

A study on effect of phototherapy on platelet count in neonates with unconjugated hyperbilirubinemia: a hospital based prospective observational study



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ABSTRACT

Background: Thrombocytopenia as a side effect of phototherapy has not been mentioned in standard literature and textbooks. Though there are few studies in this regard, but results are conflicting. **Aims and Objective:** Hence, the present study is undertaken to find out whether any significant change in platelet count occurs following phototherapy, and if there be any, to see whether the changes are transient or not. **Materials and Methods:** This prospective and observational study was carried out over a period of one and half years (1st March 2019 to 31st August 2020) on 190 new-borns admitted with idiopathic unconjugated hyperbilirubinemia needing phototherapy through consecutive enrolment. Serum bilirubin (total, conjugated and unconjugated) and platelet count were done before initiation and just after completion of phototherapy, and seven days after completion of phototherapy. Appropriate statistical tests were used to make statistical comparisons with a p-value of < 0.05 taken as significant. **Results:** Among 190 neonates, 108(56.8%) were male and 82(43.2%) were female; 90(47.4%) were preterm and 100(52.6%) were term. Mean birth weight was (2.4725 ± 0.4782) kg. Mean gestational age was (36.4316 ± 2.4802) weeks. Mean haemoglobin level was (17.3816 ± 1.0784) gm/dl. Mean age at presentation was (4.5737 ± 1.5811) days. Mean total serum bilirubin (TSB) before initiation, after completion, and 7 days after completion of phototherapy were (17.8595 ± 3.7034) mg/dl, (8.1726 ± 2.2586) mg/dl and (5.7279 ± 1.5918) mg/dl respectively. The mean duration of phototherapy required was (48.1895 ± 13.6054) hours. Mean platelet count before initiation and just after completion of phototherapy were (2,49,321.0526 ± 89,460.2101)/μL and (2,22,436.8421 ± 88,538.7173)/μL respectively. Mean platelet count 7days after completion of phototherapy was (2,46,210.5263 ± 87,442.3038)/μL. Decrease in platelet count just after completion of phototherapy was statistically significant. Fifty-nine (31.1%) out of 190 neonates developed mild thrombocytopenia (100000- < 150000/μL) just after completion of phototherapy, but none developed moderate or severe thrombocytopenia. None having thrombocytopenia manifested with clinical bleed. Platelet count raised near to pre-phototherapy level 7 days after completion of phototherapy. Fall in platelet count was found to have a positive association with increased duration of phototherapy and lower gestational age (p<0.0001). However, there was no statistically significant association (p>0.05) between reduction in platelet count with gender. **Conclusions:** Though the incidence of thrombocytopenia following phototherapy was significant, but it was mostly mild and transient, and clinically insignificant. There was significant association between decrease of platelet count with duration of phototherapy and lower gestational age.

Key words: Thrombocytopenia; phototherapy; neonatal jaundice

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INTRODUCTION

Pathological or significant neonatal jaundice due to unconjugated hyperbilirubinemia is one of the most common causes of admission to sick neonatal care unit (SNCU). Phototherapy (PT) is the most common and important modality of treatment in these patients irrespective of the etiology of jaundice. Skin rash, loose stools, hyperthermia, dehydration and electrolyte imbalance are some well-known side effects of this therapy.¹⁻³ Thrombocytopenia has not yet been mentioned as an adverse consequence of PT in any of the standard textbooks of pediatric medicine or neonatology. Though few studies have been published on this topic, results are conflicting. So, this study was done to observe the effect of phototherapy on platelet count in neonates with unconjugated hyperbilirubinemia.

MATERIALS AND METHODS

The prospective observational study was carried out in the sick newborn care unit (SNCU) in the Division of Neonatology under the Department of Pediatric Medicine, Burdwan Medical College and Hospital, West Bengal, India. Total study period was one and half year (1st March 2019 to 31st August 2020).

Inclusion criterion

Apparently healthy neonates having phototherapeutic level unconjugated hyperbilirubinemia decided as per American Academy of Pediatrics (AAP) guideline (for neonates with gestational age of 35 weeks or more)⁴ and Facility Based Newborn Care (FBNC), Ministry of Health and Family Welfare, Government of India guideline (for neonates aged less than 35 weeks),⁵ and a base line platelet count of more than 1,50,000/dl were included in the study.

