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Original Article

Paediatrics Section

Effect of Phototherapy on Various Biochemical Parameters in Neonatal Hyperbilirubinaemia: A Clinical Insight

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ABSTRACT

Introduction: Neonatal Hyperbilirubinaemia (NH) is a very common complication in newborns. It occurs due to excessive formation of unconjugated (indirect bilirubin) and inability of neonatal liver to rapidly clear it from blood. Phototherapy is the first and most common treatment for jaundice in newborns and in most cases is the only treatment required.

Aim: To assess the changes in various other biochemical parameters including proteins, enzymes, lipids, urea, creatinine and uric acid levels in plasma/serum of pre and post phototherapy treated, full term jaundiced neonates.

Materials and Methods: This prospective hospital based comparative study was conducted in the Department of Biochemistry and Paediatrics, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India, from November 2016 to March 2017, after obtaining ethical clearance from institutional ethical committee and informed consent from parents or guardians of neonates. The study included 119 neonates (64 males and 55 females) who were receiving phototherapy and their data was recorded on a predesigned proforma. Biochemical assay was measured using commercially available system pack kits on Fully Automated Clinical Chemistry Analyser, ADVIA -2400 for the biochemical parameters. The significance of the difference between the groups was assessed by student's 't'-test for pair matched samples. The p-value of <0.05 were considered statistically significant.

Results: 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. Levels of hepatic enzyme markers namely AST, ALP and LDH were also elevated significantly in the pre phototherapy group which declined significantly after phototherapy ($p<0.05$).

Levels of total cholesterol, triglycerides and VLDL showed significant decline in our study ($p<0.05$, <0.005 and <0.001 respectively), however no significant changes were observed in LDL and HDL levels in the patients treated for phototherapy. Our study also observed significant decline in uric acid ($p<0.001$), creatinine ($p<0.005$), total serum proteins ($p<0.001$) and albumin levels ($p<0.001$). There was also significant decline in the levels of electrolytes including sodium, potassium, chloride and calcium ($p<0.001$ in each case).

Conclusion: Though, it is well known that phototherapy has a beneficial effect in treatment of NH but its effect on other biochemical parameters is also noteworthy and therefore the neonate should be assessed accordingly while on treatment with phototherapy.

Keywords: Bilirubin profile, Neonatal jaundice, Unconjugataed hyperbilirubinaemia

INTRODUCTION

Neonatal Hyperbilirubinaemia (NH), is the most common disorder, affecting neonates during the 1st week of life in approximately 60% of term infants and 80% of preterm infants [1,2]. However, hyperbilirubinaemia in the newborn period can be associated with haemolytic disease, metabolic and endocrine disorders, anatomic abnormalities of the liver and infections [3]. Severe unconjugated hyperbilirubinaemia can lead to bilirubin encephalopathy with permanent neurodevelopmental handicaps whereas, conjugated hyperbilirubinaemia is a consequence of underlying systemic illness [4].

Considering that the management of NH should be done on priority basis, the most widely used therapy for unconjugated hyperbilirubinaemia is phototherapy. It is considered not only safe and well tolerated by the neonates but its main demonstrated value is that it reduces the need for exchange transfusion or pharmacologic agents [5,6].

It is known that phototherapy converts bilirubin into water soluble isomers that are easily eliminated through the gastrointestinal

tract or lost in urine [7,8]. This is because bilirubin absorbs light most strongly in the blue region of the spectrum near 460 nm wavelength. Gallium nitride Light Emitting Diodes (LEDs), which deliver high intensity light of narrow wavelength spectrum, have been developed and are increasingly being used for neonatal jaundice [9,10].

Though widely used, few side effects of phototherapy have been well documented which include hyperthermia, feed intolerance, loose stools, skin rashes, bronze baby syndrome, retinal changes, dehydration, redistribution of blood flow and genotoxicity [11-13]. In addition, limited evidences are available that depict the effect of phototherapy on some biochemical parameters of NH patients which suggest the need for future studies in this direction. Therefore, the present study was intended to determine the effect of phototherapy on various biochemical parameters including glucose, bilirubin profile, liver marker enzymes, markers of renal function, serum electrolytes, lipid profile, and uric acid in NH patients before and after phototherapy.

