sir Padampat Institute of Neonatology and Child Health (J K Lon Hospital) and SMS Medical College, Jaipur, Rajasthan, India
E-mail: meena.drdhanraj6@gmail.com

to mothers with diabetes, with onset of jaundice within 24 hours of age, with perinatal asphyxia (Apgar <4 at 1 min of birth), who had exchange transfusion, with jaundice having hypocalcemia and other biochemical parameter abnormalities prior to start of PT or babies born with apparent major congenital anomalies, small for gestational age (SGA) and large for gestational age (LGA), PT duration <48 hours and those having pathological jaundice were excluded.

Sample size was calculated at 95% confidence level, alpha error of 0.05, assuming standard deviation (SD) of 22.7 mEq/L in sodium in neonates with hyperbilirubinemia with pre- and post-PT; to get a minimum difference of at least 5 mEq/L in serum sodium level, pre- and post-PT, at study power of 80%, the required sample size was at least 154 term neonates with unconjugated hyperbilirubinemia receiving PT ≥48 hours. Data were recorded on a proforma. The data analysis was computer based; SPSS-22 was used for analysis. For categoric variables, Chi-square test was used. For continuous variables, independent samples *t*-test was used. $P < 0.05$ was considered significant.

A total of 154 babies were enrolled in the study. Two venous blood samples were collected with all aseptic precautions; first before start of PT and second after ≥48 hours of continuous PT. These blood samples were immediately sent to the laboratory for estimation of serum bilirubin, urea, creatinine, electrolytes (sodium, potassium and chloride), calcium, total protein and albumin.

The patients were divided into two groups; one group included neonates receiving PT for 48 hours and the second group had neonates who received PT for 48 to 72 hours. The comparative effect of PT was assessed on the various biochemical parameters in both groups. Blue light LED (light-emitting diode) PT was used and distance between LED bulb and baby was kept 30 cm. Eyes and genitalia of baby were covered with eye shield and diaper, respectively. The baby was taken out only for feeding.

Total and direct serum bilirubin were measured by Diazo method in Randox Rx Imola chemistry analyzer. Serum calcium was measured by Arsenazo III method in Randox Rx Imola chemistry analyzer. Standard reference value was taken as 8-11 mg/dL. Serum electrolytes (sodium, potassium and chloride) were measured by Ion selective electrodes analyzer in EasyLyte® Plus REF 2121 machine. Standard reference values were taken as sodium 135-145 mEq/L, potassium 3.5-4.5 mEq/L and chloride 92-114 mg/dL. Serum urea was measured by urease GLDH method in Randox Rx Imola chemistry analyzer. Standard reference value was taken as 10-45 mg/dL. Serum creatinine was measured by Jaffe method in Randox Rx Imola chemistry analyzer. The standard reference value was taken as 0.42-1.2 mg/dL. Serum total protein was measured by colorimetric biuret test by Randox Rx Imola chemistry analyzer. Standard reference value was taken as 4.6-7.4 g/dL. Serum albumin was measured by Bromocresol Green (BCG) end point method in Randox Rx Imola chemistry analyzer. Standard reference value was taken as 3.5-5.5 g/dL.

RESULTS

The baseline characteristics of study participants are depicted in Table 1.

The baseline demographic and biochemical profile of subjects is depicted in Table 2.

Comparative analysis of various biochemical parameters like bilirubin, urea, creatinine, sodium, potassium, chloride, calcium, total protein and albumin revealed that all these parameters were significantly reduced after PT. This difference in parameters was statistically significant. On the other hand, there was statistically nonsignificant difference in corrected calcium ($p = 0.945$) (Tables 3 and 4).

Out of 114 patients (PT till 48 hours), 27 patients (23.68%) developed hypocalcemia ($p < 0.0001$), while out of 40 patients (PT till 48-72 hours) 9 patients (22.50%) developed hypocalcemia ($p = 0.002$). Difference in both groups were statistically significant. Hypocalcemia was observed in 20 patients (28.99%) 3 days old as compared to 7 patients (15.56%) aged >3 days receiving PT till 48 hours. The difference was not statistically significant ($p = 0.118$). Similar findings were observed in patients receiving PT till 48 to 72 hours in 5 patients (31.25%) 3 days old as compared to 4 patients (16.67%) >3 days age. The difference was not statistically significant ($p = 0.441$) (Scatter diagram 1).

There was a significant positive correlation observed between serum calcium before and after PT till 48 hours (Coefficient of correlation = 0.043, $p = 0.025$) (Scatter diagram 2).

It suggests a positive correlation but p value was nonsignificant ($p = 0.140$) and coefficient of determination $R^2 = 0.056$.

