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EVALUATION OF THE EFFECTS OF PHOTOTHERAPY ON VARIOUS BIOCHEMICAL PARAMETERS IN NEONATAL HYPERBILIRUBINEMIA

Paediatrics

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ABSTRACT

BACKGROUND: Neonatal jaundice has been the most common physical finding during the earlier week of life. High values of unconjugated bilirubin can develop encephalopathy and later kernicterus. The aims of phototherapy are to avoid the occurrence of encephalopathy or kernicterus. Phototherapy has many side effects like dehydration, temperature instability, skin rashes, retinal damage, hypocalcemia, electrolyte imbalance.
AIM: Aim is to investigate the effect of phototherapy in full term neonate with unconjugated hyper bilirubinemia on various biochemical parameters before and after >48 hr phototherapy.
MATERIAL AND METHODS: The study was conducted in the department of pediatrics, S.P.M.C.H.I. (J.K. Lon Hospital) and hospitals attached to SMS Medical College, Jaipur, Rajasthan from June 2019 – July 2020. It was a Hospital based prospective comparative observational study. The required sample size was at least 154 Full term neonates (37 completed weeks to 42 weeks) with unconjugated Hyperbilirubinemia receiving phototherapy ≥ 48 hr. All data were collected and analyzed with the help of suitable statistical parameters.
RESULTS: Present study found that all parameters (Serum Bilirubin, Urea, Creatinine, Calcium, Total Protein, And Albumin except Serum Electrolyte) has shown similar trends i.e. statistically significant findings in both groups before and after phototherapy. Whereas serum electrolyte has different pattern in both groups, it showed statistically significant results only in group-I.
CONCLUSION: our study concluded that phototherapy is beneficial modality with judicious calculation of the risk benefit ratio.

KEYWORDS

Neonatal hyperbilirubinemia, Phototherapy, Serum bilirubin, Serum electrolyte

INTRODUCTION:

Neonatal jaundice has been the most common physical finding during the earlier week of life. Neonatal hyperbilirubinemia (NH) nearly influences 80% preterm and 60% term babies during initial weeks of life (1).

Among term newborn 6.1% have a serum bilirubin over 12.9 mg/dl. Serum bilirubin over 15 mg/dl is present in 3% of term newborns at the time of admission. If untreated severe unconjugated hyperbilirubinemia becomes potentially neurotoxic (2). Hyperbilirubinemia in neonates is a manifestation of underdeveloped biliary system. It is the frequent cause for newborns getting admitted again in primary days of life. Premature infants when compared to term neonates have higher frequency of hyperbilirubinemia necessitating intervention (3).

High values of unconjugated bilirubin can develop encephalopathy and later kernicterus. Hyperbilirubinemia can be treated either by phototherapy (PT) or exchange transfusion or pharmacologic agents. Phototherapy (PT) plays a major role in prevention of rise of bilirubin to dangerous levels causing neurological damage (4). Phototherapy is not a harmless intervention; still it can produce adverse effects such as dehydration, temperature instability, skin rashes, loose stools, retinal damage, hypocalcemia, bronze baby syndrome, redistribution of blood flow. It causes photo oxidation of bilirubin into water soluble or less lipophilic colorless form of bilirubin which is readily excreted in bile, feces and urine (5).

Ultimate value of phototherapy relies on the kind of light source used (i.e. dosage, spectral release curve, deepness of infiltration), the space amidst the light and the infant, the surface area to be treated, the etiology of the jaundice and also value of total serum bilirubin at onset of phototherapy (6). The aims of phototherapy are to avoid the occurrence of encephalopathy or kernicterus and to reduce the need of exchange transfusion (7).

Apart from mentioned side effects, some study evaluated other adverse effects of phototherapy on serum electrolytes like Hypocalcemia is one of the known bad effect (8). Hypocalcemia is defined as total serum calcium concentration of <7mg/dl (1.75mmol/L) in preterm and serum calcium <8mg/dl (2 mmol/L) in term neonates. It can cause serious complications like neuromuscular irritability, myoclonic jerks, jitteriness, convulsion, cyanosis, apnea and laryngospasm. Cardiac manifestations like tachycardia, heart failure, prolonged QT interval and decreased contractibility are also seen due to hypocalcemia (9).

The overall prevalence of hypocalcemia in neonates receiving phototherapy was suggested to be 8.7% in full-term newborn (3). Another study reflects a little difference between pre and post phototherapy plasma calcium levels ($p<0.05$) The relation of hypocalcemia with phototherapy is an important aspect to be considered due to the potential complications of hypocalcemia. This study aims to assess the burden of hypocalcemia and changes in biochemical parameters in term neonates treated with phototherapy that would be an important clue in modifying strategies and research priorities.