MATERIALS AND METHODS

This prospective hospital based comparative study was conducted in the Department of Biochemistry and Paediatrics, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India, from November 2016 to March 2017, after obtaining ethical clearance from institutional ethical committee and informed consent from parents or guardians of neonates.

The study included 119 neonates (64 males and 55 females) who were receiving phototherapy and their data was recorded on a predesigned proforma. The neonates with conjugated hyperbilirubinaemia, babies undergoing exchange transfusion, babies with >14 days jaundice and any associated co-morbidities like birth asphyxia, sepsis, renal failure or mothers taking anticonvulsant drugs were excluded from the study.

Venous blood sample was collected aseptically and allowed to clot. Serum was separated by centrifugation at 3000 rpm for 5 minutes and was subsequently used for estimation of the following parameters: Blood glucose, Bilirubin profile (total bilirubin, direct and indirect bilirubin); Protein profile (total protein, albumin, globulin and A/G ratio); Hepatic marker enzymes [Alanine Aminotransaminase (ALT), Aspartate Aminotransaminase (AST), Lactate Dehydrogenase (LDH) and Alkaline Phosphatase (ALP)]; markers of renal function (urea and creatinine); Lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C and VLDL-C); Serum electrolytes (sodium, potassium, chloride and calcium) and uric acid.Serum cholesterol, serum triglycerides, glucose, urea, creatinine and uric acid were estimated using standard colorimetric enzymatic methods on Advia 2400, Germany. Serum cholesterol estimation was carried out by using cholesterol esterase and cholesterol oxidase enzymes [14]. Serum trigycerides were determined after enzymatic hydrolysis with lipase and production of H_2O_2 by glycerol kinase and glycerol phosphate oxidase [15]. Glucose was measured using glucose oxidase enzyme [16]. H_2O_2 produced in all three methods converts 4-amino antipyrene to red colored quinoneimine dye in presence of peroxidase enzyme. Serum urea was assayed by urease enzyme, creatinine by Jaffe's kinetic method and uric acid by uricase method. HDL-C levels were analysed by direct method according to standard protocol [17]. Direct LDL-C assay was based on the clearance method. Serum electrolytes were also analysed on Advia 2400 by ISE indirect and calcium by Arsenazo method. For total protein, Biuret method was used and BCG estimation was done for albumin. LDH was assayed by measuring concentration of NADH in Lactate/NAD method.

All infants with gestational age of more the 35 weeks were enrolled in this study from the Department of Neonatology of Safdarjung Hospital. Criteria for intervention and starting phototherapy were based on the days of age and level of TSB as defined by the American Academy of Pediatrics (AAP) Clinical Practice Guidelines published in 2004 [18].

An overhead LED phototherapy system (Bird Meditech, Thane, Maharashtra; intensity: >25 μW/cm^2/nm, spectrum 450-470 nm) was used. None of the infants in this study exhibited any other apparent clinical signs and did not receive other medical interventions.

These patients received phototherapy generally ranging from 48 hours to 96 hours. However, majority received it for 72 hours. Samples were analysed at 0 hour (first sample of pre phototherapy) and at the discontinuation of phototherapy (second sample of post phototherapy). The first sample was considered as control. Comparative study was made between these two sample groups to determine the changes in various biochemical parameters.

STATISTICAL ANALYSIS

Data was tabulated in MS Excel and statistical analysed by using GraphPad online calculator. Descriptive statistical analysis was done and continuous variables were described as mean and standard deviation. Student's 't' test has been used for pair matched samples with a confidence limit of 95%. The p-value <0.05 were considered to be statistically significant.