Exclusion criteria

Neonates with conjugated hyperbilirubinemia, ABO and Rh incompatibility, septicemia, birth asphyxia, renal failure, hemangioma, antiplatelet drugs given to mother or baby, congenital anomalies were excluded.

Sample Size was 190, calculated with the formula, $n = z^2 pq / d^2$ (z =standard normal variate taken as 1.96 considering 5% type 1 error and $p < 0.05$, p =prevalence/expected proportion of neonates likely to develop thrombocytopenia after receiving PT which was taken as 50% or 0.5 as results from previously available studies were conflicting, $q = 1 - p$, d =absolute error/precision/clinically allowable error which was taken as 7.5% or 0.075). Sampling technique employed was consecutive enrollment till sample size was reached. An informed written consent

was obtained from every parent of the newborns before enrolling them in the study. Study was approved by Hospital Ethical Committee and Scientific Committee (vide memo no BMC/379/2019).

After initial history taking, clinical examination and laboratory investigations, all babies were put to continuous phototherapy with interruption only during breast feeding. The neonates were followed up daily for monitoring the side effects. Total serum bilirubin (TSB) and platelet count were measured before initiation of phototherapy, just after completion of phototherapy and seven days after completion of phototherapy. Platelet count before initiation of PT was taken as control value for respective neonate. Platelet count $< 150,000/\text{mm}^3$ was taken as the definition of thrombocytopenia. Mild, moderate and severe thrombocytopenia were graded when platelet counts were between $(100,000 \text{ to } 150,000)/\text{mm}^3$, $(50,000 - 100,000)/\text{mm}^3$ and less than $50,000/\text{mm}^3$ respectively. Platelet count above $4,50,000/\text{mm}^3$ was considered as thrombocytosis.

Other parameters studied were sex, birth weight, gestational age (term and preterm), postnatal age (in days), blood group (of both mother and baby), hemoglobin level, mode of delivery and duration of phototherapy. Serum bilirubin was measured by diazo method using semi-automated clinical chemistry analyzer Chem 7, ERBA, Transasia, India. Platelet count was measured by automated hematology analyzer and was confirmed by microscopy. All data were recorded in a pre-designed case sheet.

Statistical methods

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests was applied for analyzing the difference in mean involving independent samples or unpaired samples. Paired t-tests, one-way ANOVA and chi-squared tests (χ^2 test) were also used for data analysis. P-value < 0.05 was considered for statistically significant.

RESULTS

A total of 190 neonates were included in the present study. Among them 108(56.8%) neonates were male and 82(43.2%) were female; 90(47.4%) neonates were preterm and 100(52.6%) were term. One hundred and thirty-nine (73.2%) neonates were delivered by vaginal delivery (VD) and 51(26.8%) neonates were delivered by lower uterine caesarean section (LUCS) (Table. 1).

Mean birth weight of the neonates was $2.4725 \pm .4782$ kg. Mean gestational age was 36.4316 ± 2.4802 weeks. The average age of presentation for phototherapy was 4.5737 ± 1.5811 postnatal days (Table. 2). Mean haemoglobin level of the neonates was 17.3816 ± 1.0784 gm/dl. Mean TSB before initiation of phototherapy, just after completion and 7 days after completion of phototherapy were 17.8595 ± 3.7034 mg/dl, 8.1726 ± 2.2586 mg/dl and 5.7279 ± 1.5918 mg/dl respectively. The mean duration of phototherapy required was 48.1895 ± 13.6054 hours (Table.2).

In our study, mean platelet count before initiation of phototherapy and just after completion of it were $2,49,321.0526 \pm 89,460.2101/\mu\text{L}$ and $2,22,436.8421 \pm 88,538.7173/\mu\text{L}$ respectively. Mean platelet count recorded 7 days after completion of PT was $2,46,210.5263 \pm 87,442.3038/\mu\text{L}$ (Table. 3A).