Change in mean values of serum total bilirubin level, serum urea, serum creatinine, serum protein, serum albumin, serum calcium before and after PT (PT till 48 hours) and (PT till 48-72 hours) were found to be

Table 1. Baseline Characteristics of Study Participants (n = 154)

Residential status	Urban-85 (55.19%)		Rural-69 (44.81%)
Male:Female (ratio)	Males-103 (66.88%)	Females-51 (33.12%)	Ratio (M:F) = 2.019
Age- and gender-wise distribution	Male (103)	Female (51)	100%
1-2 days	40 (38.83%)	10 (19.51%)	50 (32.47)
3-4 days	43 (41.75%)	28 (54.90%)	71 (46.10)
5-6 days	16 (15.53%)	12 (23.53%)	28 (18.18)
>6 days	04 (3.88%)	01 (1.96%)	5 (3.25)
Onset of jaundice	Male (103)	Female (51)	Total frequency (100%)
2-3 days	23 (21.90%)	13 (25.49%)	36 (23.38)
4-5 days	61 (58.10%)	27 (52.94%)	88 (57.14)
6-7 days	19 (18.10%)	11 (21.57%)	30 (19.48)
Place of delivery	Inborn-103 (66.88%)	Outborn-51 (33.12%)	Total (154)
Mode of delivery	Vaginal delivery-65 (42.21%)	Cesarean section-89 (57.79%)	Total (154)

Table 2. Biochemical Parameters of Study Population (n = 154) at Admission

Parameters	Mean	SD	Median	Range
Age (days)	3.30	1.68	3.00	1.00-10.00
Day of onset of jaundice	4.51	1.28	4.00	2.00-10.00
Duration of PT (hours)	52.22	8.27	48.00	48.00-72.00
Total serum bilirubin (mg/dL)	18.55	2.62	17.84	14.10-24.30
Serum urea (mg/dL)	27.65	6.76	28.00	10.00-45.00
Serum creatinine (mg/dL)	0.77	0.18	0.77	0.42-1.20
Serum sodium (mEq/L)	139.77	3.15	139.50	135.0-145.00
Serum potassium (mEq/L)	4.42	0.50	4.45	3.50-5.50
Serum chloride (mg/dL)	106.46	4.54	107.00	92.00-114.00
Serum calcium (mg/dL)	9.07	0.65	8.90	8.00-10.80
Corrected calcium (mg/dL)	9.28	0.68	9.20	8.00-11.00
Total protein (g/dL)	5.60	0.63	5.50	4.60-7.40
Albumin (g/dL)	3.73	0.21	3.70	3.5-5.5

statistically significant. Out of 154 patients, 114 patients received PT till 48 hours and 40 patients received PT till 48 to 72 hours. There was a significant decline in serum urea levels after PT in both groups, but the decline was within defined range.

Out of 114 patients (PT till 48 hours), 10 patients (8.77%) developed hypoproteinemia ($p = 0.001$); this difference was statistically significant, while out of 40 patients (PT till 48-72 hours), only 1 patient (2.50%) developed hypoproteinemia ($p = 0.314$); this difference was nonsignificant statistically.

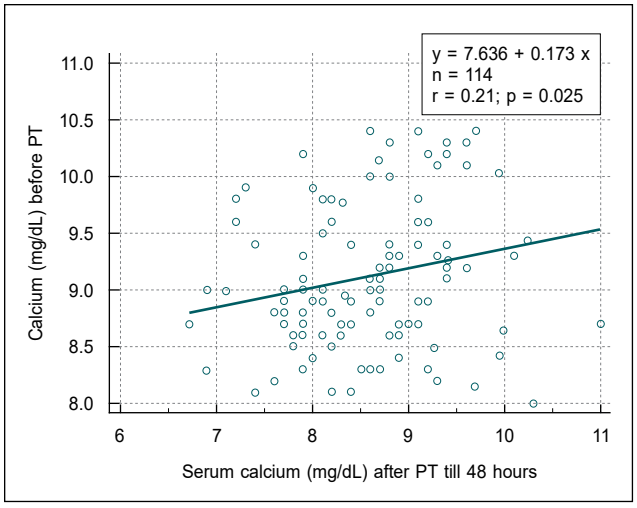
Out of 114 patients (PT till 48 hours), 38 patients (33.33%) developed hyponatremia ($p < 0.0001$). Similarly, out of 40 patients (PT till 48-72 hours),

Table 3. Biochemical Parameters Before and After PT (n = 154)

Biomarker	Before	After	t value	P value
Serum bilirubin (Total)	18.55 ± 2.62	9.38 ± 2.75	43.14	<0.0001
Serum urea	27.65 ± 6.76	21.66 ± 7.17	8.65	<0.0001
Serum creatinine	0.77 ± 0.18	0.65 ± 0.20	6.63	<0.0001
Serum sodium	139.77 ± 3.15	137.69 ± 5.24	4.59	<0.0001
Serum potassium	4.42 ± 0.50	4.17 ± 0.52	5.75	<0.0001
Serum chloride	106.46 ± 4.54	105.13 ± 5.68	2.23	0.026
Serum calcium	9.07 ± 0.65	8.58 ± 0.81	6.58	<0.0001
Corrected calcium	9.28 ± 0.68	9.29 ± 0.77	0.06	0.945
Total protein	5.60 ± 0.63	5.23 ± 0.61	8.20	<0.0001
Albumin	3.73 ± 0.21	3.10 ± 0.43	16.90	<0.0001