RESULTS

In the present study, 119 neonates, showed significant changes after phototherapy, in various biochemical parameters. Marked alterations were observed in levels of bilirubin profile markers, liver marker enzymes and serum proteins in patients of NH after receiving phototherapy. Serum AST, ALP, LDH activities, total proteins, albumin levels and A/G ratio were significantly low ($p<0.05$ in each case) in NH patients after phototherapy (Group II) as compared to NH patients, before phototherapy (Group I), that served as control [Table/Fig-1]. Serum ALT activity and

Parameters	Group I (n=119)	Group II (n=119)	t-value	p-value
Total Bilirubin (mg/dL)	16.39±5.46	11.23±3.49	1.60	0.0001 **
Direct Bilirubin (mg/dL)	1.71±1.37	1.33±0.46	0.030	0.0087 ††
Indirect Bilirubin (mg/dL)	14.68±4.8	9.90±3.4	1.84	0.0001 **
AST	75.12±38.9	60.94±39.5	0.043	0.0126 †
ALT	23.98±18.57	25.10±17.98	0.378	0.74 NS
ALP	208.60±94.04	163.21±67.43	1.98	0.0002 **
LDH	720.3617± 280.9	642.2553± 242.5	0.098	0.0395 †
Total Protein (gm/dL)	6.36±1.54	5.62±1.13	7.13	0.0002 **
Albumin (gm/dL)	4.03±0.67	3.55±0.45	3.97	0.0001 **
Globulin (gm/dL)	2.34±1.12	2.07±1.03	0.012	0.0868 NS
A:G ratio	1.45±0.38	1.08±0.09	0.200	0.0001 **

[Table/Fig-1]: Effect of phototherapy on bilirubin profile, liver marker enzymes and serum proteins in the study group subjects.
Note: Results are expressed in mean ± SD; **p < 0.001; *p< 0.005; †† p < 0.01:† p< 0.05; NS Non significant

Parameters	Group I (n=119)	Group II (n=119)	t-value	p-value
Sodium (mEq/L)	159.38±22.7	148.80±10.9	1.42	0.001**
Potassium (mEq/L)	6.095±1.4	5.28±1.08	3.64	0.001**
Chloride (mg/dl)	122.46±18.9	108.55±9.8	1.79	0.001**
Calcium (mg/dL)	9.34±1.21	8.38±1.05	1.19	0.001**
Urea (mg/dL)	52.10±26.3	45.14±27.8	0.0017	0.0751NS
Creatinine (mg/dL)	0.71±0.36	0.53±0.46	0.068	0.0029*
Uric Acid (mg/dL)	4.03±0.67	3.55±0.45	3.7	0.001**
Phosphorus (mg/dL)	7.24±2.25	6.67±2.46	0.044	0.0958NS

[Table/Fig-2]: Effect of phototherapy on serum electrolytes, markers of renal function, serum uric acid and phosphorus levels in the study group subjects.
Note: Results are expressed in mean ± SD; **p < 0.001; *p< 0.005; †† p < 0.01:† p< 0.05; NS Non significant

Paramaters	Group I (n=119)	Group II (n=119)	t-value	p-value
Glucose (mg/dL)	57.11±48.30	54.89±43.39	0.34	0.74NS
Total Cholesterol (mg/dL)	138.82±36.98	128.53± 27.41	0.023	0.029†
Triglycerides (mg/dL)	179.09±68.45	150.59± 59.82	2.23	0.0023*
HDL-C (mg/dL)	28.74±9.99	27.58±9.13	0.125	0.4388NS
LDL-C (mg/dL)	69.70±26.84	67.01±21.13	0.154	0.4388NS
VLDL-C (mg/dL)	40.37±13.7	33.94±11.17	2.33	0.0005**

[Table/Fig-3]: Effect of phototherapy on blood glucose levels and lipid profile in the study group subjects.
Note: Results are expressed in mean ± SD; **p< 0.001; *p< 0.005; †† p< 0.01:† p< 0.05; NS Non significant.

globulin levels were altered non significantly (p>0.05 each) in phototherapy received patients. However, no significant changes were observed in blood glucose levels in Group I and Group II (p>0.05). Interestingly, markers of renal function, serum electrolytes and uric acid levels were also affected after phototherapy [Table/Fig-2] in NH patients as compared to Group I patients. Effect of phototherapy on lipid profile and blood glucose levels is depicted in [Table/Fig-3].