There is paucity of literature which depict the effect of phototherapy on some biochemical parameters of Neonatal hyperbilirubinemia patients which suggest the need for future studies in this direction. Therefore, the present study was intended to determine the effect of phototherapy in full term neonate with unconjugated hyper bilirubinemia on various biochemical parameters including serum calcium, bilirubin profile, serum total protein, albumin, urea, creatinine, serum electrolytes in NH patients before and after >48 hr phototherapy.

MATERIAL AND METHODS:

The study was conducted in the department of pediatrics, S.P.M.C.H.I. (J.K. Lon Hospital) and hospitals attached to SMS Medical College, Jaipur, Rajasthan from June 2019 – July 2020 after the approval of Institutional ethical committee and was carried out after explaining the procedures in detail and getting written informed consent from the subject's Parents. It was a Hospital based prospective comparative observational study. Sample was calculated at 95% confidence level, alpha error of 0.05 assuming standard deviation of 22.7 in sodium mEq/L in neonate with hyper bilirubinemia with pre and post phototherapy as per reference article. To get a minimum difference of at least 5mEq/L in serum sodium level pre & post phototherapy at study power of 80%. The required sample size was at least **154** Full term neonates with unconjugated Hyperbilirubinemia receiving phototherapy ≥ 48 hr. Full term neonates (37 completed weeks to 42 weeks) with unconjugated hyper bilirubinemia requiring phototherapy ≥48 hr. were included. Baby born to a diabetic mother, onset of jaundice within 24 hrs of age, perinatal asphyxia (Apgar <4 at 1 minute of birth), had exchange transfusion, jaundice having hypocalcemia and other biochemical parameter abnormality prior to the start of

phototherapy, Phototherapy duration <48 hrs, Pathological jaundice were excluded.

All clinical investigations were conducted according to the standard protocol. Data was recorded as per Performa. The data analysis was computer based; SPSS-22 was used for analysis. For categorical variables chi-square test was used. For continuous variables independent samples' *t*-test was used. *p*-value <0.05 was considered as significant.

We enrolled 212 babies in our study but after applying inclusion and exclusion criteria 58 Patients (38 patients having electrolyte abnormality before phototherapy, 16 patients required phototherapy <48 hr and 4 patients required exchange transfusion) were excluded from study, thus 154 full term babies were taken.

After taking all aseptic precautions two venous blood samples were taken first before start of phototherapy and second after ≥ 48 hr of continuous phototherapy and these blood samples were immediately sent to laboratory for estimation of serum bilirubin, urea, creatinine, electrolytes (sodium, potassium and Chloride), calcium, total protein and albumin.

We made two groups of patients out of which for one group phototherapy was given for 48 hr and for second group 48-72 hr phototherapy was given under aseptic precautions and comparative effect of phototherapy was assessed on these various biochemical parameters in both groups. In our study we used blue light LED phototherapy.

RESULTS:

Majority of neonates enrolled in this study were in the age group 3-4 days (46.10%) of life with mean age 3.30±1.68 days and less number of neonates were enrolled in >6 days. Majority of patients in the study were male (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%). Majority of patients 89 (57.79%)were LSCS delivered.

There was statistically significant difference in parameters after phototherapy. On the other hand there was no statistically significant difference in corrected calcium (p=0.945) **(Table-1).**

Table 1 : 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
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

Present study found that all parameters (Serum Bilirubin, Urea, Creatinine, Calcium, Total Protein, And Albumin except Serum Electrolyte) has shown similar trends i.e. statistically significant findings in both groups before and after phototherapy. Whereas serum electrolyte has different pattern in both groups, it showed statistically significant results only in group-I **(Table-2).**

Table 2 Comparative study of parameters before and after phototherapy in Both Groups