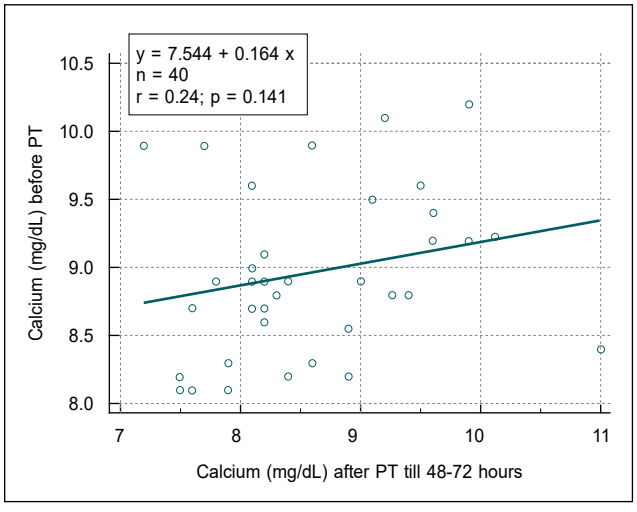
Table 4. Correlation of Parameters with Duration of PT

Parameters	PT till 48 hours (n = 114)		P value	PT till 48-72 hours (n = 40)		P value
	Before PT	After PT		Before PT	After PT	
Serum urea (mg/dL)						
10-45 mg/dL	114 (100%)	114 (100%)	NA	40 (100%)	40 (100%)	NA
<10 or >45 mg/dL	—	—		00	00	
Serum creatinine (mg/dL)						
0.42-1.2 mg/dL	114 (100%)	104 (91.23%)	0.001	40 (100%)	39 (97.50%)	0.314
<1.2 mg/dL		10 (8.77%)		00	01 (2.50%)	
Serum sodium						
135-145 mEq/L	114 (100%)	76 (66.67%)	<0.0001	40 (100%)	30 (75.00%)	0.001
<135 mEq/L		38 (33.33%)		—	10 (25.00%)	
Serum potassium						
3.5-5.5 mEq/L	114 (100%)	105 (92.11%)	<0.0001	40 (100%)	37 (92.50%)	0.0002
<3.5 mEq/L		09 (7.89%)		—	03 (7.50%)	
Serum chloride (mg/dL)						
92-114	114 (100%)	109 (95.61%)	<0.0001	40 (100%)	36 (90.00%)	0.115
>114		05 (4.39%)		—	04 (10.00%)	
Serum calcium (mg/dL)						
8.0-11 (mg/dL)	114 (100%)	87 (76.32%)	<0.0001	40 (100%)	31 (77.50%)	0.002
<8.0 (mg/dL)	—	27 (23.68%)		—	09 (22.50%)	
Total protein						
4.6-7.4 g/dL (Normal)	114 (100%)	100 (87.72%)	<0.0001	40 (100%)	35 (87.50%)	0.054
<4.6 g/dL	—	14 (12.28%)		00	05 (12.50%)	
Albumin						
3.5-5.5 g/dL (Normal)	114 (100%)	20 (17.54%)	<0.0001	40 (100%)	13 (32.50%)	<0.0001
<3.5 g/dL	—	94 (82.46%)		00	27 (67.50%)	



Scatter diagram 1. Serum calcium before and after PT till 48 hours (n = 114).

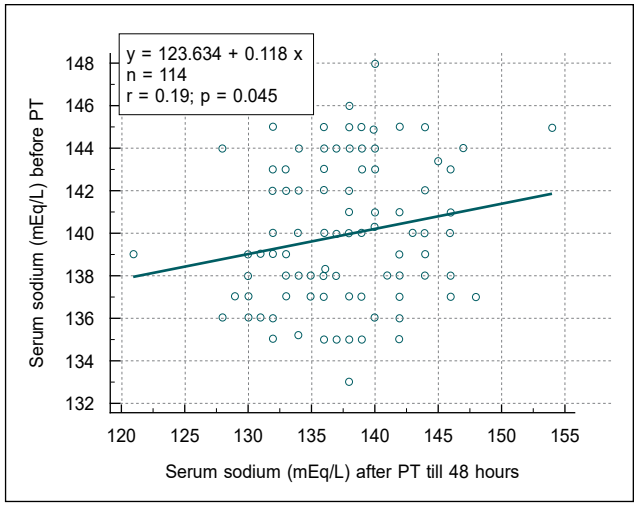
Regression Equation (n =114). Coefficient of determination R^2 = 0.04387					
y = 7.6358 + 0.1729 x					
Parameter	**Coefficient**	**SE**	**95% CI**	**t value**	**P value**
Intercept	7.6358	0.6581	6.3319 to 8.9396	11.6033	<0.0001
Slope	0.1729	0.07626	0.02177 to 0.3240	2.2668	0.0253



Scatter diagram 2. Serum calcium before and after PT till 48-72 hours (n = 40).

Regression Equation					
y = 7.5444 + 0.1642 x					
Parameter	**Coefficient**	**SE**	**95% CI**	**t value**	**P value**
Intercept	7.5444	0.9388	5.6440 to 9.4449	8.0365	<0.0001
Slope	0.1642	0.1092	–0.05684 to 0.3851	1.5037	0.1409

10 patients (25%) developed hyponatremia (p = 0.001). In both groups, the difference was statistically significant (Scatter diagram 3).