DISCUSSION

The guidelines for using phototherapy that were published in 2004 by the Americal Academy of Pediatrics are based primarily on the Total Serum Bilirubin (TSB) levels [18]. Therefore, the commonly used criteria for treatment of NH are based on TSB measurements.

However, in the present study, we evaluated various biochemical parameters in the serum of newborn children having NH, before and after phototherapy to elucidate the dynamics of phototherapy. The results of all 119 patients who received phototherapy were analysed.

Jaundice appears in the newborn infants as their livers do not make sufficient bilirubin glucuronyl transferase enzyme because of which high levels of unconjugated bilirubin appear in blood. Phototherapy converts bilirubin into water soluble isomers lumibilirubin that are easily eliminated through the gastrointestinal tract or lost in urine.

The levels of total bilirubin, direct and indirect bilirubin was elevated significantly in patients before phototherapy and came down to normal levels after phototherapy [Table/Fig-1].

Our study showed that serum levels of lipids such as total cholesterol, triglycerides and VLDL are decreased in post-

phototherapy group compared to pre phototherapy group [Table/ Fig-3]. However, review of the literature revealed only one in vivo study on the levels of serum lipids of jaundiced newborns which showed contrasting results from our study, about levels of serum triglycerides in post phototherapy treated newborns [Table/ Fig-4].

Author	Mean ± SD Serum Lipid Levels			p-value
	Para-meters	Phototherapy (in mg/dL)		
		Before	After	
Present study	Total cholesterol	138.82± 36.98	128.53± 27.41	<0.05
	TG	179.09± 68.45	150.59± 59.82	<0.005
Hadjigeorgiou E et al., [19]	Total cholesterol	185.1±8	167.8±6.3	<0.025
	TG	84.7±9.4	84.6±7.7	NS*

[Table/Fig-4]: Comparison of mean serum lipid levels before and after phototherapy in term neonates with previous studies.
*Non Significant

The decrease in total cholesterol and triglycerides in our study may be the result of photodynamic stress which leads to lipid peroxidation. However no significant change was observed for LDL and HDL levels. The studies of Yoshino S et al., [20] showed that TSB was inversely associated with LDL and VLDL and Bhuiyan AR et al., [21] showed positive correlation with HDL levels. These contrasting results may be due to small number of participants in our study and needs further evaluation. Blood glucose levels in neonates did not show significant change which could be due to feeding and also attributed to infant's ability to maintain glucose homeostasis [22].

Liver is the site of albumin synthesis and also possibly of some of α and β Globulin. Our study observed a significant decline in total proteins, albumin and A/G ratio ($p < 0.001$ each), in post phototherapy group, although their serum values are in normal range. However, no significant change was observed for the levels of globulins [Table/Fig-1]. This could be the result of photo-oxidation of various substances or structures that occurs as a result of phototherapy [23]. In liver diseases, transaminases are increased where rise in AST is much higher than ALT [24]. LDH enzyme is widely distributed, found in all cells in man, but is especially plentiful in cardiac and skeletal muscles, liver, kidney and the red blood cells. In liver disease, an increased activity is found particularly in infectious hepatitis, but the increase is not as great as that of the transaminases and its behavior is less predictable and less specific [24]. Similarly, ALP enzyme is found in a number of organs, most plentiful in bones and liver, then in small intestine, kidney and placenta. Increase in serum ALP levels are found in both infectious hepatitis (viral hepatitis) and post hepatic jaundice (extrahepatic obstruction) but the rise is usually much greater in cases of obstructive jaundice [24]. However like LDH, the rise is less specific. Thus, the levels of enzymes AST, ALP and LDH were elevated in pre-phototherapy group, which can be attributed to the immaturity of the liver functions and decreased significantly, approximately reaching the baseline levels in the post-phototherapy group [Table/ Fig-1]. Serum creatinine (SeCr) concentration is usually the sole available marker of Glomerular Filtration Rate (GFR) in clinical practice, especially in Neonatal Intensive Care Units (NICUs). There occured significant decrease in SeCr levels following phototherapy whereas decrease in urea levels were insignificant [Table/Fig-2]. Our results are consistent with the study done in recent past, depicting positive association between serum total bilirubin and serum creatinine [25]. We also observed significant decrease in serum uric acid levels in neonates following phototherapy ($p < 0.005$). This decrease can either be the effect of direct photo decomposition or due to the inhibitory effect of riboflavin deficiency on uric acid formation [26].