Table 1: Demographic profile of the study population (n=190)

Demographic parameters	Frequency	Percentage
Gender	Male	108
	Female	82
Mode of delivery	VD	139
	LSCS	51
Maturity	Preterm	90
	Term	100

In 187 neonates (98.4%), mean platelet count before initiation of phototherapy were in between $1,50,000/\mu\text{L}$ and $4,50,000/\mu\text{L}$, and in 3 neonates (1.6%) value was $>450,000/\mu\text{L}$ (Table. 3B). In 59(31.1%) neonates, platelet count just after completion of phototherapy were in the range of $1,00,000/\mu\text{L}$ to less than $1,50,000/\mu\text{L}$ and in 131(68.9%) neonates' values were in between $1,50,000/\mu\text{L}$ and $4,50,000/\mu\text{L}$. Seven days after days of completion of phototherapy, platelet count was in the range of $1,50,000/\mu\text{L}$ to $4,50,000/\mu\text{L}$ in 188(98.9%) neonates; and 2 neonates (1.1%) had a count of more than $4,50,000/\mu\text{L}$ (Table.3B).

Table. 4A shows actual mean platelet counts in the study population (n=190) before initiation of PT, after completion of different durations of PT required, and the corresponding values 7 days after completion of phototherapy. Figure 1 is the graphical representation of the same data series. Decrease in mean platelet count was found after completion of different durations of phototherapy required, and the results were statistically significant ($p < 0.0001$). Mean platelet count 7 days after completion of phototherapy almost returned back to pre-phototherapy levels (Table.4A and Figure.1).

Table. 4B shows the actual fall in platelet counts in the study population (n=190) in relation to duration of phototherapy

Table 2: Mean, standard deviation, range and median of various parameters (n=190)

Attribute	Mean	SD	Minimum	Maximum	Median
Birth weight (kg)	2.4725	0.4782	1.2500	3.4500	2.5800
Gestational age(week)	36.4316	2.4802	30.0000	40.0000	37.0000
Haemoglobin (gm/dl)	17.3816	1.0784	15.3000	19.3000	17.4000
Age of presentation(days)	4.5737	1.5811	2.0000	8.0000	5.0000
TSB before phototherapy(mg/dl)	17.8595	3.7034	8.5000	23.5000	18.7000
TSB after completion of phototherapy	8.1726	2.2586	3.5000	12.9000	8.6000
TSB 7days after phototherapy	5.7279	1.5918	3.0000	9.2000	5.4500
Duration of phototherapy(hours)	48.1895	13.6054	24.0000	84.0000	48.0000

Table 3A: Mean platelet counts and their relation to phototherapy (n=190)

Platelet count	Mean	SD	Minimum	Maximum	Median
Before initiation of PT	2,49,321.0526	89,460.2101	1,52,000.0000	4,70,000.0000	2,25,500.0000
After completion of PT	2,2,436.8421	88,538.7173	1,20,000.0000	4,33,000.0000	2,05,000.0000
7days after completion of PT	2,46,210.5263	87,442.3038	1,50,000.0000	4,60,000.0000	2,22,000.0000

Table 3B: Range of platelet counts and their relation to phototherapy (n=190)

Time of analysis	Platelet count (range)	Frequency	Percent
Before initiation of PT	150000- 450000	187	98.4
	>450000	3	1.6
	Total	190	100
Just after completion of PT	100000- <150000	59	31.1
	150000- 450000	131	68.9
	Total	190	100
7 days after completion of PT	150000- 450000	188	98.9
	>450000	2	1.1
	Total	190	100.0

received. Fall in platelet count was positively associated with increasing duration of phototherapy ($p < 0.0001$).

In the present study, fall in mean platelet count just after completion of phototherapy was more prominent among preterm neonates ($p < 0.0001$) (Table.5).

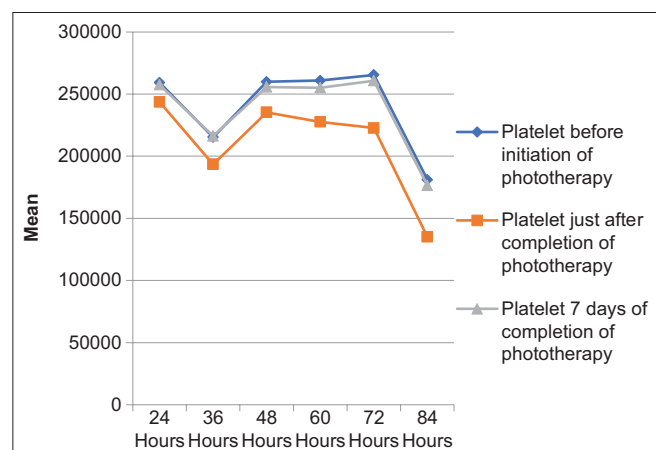


Figure. 1: Relationship between mean platelet count and duration of phototherapy given

Gender and blood group of the neonates, maternal age, parity and mode of delivery did not have any association with fall in platelet count following phototherapy.