Scatter diagram 3. Serum sodium before and after PT till 48 hours (n = 114).

Regression Equation					
y = 123.6336 + 0.1184 x					
Parameter	**Coefficient**	**SE**	**95% CI**	**t value**	**P value**
Intercept	123.6336	8.0217	107.7397 to 139.5275	15.4125	<0.0001
Slope	0.1184	0.05837	0.002717 to 0.2340	2.0279	0.0449

A significant positive correlation was observed between serum sodium before and after PT till 48 hours (Coefficient of correlation = 0.035, p = 0.04).

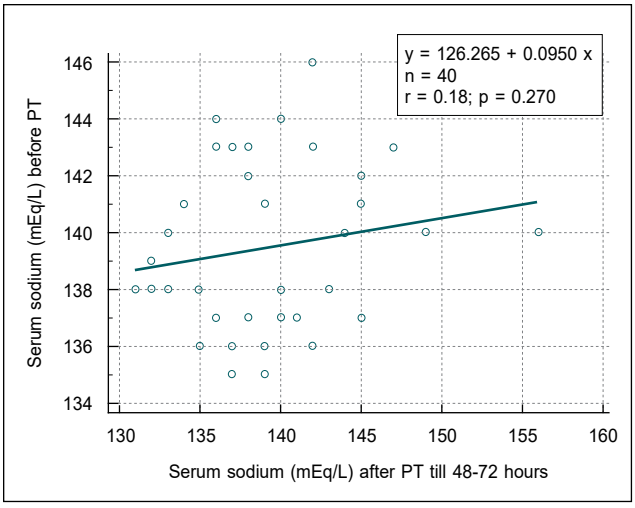
Scatter diagram 4 shows the correlation between serum sodium before and after PT till 48 to 72 hours It depicts a positive correlation but p value was nonsignificant (p = 0.27) and coefficient of determination R^2 = 0.031.

Out of 114 patients (PT till 48 hours), 9 patients (7.89%) developed hypokalemia (p < 0.0001) and out of 40 patients (PT till 48-72 hours), 12 patients (30%) developed hypokalemia (p = 0.0002). This difference was statistically significant in both groups (Scatter diagram 5).

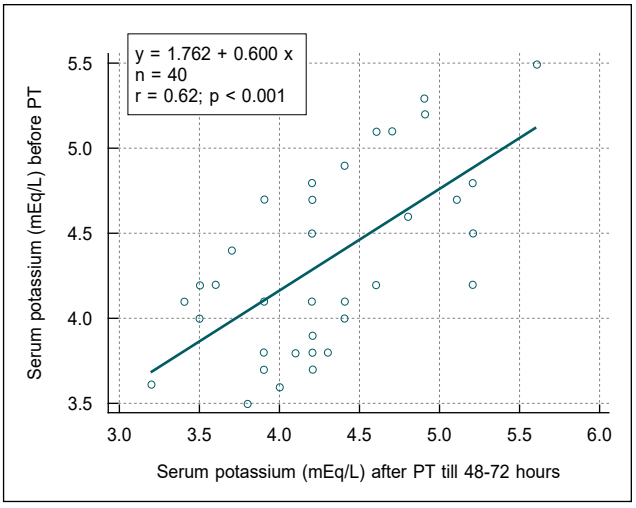
Scatter diagram 5 shows the significant positive correlation between serum potassium before and after PT till 48 hours with significant p value (p < 0.0001) and coefficient of determination R^2 = 0.18.

Scatter diagram 6 shows the significant positive correlation between serum potassium before and after PT till 48 to 72 hours with significant p value (p < 0.0001) and coefficient of determination R^2 = 0.38.

Out of 114 patients (PT till 48 hours), 5 patients (4.3%) developed hyperchloremia (p < 0.0001), the difference was statistically significant, while out of 40 patients, 4 patients (10%) developed hyperchloremia (p = 0.115), the difference was insignificant statistically.

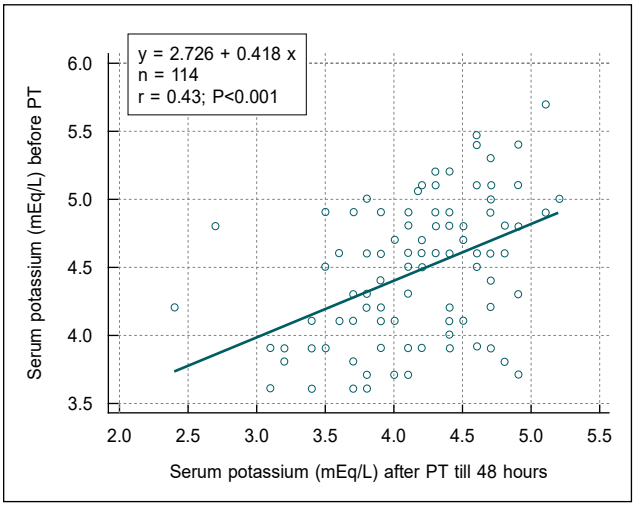


Scatter diagram 4. Serum sodium before and after PT till 48-72 hours (n = 40).



Scatter diagram 6. Serum potassium before and after PT till 48-72 hours (n = 40).