In the present study, there was 10.27% decline in serum calcium levels after phototherapy with p-value of < 0.001. However, this decline was not accompanied by signs and symptoms associated with hypocalcaemia like jitteriness, convulsions, or apnoea in this study group. Our results are in accordance with few studies in the recent past that stressed on the incidence of hypocalcaemia following phototherapy [Table/ Fig-5].

Author	Mean ± SD serum calcium level		p-value
	Before Phototherapy (in mg/dL)	After Phototherapy (in mg/dL)	
Present study	9.34±1.21	8.38±1.05	<0.001
Eghbalian F et al.,[27]	9.85±1.23	9.09±0.93	<0.001
Taheri PA et al.,[28]	9.8±0.80	9.5±0.90	<0.05
Karamifar H et al.,[29]	9.53±0.92	9.3±1.11	0.043

[Table/Fig-5]: Comparison of mean serum calcium levels before and after phototherapy in term neonates with previous studies.

We also observed significant differences in sodium, potassium and chloride levels (p-value of < 0.001 in each case).

There are very few studies highlighting the changes in other electrolytes which are induced by phototherapy. Incidence of hyponatraemia in our study group was 2.2%.

Mean serum sodium levels were significantly decreased after phototherapy. Our study is in line with the study conducted by Reddy AT et al., [30] [Table/Fig-6].

Thus, it infers that babies are at risk of electrolyte imbalance following phototherapy and should be closely monitored. However, further studies are needed to document these changes with respect to duration of phototherapy and gestational age of infants.

Author	Mean±SD serum sodium level		p-value
	Before Phototherapy (in mEq/L)	After Phototherapy (in mEq/L)	
Present study	159.38±22.7	148.80±10.9	<0.001
Reddy AT et al.,[30]	139.02±3.12	138.16±3.36	<0.001

[Table/Fig-6]: Comparison of mean serum sodium levels before and after phototherapy in term neonates with previous studies.

LIMITATION

The population size was small and only included patients from southern region of the National Capital Territory of Delhi, as well as the adjoining areas of the neighbouring State. Thus, our population was not representative of the entire Indian population.

CONCLUSION

The present study reveals that the total bilirubin, direct bilirubin and indirect bilirubin along with total proteins, albumin and A/G ratio declined in the neonates after treatment with phototherapy. Levels of enzymes like AST, ALP and LDH were also seen to decrease after phototherapy, probably approaching the normal values as liver starts resuming the normal functions. Total cholesterol, triglycerides and VLDL levels decreased significantly, however no change was observed in the levels of other lipoproteins like HDL and LDL. Dyselectrolytaemia, noted as decrease in levels of calcium, sodium, potassium and chloride in our study suggests that newborns should be closely monitored in order to prevent the related complications. We also documented significant decrease in the levels of uric acid and creatinine in blood of neonates with hyperbilirubinaemia. Thus we infer that NH is a highly treatable condition where timely intervention can eliminate much of its ill-effects. However imbalance in electrolytes is of concern and needs continuous monitoring. Also, the significant effect of phototherapy on other biochemical markers may also serve to include these complementary biomarkers for monitoring of NH in future studies. However, the findings of our study should be potentiated with other similar longitudinal studies with larger population.

Till date, various studies have been done, taking into account only few parameters. But our study has considered various biochemical parameters at a time to see the overall effect of phototherapy, if any. Moreover, we have not come across any literature highlighting the levels of uric acid and creatinine in pre and post phototherapy groups.

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