Parameters	PT till 48 hrs [n=114] (Group-I)		P value	PT till 48-72hrs [n=40] (Group-II)		P value
	Before PT	After PT		Before PT	After PT	
BilirubinTotal (mg/dl)	17.33±1.69	8.70±2.53	<0.0001	22.02±1.40	11.32±2.46	<0.0001
BilirubinDirect (mg/dl)	1.07±0.45	0.69±0.25	<0.0001	1.36±0.41	0.77±0.23	<0.0001
Creatinine (mg/dl)	0.75±0.18	0.61±0.20	<0.0001	0.83±0.17	0.74±0.19	0.013
Urea (mg/dl)	27.01±6.49	21.38±6.99	<0.0001	29.47±7.26	22.47±7.69	0.0001
Sodium (mEq/L)	139.88±3.25	137.32±5.17	<0.0001	139.45±2.85	138.74±5.36	0.433
Potassium (mEq/L)	4.46±0.49	4.14±0.50	<0.0001	4.33±0.53	4.28±0.55	0.507
Chloride (mg/dl)	106.12±4.54	104.51±5.64	0.023	107.42±4.46	106.89±5.48	0.638
Calcium (mg/dl)	9.12±0.67	8.59±0.81	<0.0001	8.94±0.58	8.55±0.84	0.009
Total protein (gm/dl)	5.52±0.60	5.16±0.59	<0.0001	5.81±0.69	5.44±0.66	0.0001
Albumin (gm/dl)	3.74±0.21	3.05±0.42	<0.0001	3.70±0.18	3.27±0.42	<0.0001

DISCUSSION:

Bilirubin encephalopathy is the most serious complication of jaundice and phototherapy is the current modality of choice for treatment of unconjugated hyperbilirubinemia.

Majority of neonates enrolled in this study were in the age group 3-4 days (46.10%) of life with mean age 3.30±1.68 days and less number of neonates were enrolled in >6 days. Majority of patients in the study were male (66.88%) with male female ratio being 2.01:1.74 days

All biochemical parameters viz bilirubin, urea, creatinine, sodium, potassium, chloride, calcium, albumin, total protein got significantly declined after phototherapy. But on other hand there was statistically non-significant decline in corrected calcium post phototherapy.

Mean serum total bilirubin levels before and after PT (PT till 48 hr) 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 hr) 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).

In the newborn infants Jaundice appears as sufficient glucuronyl-transferase enzyme is not produced by their liver, because of this, high levels of unconjugated bilirubin remains in blood. Phototherapy lead to conversion of bilirubin into water soluble isomers lumirubin that is easily eliminated through the gastrointestinal tract or urine (10). **Suneja S et al (2018)** found that the levels of bilirubin profile were elevated significantly in patients prior to phototherapy and returned to normal generally after 48 hours to 96 hours of phototherapy (10). **Shahsavari Gh et al (2017)** reported that in patients who undergone phototherapy for hyperbilirubinemia, bilirubin levels were significantly declined after phototherapy (11).

In present study the mean serum urea serum levels pre and post PT for 48 hr 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 48-72 hr 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 hr and 40 patients receiving PT for 48- 72 hr, 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 hr) 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 hr) 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 hr) 10 patients (8.77%) developed hypo-creatininemia (p=0.001), this difference was statistically significant.

In present study the mean sodium levels were declining from 139.88±3.25 mEq/L to 137.32±5.17 mEq/L after 48 hr of PT, the changes were statistically significant (p<0.001). In contrast after 48-72 hr PT the mean sodium levels were declining from 139.45±2.85 mEq/L to 138.74±5.36 mEq/L, the changes were found to be statistically non significant (p=0.433). Hyponatremia had been postulated to emerged as side effect of phototherapy due to impaired absorption or due to insufficient fluid replacements (12,13). Out of 114 patients (PT till 48 hr) 38 patients (33.33%) developed hyponatremia, this change was statistically significant (p<0.0001). Similarly out of 40 patients (PT till

48-72 hr) 10 patients (25%) developed hyponatremia. This difference was also statistically significant. In our study not any single patient developed symptoms of hyponatremia. **Purohit A et al (2020)** found that the mean sodium decreased from 146.6±6.2 to 141.3±6.1mEq/L (14). **Rangaswamy KB et al (2019)** observed that the incidence of Sodium changes were found to be statistically significant after phototherapy (p<0.01) (15). **Reddy A et al (2015)** found that the incidence of hyponatremia following phototherapy was higher when the duration of phototherapy was >48 hours when compared to <48 hours (16).

In present study the mean potassium level were 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 48-72 hours PT, mean potassium levels were declined from 4.33±0.53 mEq/L to 4.28±0.55 mEq/L, these changes were statistically insignificant (p<0.507). Hypokalemia observed as side effect of phototherapy 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 phototherapy (12,13).

Out of 114 patients (PT till 48 hr), 9 patients (7.89%) developed hypokalemia (p<0.0001) and out of 40 patients (PT till 48-72 hr) 12 patients (30%) developed hypokalemia (p=0.0002). In our study no patient developed symptomatic hypokalemia. **Purohit A et al (2020)** found that the mean potassium declined from 4.7±0.47 mEq/L to 4.2±0.51 mEq/L (14). **Rangaswamy KB et al (2019)** observed that the incidence of potassium changes were found to be statistically significant after phototherapy (p<0.01) but all are asymptomatic (15). Another study done by **Reddy A et al (2015)** found that there was no significant changes in potassium level following phototherapy probably because of difference in study settings (16).