Regression Equation					
y = 126.2652 + 0.09503 x					
Parameter	**Coefficient**	**SE**	**95% CI**	**t value**	**P value**
Intercept	126.2652	11.7954	102.3867 to 150.1438	10.7046	<0.0001
Slope	0.09503	0.08495	–0.07695 to 0.2670	1.1186	0.2703



Scatter diagram 5. Potassium before and after PT till 48 hours (n = 114).

Regression Equation					
y = 2.7263 + 0.4184 x					
Parameter	**Coefficient**	**SE**	**95% CI**	**t value**	**P value**
Intercept	2.7263	0.3479	2.0370 to 3.4157	7.8360	<0.0001
Slope	0.4184	0.08335	0.2532 to 0.5835	5.0198	<0.0001

Out of 114 patients (PT till 48 hours), 14 patients (12.28%) developed hypoproteinemia. This difference was statistically significant ($p < 0.0001$). Out of 40 patients (PT till 48-72 hours), 5 patients developed hypoproteinemia, this difference was statistically insignificant ($p = 0.054$). Out of 114 patients (PT till 48 hours), 94 patients (82.46%) developed hypoalbuminemia ($p < 0.0001$) and out of 40 patients (PT till 48-72 hours), 27 patients (67.50%) developed hypoalbuminemia ($p < 0.0001$). The difference in both groups were statistically significant.

Regression Equation					
y = 1.7620 + 0.6001 x					
Parameter	**Coefficient**	**SE**	**95% CI**	**t value**	**P value**
Intercept	1.7620	0.5302	0.6886 to 2.8353	3.3232	0.0020
Slope	0.6001	0.1229	0.3513 to 0.8488	4.8836	<0.0001

DISCUSSION

Out of 154 patients, 103 patients (66.68%) were inborn and 51 patients (32.12%) were outborn. Most of the neonates (46.10%) enrolled in this study were in the age group 3 to 4 days of life. Males were (66.88%) with male:female ratio being 2.01:1. The study population consisted of 85 urban infants (55.19%) and 69 rural infants (44.81%). About 89 (57.79%) neonates were lower-segment cesarean section (LSCS) delivered. Khan et al (2016) observed that the mean age of the neonates presenting with neonatal hyperbilirubinemia was 8.35 ± 6.74 days[5]. Karan et al also observed preponderance to male baby with male and female ratio being 1.45:1.12; out of 74 subjects[6]. In Kale et al (2020) study, out of 100; 35% neonates had normal vaginal delivery and 65% were delivered by cesarean section and the mean age on the onset of hyperbilirubinemia was 4.73 ± 1.56 days[7].

In present study, 50 patients were admitted in first 2 days of life. Of these, 40 patients (80%) were male and

10 were female (20%). On the other hand, 71 patients were admitted between 3rd and 4th days of life, out of which 43 were male (60.56%) and 28 were female (39.43%). This male preponderance was probably due to the prejudiced care of male baby.

All biochemical parameters viz. bilirubin, urea, creatinine, sodium, potassium, chloride, calcium, albumin, total protein were significantly reduced after PT. But, there was a statistically nonsignificant decline in corrected calcium post-PT.

The mean serum total bilirubin levels before and after PT (PT till 48 hours) were 17.33 ± 1.69 and 8.70 ± 2.53 mg/dL, respectively; this change was found to be statistically significant ($p < 0.0001$). Similarly, mean serum total bilirubin levels before and after PT (PT till 48-72 hours) were 22.02 ± 1.40 and 11.32 ± 2.46 mg/dL, respectively. This difference was also found to be significant statistically ($p < 0.0001$).

Suneja et al (2018) found that the levels of bilirubin profile were elevated significantly in patients prior to PT and returned to normal generally after 48 hours to 96 hours of PT[8]. Shahsavari et al (2017) also reported that in patients who underwent PT for hyperbilirubinemia, bilirubin levels were significantly declined after PT[9].

In present study, the mean serum urea serum levels pre- and post-PT for 48 hours were 27.01 ± 6.49 and 21.38 ± 6.99 mg/dL, respectively, this difference was statistically significant ($p < 0.0001$). Similarly, mean serum urea levels pre- and post-PT for 48 to 72 hours were 29.47 ± 7.26 and 22.47 ± 7.69 mg/dL, respectively, this difference was also statistically significant ($p < 0.0001$). In the present study, out of 154 patients, 114 patients receiving PT for 48 hours and 40 patients receiving PT for 48 to 72 hours, there was significant decline in urea levels but the levels were within normal defined range.

Mean serum creatinine level pre- and post-PT (PT till 48 hours) were 0.75 ± 0.18 and 0.61 ± 0.20 mg/dL, respectively, this difference was statistically significant ($p < 0.0001$). Similarly, mean serum creatinine level before and after PT (PT till 48-72 hours) were 0.83 ± 0.17 mg/dL and 0.74 ± 0.19 mg/dL, respectively, this difference was also statistically significant ($p = 0.013$). Out of 114 patients (PT till 48 hours) 10 patients (8.77%) developed hypocreatininemia ($p = 0.001$), this difference was statistically significant while out of 40 patients (PT till 48-72 hours), 1 patient (2.50%) developed hypocreatininemia ($p = 0.314$), this difference was nonsignificant statistically. Serum creatinine concentration is usually the sole available marker of glomerular filtration rate (GFR) in clinical practice[10-14].

Our results are consistent with the study done in recent past, depicting positive association between serum total bilirubin and serum creatinine.

In present study, the mean sodium levels declined from 139.88 ± 3.25 mEq/L to 137.32 ± 5.17 mEq/L after 48 hours of PT; the changes were statistically significant ($p < 0.001$). In contrast after 48 to 72 hours PT, the mean sodium levels declined from 139.45 ± 2.85 mEq/L to 138.74 ± 5.36 mEq/L; the changes were found to be statistically nonsignificant ($p = 0.433$). Hyponatremia had been postulated to emerged as side effect of PT due to impaired absorption or due to insufficient fluid replacements[10-14].

Out of 114 patients (PT till 48 hours), 38 patients (33.33%) developed hyponatremia; this change was statistically significant ($p < 0.0001$). Similarly, out of 40 patients (PT till 48-72 hours), 10 patients (25%) developed hyponatremia. This difference was also statistically significant. In our study, any patient did not developed symptoms of hyponatremia. Purohit et al (2020) found that the mean sodium decreased from 146.6 ± 6.2 mEq/L to 141.3 ± 6.1 mEq/L[10]. Rangaswamy et al (2019)[11] observed that the incidence of sodium changes was found to be statistically significant after PT ($p < 0.01$), but any neonate didn't develop any signs or symptoms of hyponatremia. Reddy et al (2015) found that the incidence of hyponatremia following PT was higher when the duration of PT was >48 hours when compared to <48 hours[13].

In present study, the mean potassium level declined from 4.46 ± 0.49 mEq/L to 4.14 ± 0.50 mEq/L after 48 hours of PT; these changes were significant statistically ($p < 0.001$). In contrast after 48 to 72 hours PT, the mean potassium levels declined from 4.33 ± 0.53 mEq/L to 4.28 ± 0.55 mEq/L; these changes were statistically insignificant ($p < 0.507$). Hypokalemia was observed as a side effect of PT due to impaired absorption or due to insufficient fluid replacements. Past studies have stated that absorption of water, sodium chloride and potassium was significantly impaired in the patients receiving PT[12,13].

Out of 114 patients (PT till 48 hours), 9 patients (7.89%) developed hypokalemia ($p < 0.0001$) and out of 40 patients (PT till 48-72 hours), 12 patients (30%) developed hypokalemia ($p = 0.0002$). In our study, no patient developed symptomatic hypokalemia. Purohit et al (2020) found that the mean potassium declined from 4.7 ± 0.47 mEq/L to 4.2 ± 0.51 mEq/L[10]. Rangaswamy et al (2019) observed that the incidence of potassium changes was found to be statistically significant after

PT ($p < 0.01$) but none of the neonates developed any signs of hypokalemia[11]. In yet another study, Reddy et al (2015) found no significant changes in potassium level following PT probably because of difference in study settings[13].

Mean serum chloride levels before and after PT (PT till 48 hours) were 106.12 ± 4.54 and 104.51 ± 5.64 mg/dL, respectively; this change was found to be statistically significant ($p = 0.023$). While the mean serum chloride levels before and after PT (PT till 48-72 hours) were 107.42 ± 4.46 and 106.89 ± 5.48 mg/dL, respectively; the difference was statistically nonsignificant ($p = 0.638$). Similar to this finding, Reddy et al (2015) also reported no significant changes in chloride levels following PT in neonates with hyperbilirubinemia. Currently, there is lack of adequate literature regarding effects of PT on electrolytes[13].

In present study, the mean calcium levels reduced from 9.12 ± 0.67 mEq/L to 8.59 ± 0.81 mEq/L after 48 hours of PT ($p < 0.001$). Similarly after 48 to 72 hours PT, the mean calcium levels were declined from 8.94 ± 0.58 mEq/L mEq/L to 8.55 ± 0.84 mEq/L ($p = 0.009$), these changes were found to be statistically significant in both groups. This effect may be attributed to increased urinary calcium excretion. In addition, PT can also affect calcium homeostasis by inhibiting pineal secretion of melatonin, which blocks the effect of cortisol on bone calcium, consequently leading to hypocalcemia. Cortisol also exerts a direct hypocalcemic effect by increasing bone uptake of calcium as well[14].

Out of 114 patients (PT till 48 hours), 27 patients (23.68%) developed hypocalcemia ($p < 0.0001$). Similarly, out of 40 patients (PT till 48-72 hours), 9 patients (22.50%) developed hypocalcemia ($p = 0.002$), the changes in both groups were statistically significant. Purohit et al (2020) found that the mean calcium decreased from 9.4 ± 0.73 mg/dL to 8.4 ± 0.68 mg/dL ($p < 0.05$)[10]. Khan et al (2016) found that serum calcium level before and after 24 hours of initiating PT was 8.73 ± 0.68 and 7.47 ± 0.82 mg/dL, respectively. Frequency of hypocalcemia, in term jaundiced neonates, receiving PT were observed in 22.76% of neonates[5].