Mean serum chloride levels before and after PT (PT till 48 hr) 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 hr) were 107.42±4.46 and 106.89±5.48 mg/dl respectively, the difference was statistically insignificant (p=0.638). Similar to this finding, **Reddy A (2015)** also reported that there was no significant changes in chloride levels following phototherapy in neonates with hyperbilirubinemia (16). In present study the mean calcium levels were declined from 9.12±0.67 mEq/L to 8.59±0.81 mEq/L after 48 hours of PT (p<0.001), similarly after 48-72 hours PT, mean calcium levels were declined from 8.94±0.58 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 and consequently leading to hypocalcemia.

Out of 114 patients (PT till 48 hr) 27 patients (23.68%) developed hypocalcemia (p<0.0001), similarly out of 40 patients (PT till 48-72 hr) 9 patients (22.50%) developed hypocalcemia (p=0.002), the changes in both groups were statistically significant. **Purohit A et al (2020)** found that the mean calcium decreased from 9.4±0.73 mg/dl mEq/L to 8.4±0.68 mEq/L (p<0.05) (14). **Mashal Khan et al (2015)** found that serum calcium level before and after 24 hours of initiating phototherapy was 8.73±0.68 mg/dl and 7.47±0.82 mg/dl respectively (17).

In the present study patients receiving PT for 48 hr in ≤3 days old neonates mean serum calcium levels before and after PT were 9.09±0.66 and 8.55±0.90 mg/dl respectively (p<0.0001). Similarly in >3 days old neonates 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 48-72 hr in ≤3 days old babies mean calcium levels 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 mean calcium level before and after PT were 9.00±0.59 and 8.63±0.93 mg/dl respectively. Difference was statistically insignificant (p=0.095).

Present study showing that in male patients receiving PT for 48 hr 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 hr the mean calcium levels before and after PT were 9.25±0.70 and 8.97±1.00 mg/dl respectively, the difference was being statistically insignificant (p=0.106).

While in male patients receiving PT for 48-72 hr the mean calcium levels before and after PT were 8.47±0.44 and 7.82±0.32 mg/dl respectively (p=0.004). Similarily female babies receiving PT for 48-72 hr the mean calcium levels before and after were 9.01±0.56 and 8.43 ±0.46 mg/dl respectively (p=0.037). Difference in both was significant statistically. In our study all patients who developed hypocalcemia were asymptomatic.

Goyal S. et al (2018) found the difference between pre and post phototherapy serum calcium levels were found to be statistically significant (18). **Pankaj Kumar Singh et al (2017)** found that after 48 hour phototherapy a significant fall in calcium level in 30% of term & 70% of preterm neonates was observed (19). Whereas **Taheri PA et al (2013)** observed that prevalence of phototherapy associated hypocalcemia was not so high, probably because of smaller duration of Phototherapy in their study (20).

Out of 114 patients (PT till 48 hr) 14 patients (12.28%) developed hypoproteinemia, the change was statistically significant (p<0.0001). while out of 40 patients (PT till 48-72 hr) 5 patients (12.50%) developed hypoproteinemia, the change was statistically non significant (p=0.054). Mean serum protein before and after PT (PT till 48 hr) was 5.52±0.60 and 5.16±0.59 gm/dl respectively (p<0.0001). Similarly mean serum protein before and after PT (PT till 48-72 hr) was 5.81±0.69 and 5.44±0.66 gm/dl respectively (p=0.0001). The difference in both groups was being statistically significant.

Out of 114 patients (PT till 48 hr) 94 patients (82.46%) developed hypoalbuminemia (p<0.0001) and out of 40 patients (PT till 48-72 hr) 27 patients (67.50%) developed hypoalbuminemia (p<0.0001). The decline was statistically significant in both groups. Mean serum albumin before and after PT till 48 hr was 3.74±0.21 and 3.05±0.42 gm/dl respectively (p<0.0001). Similarly mean serum albumin before and after PT till 48-72 hr was 3.70±0.18 and 3.27±0.42 gm/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 phototherapy (10).

CONCLUSION:

Our study concluded that phototherapy is beneficial modality with judicious calculation of the risk-benefit ratio.

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ABBREVIATIONS

LSCS : Caesarian Section
SPMCHI : Sir Padampat Maternal and Child Health Institute

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