In the present study, among the patients receiving PT for 48 hours, majority were 3 days old (69/114) while 45/114 patients were >3 days old. Prevalence of hypocalcemia was observed in 20 of the of 3 days old patients (28.99%) and 7 patients (15.56%) >3 days old. Difference was statistically nonsignificant ($p = 0.118$). While on other hand, in patients receiving PT for 48 to 72 hours, in both groups 3 days (16/40 patients) and >3 days old (24/40) the difference was nonsignificant ($p = 0.441$).

In the present study, mean serum calcium levels in 3 days old neonates before and after PT for 48 hours were 9.09 ± 0.66 and 8.55 ± 0.90 mg/dL, respectively ($p < 0.0001$). Similarly, in >3 days old neonates, the mean calcium levels before and after PT were 9.16 ± 0.68 and 8.65 ± 0.66 mg/dL, respectively ($p = 0.0002$). In both groups, decline in mean calcium was statistically significant.

While in patients receiving PT for 48 to 72 hours, mean calcium levels in 3 days old babies before and after PT were 8.87 ± 0.57 and 8.44 ± 0.69, respectively. Difference was statistically significant ($p = 0.28$). In contrast, in >3 days old babies, the mean calcium levels before and after PT were 9.00 ± 0.59 and 8.63 ± 0.93 mg/dL, respectively. This difference was statistically insignificant ($p = 0.095$). Possible explanation being effective establishment of feeding in neonates during late phase of life.

The present study revealed that in male patients receiving PT for 48 hours, the mean serum calcium levels before and after PT were 9.03 ± 0.63 and 8.46 ± 0.71 mg/dL, respectively; the difference was statistically significant ($p < 0.0001$). In contrast in female babies receiving PT for 48 hours, the mean calcium levels before and after PT were 9.25 ± 0.70 and 8.97 ± 1.00 mg/dL, respectively; the difference was statistically insignificant ($p = 0.106$). In male patients receiving PT for 48 to 72 hours, the mean calcium levels before and after PT were 8.47 ± 0.44 and 7.82 ± 0.32 mg/dL, respectively ($p = 0.004$). Similarly, in female babies receiving PT for 48 to 72 hours, the mean calcium levels before and after were 9.01 ± 0.56 and 8.43 ± 0.46 mg/dL, respectively; ($p = 0.037$) significant statistically. In our study, all patients who developed hypocalcemia were asymptomatic.

Goyal et al (2018) found statistically significant difference between pre- and post-PT serum calcium levels[15]. Rozario et al (2017) also found statistically significant decline in calcium level after 48-hour PT.[16] Singh et al (2017) observed a significant fall in calcium level in 30% of term and 70% of preterm neonates after 48-hour PT[17]. Reddy et al (2015) found that incidence of hypocalcemia following PT was higher when the duration of PT was >48 hours when compared to <48 hours[12,13]. In contrast to these studies, Alizadeh-Taheri et al (2013) observed that the prevalence of PT associated hypocalcemia was not so high, probably because of the shorter duration of PT in their study.[18]

Out of 114 patients (PT till 48 hours), 14 patients (12.28%) developed hypoproteinemia, the change was

statistically significant ($p < 0.0001$). While out of 40 patients (PT till 48-72 hours), 5 patients (12.50%) developed hypoproteinemia, the change was statistically nonsignificant ($p = 0.054$). Mean serum protein before and after PT (PT till 48 hours) was 5.52 ± 0.60 and 5.16 ± 0.59 g/dL, respectively ($p < 0.0001$). Similarly, mean serum protein before and after PT (PT till 48-72 hours) was 5.81 ± 0.69 and 5.44 ± 0.66 g/dL, respectively ($p = 0.0001$). The difference in both groups was statistically significant.

Out of 114 patients (PT till 48 hours), 94 patients (82.46%) developed hypoalbuminemia ($p < 0.0001$) and out of 40 patients (PT till 48-72 hours), 27 patients (67.50%) developed hypoalbuminemia ($p < 0.0001$). This decline was statistically significant in both groups. The mean serum albumin before and after PT till 48 hours was 3.74 ± 0.21 g/dL and 3.05 ± 0.42 g/dL, respectively ($p < 0.0001$). Similarly, mean serum albumin before and after PT till 48 to 72 hours was 3.70 ± 0.18 and 3.27 ± 0.42 g/dL, respectively ($p < 0.0001$), this decline was statistically significant in both groups. Our study observed a significant decline in total proteins, albumin, which could be the result of photo-oxidation of various substances or structures that occurs as a result of PT[12,19-21]. Serum calcium and sodium before PT showed weak positive correlation with levels after PT among both the groups (PT till 48 hours as well as PT 48-72 hours). Serum potassium before PT showed moderate positive correlation with levels after PT till 48 hours, and strong positive correlation with levels after PT 48 to 72 hours.

CONCLUSIONS

In the present study, we observed significant reduction in blood urea and serum creatinine levels as beneficial effects of PT along with serum bilirubin. On other hand, we observed other changes like dyselectrolytemia, especially hyponatremia, hypokalemia and hypocalcemia may prove to be alarming for future reference. In our study, none of the patient developed any adverse symptoms of dyselectrolytemia and hypocalcemia. Therefore, this warrants close and more meticulous monitoring of unwanted side effects so that they do not become life-threatening complications. Hence, PT must be used judiciously considering the risk-benefit ratio. In many studies, we found that PT had an effect on these biochemical parameters in preterm babies also, so we recommend much larger studies in preterm babies. We also recommend further studies to compare the parameters in preterm and full-term babies. We also recommend to measure flux of PT in further studies.

Hence, serum calcium, serum electrolyte, blood urea, serum creatinine, serum total protein and albumin must be monitored in each and every patient requiring PT as it was found that serum calcium and electrolyte imbalance is common after PT. Babies should be closely watched for sign and symptoms of hypocalcemia, hyper-/hyponatremia, hyper-/hypokalemia like seizure, tetany, lethargy, arrhythmia, constipation, diarrhea, etc. Parents should be sensitized towards early recognition of jaundice in neonates.

REFERENCES

1. Kliegman RM. Jaundice and hyperbilirubinemia in the New-born. In: Behrman R (Ed.). Nelson Textbook of Pediatrics. 20th Edition. Philadelphia: Elsevier; 2015. pp. 871-5.
2. Gregory ML, Martin CR, Cloherty JP. Neonatal hyperbilirubinemia. In: Cloherty JP, Eichenward EC, Stark AR (Eds.). Manual of Neonatal Care. 7th Edition. Philadelphia: Lippincott Williams and Wilkins; 2015. pp. 304-28.
3. Yadav RK, Sethi RS, Sethi AS, Kumar L, Chaurasia OS. The evaluation of effect of phototherapy on serum calcium level. People's J Sci Res. 2012;5(2):1-4.
4. Eghbalian F, Monsef A. Phototherapy-induced hypocalcemia in icteric newborns. Iran J Med Sci. 2002;27(4): 169-71.
5. Khan M, Malik KA, Bai R. Hypocalcemia in jaundiced neonates receiving phototherapy. Pak J Med Sci. 2016;32(6): 1449-52.
6. Karan S, Rajak P, Basu M. A comparative study of electrolyte changes in newborns delivered after 35 weeks of gestation before and after receiving phototherapy in a tertiary care hospital. IOSR-JDMS. 2020;19(10):27-34.
7. Kale AV, Jadhao PU, Valecha A, Kethepalli S. The effect of phototherapy on serum calcium level in neonates with hyperbilirubinemia: a cross-sectional study. Int J Contemp Pediatr. 2020;7(8):1772-6.
8. Suneja S, Kumawat R, Saxena R. Effect of phototherapy on various biochemical parameters in neonatal hyperbilirubinaemia: a clinical insight. Indian J Neonat Med Res. 2018;6(2):PO13-PO18.
9. Shahsavari G, Firouzi M, Mahdavifard S, Joudaki A, Birjandi M. Phototherapy motivates protein and lipid oxidation in jaundiced term and late term neonates. Caspian J Pediatr Sep. 2017;3(2):248-52.
10. Purohit A, Verma SK. Electrolyte changes in the neonates receiving phototherapy. Int J Contemp Pediatr. 2020;7(8): 1753-7.
11. Rangaswamy KB, Yeturi D, Gowda BL AN, Krishna C, Samyuktha. Study of sodium and potassium changes in term neonates receiving phototherapy. Int J Contemp Pediatr. 2019;6(3):1076-9.
12. Ezzeldin Z, Mansi Y, Abdelhamid TA, Sabry M. The effect of hat on phototherapy-induced hypocalcemia in jaundiced full-term neonates. Dovepress. 2015;5:73-8.

13. Reddy AT, Vani Bai K, Shankar SU. Electrolyte changes following phototherapy in neonatal hyperbilirubinemia. Int J Sci Res. 2015;4(7):752-8.
14. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114(1):297-316.
15. Goyal S, Srivastava A, Bhattacharjee P, Goyal I, Malhotra K. Effect of phototherapy on serum calcium levels in neonates receiving phototherapy for neonatal jaundice. Int J Res Med Sci. 2018;6(6):1992-5.
16. Rozario CI, Pillai PS, Ranamol T. Effect of phototherapy on serum calcium level in term newborns. Int J Contemp Pediatr. 2017;4(6):1975-9.
17. Singh PK, Chaudhuri PK, Chaudhary AK. Phototherapy induced hypocalcemia in neonatal hyperbilirubinemia. IOSR-JDMS. 2017;16(4):35-8.
18. Alizadeh-Taheri P, Sajjadian N, Eivazzadeh B. Prevalence of phototherapy induced hypocalcemia in term neonate. Iran J Pediatr. 2013;23(6):710-1.
19. Kemper K, Horwitz RI, McCarthy P. Decreased neonatal serum bilirubin with plain agar: a meta-analysis. Pediatrics. 1988;82(4):631-8.
20. Bratlid D. Bilirubin toxicity: pathophysiology and assessment of risk factors. N Y State J Med. 1991;91:489-92.
21. Singh M, Singh M, Tiwari S. Effect of exchange transfusion in bilirubin and calcium level in neonatal hyperbilirubinemia. Int J Med Res Rev. 2015;3(7):733-7.

■■■■