DISCUSSION

It was found that platelet count had decreased significantly just after phototherapy but it was transient because platelet count again raised near to pre phototherapy level seven days after completion of phototherapy. In 187 neonates (98.4%), mean platelet count before initiation of phototherapy were in between 1,50,000/ μ L and 4,50,000/ μ L, and in 3 neonates (1.6%) value was >450000/ μ L (Table. 3B). In 59(31.1%) neonates, platelet count just after completion of phototherapy were in the range of 1,00,000/ μ L to less than 1,50,000/ μ L and in 131(68.9%) neonates' values were in between 1,50,000/ μ L and 4,50,000/ μ L. Seven days after days of completion of phototherapy, platelet count was in the range of 1,50,000/ μ L to 4,50,000/ μ L in 188(98.9%) neonates; and 2 neonates (1.1%) had a count of more than 4,50,000/ μ L (Table.3B). Among 190 neonates under our study, 59(31.1%) neonates developed

Duration of phototherapy required	Platelet count before initiation of PT		Platelet count just after completion of PT		Platelet count 7 days after completion of PT		p-value
	Mean	SD	Mean	SD	Mean	SD	
24 Hours	2,59,222.2222	83,383.2792	2,43,666.6667	83,637.8749	2,57,500.0000	84,048.4804	0.0320
36 Hours	2,15,272.7273	57,137.2740	1,93,409.0909	57,988.0975	2,16,318.1818	54,346.7646	0.0450
48 Hours	2,59,800.0000	96,020.8636	2,35,246.1538	95,480.5332	2,55,723.0769	94,712.3124	0.0120
60 Hours	2,60,822.2222	88,233.7518	2,27,644.4444	88,196.6180	2,55,111.1111	86,529.0866	<0.0001
72 Hours	2,65,437.5000	1,27,024.9155	2,22,625.0000	1,21,104.8444	2,60,750.0000	12,3913.6796	<0.0001
84 Hours	1,81,000.0000	0.0000	1,35,000.0000	0.0000	1,76,500.0000	2,121.3203	<0.0001
p-value	0.0754		0.0981		0.1344		

Duration of phototherapy required	Number of neonates	Mean	SD	Minimum	Maximum	Median	p-value
24 Hours	18	15555.5556	3311.6945	7000.0000	21000.0000	16000.0000	<0.0001
36 Hours	44	21863.6364	4348.7015	10000.0000	32000.0000	22000.0000	
48 Hours	65	24553.8462	12187.3792	2000.0000	110000.0000	24000.0000	
60 Hours	45	33177.7778	4711.1516	21000.0000	42000.0000	34000.0000	
72 Hours	16	42812.5000	24752.6935	32000.0000	135000.0000	37500.0000	
84 Hours	2	46000.0000	.0000	46000.0000	46000.0000	46000.0000	

Platelet count	Maturity	Mean	SD	Minimum	Maximum	Median	p-value
Before phototherapy	Preterm	215344.4444	74994.2561	152000.0000	460000.0000	181500.0000	<0.0001
	Term	279900.0000	90712.0541	160000.0000	470000.0000	275000.0000	
After completion of phototherapy	Preterm	189633.3333	73805.1565	120000.0000	433000.0000	156500.0000	
	Term	251960.0000	90608.5955	121000.0000	429000.0000	243500.0000	
7days after completion of phototherapy	Preterm	213866.6667	73326.7583	150000.0000	457000.0000	180000.0000	
	Term	275320.0000	89199.5697	156000.0000	460000.0000	269000.0000	

mild thrombocytopenia (100000- <150000/ μ L) just after phototherapy but no bleeding manifestation was there. Khera S et al⁶ reported in their study that 35 (35%) neonates among a total study population of 100 had thrombocytopenia and majority of them (74%) had mild thrombocytopenia, and thrombocytopenia was transient. Bhargava O et al⁷ observed that majority of the neonates had mild (58.2%) and moderate (20.8%) thrombocytopenia during the first 48 hours of phototherapy, usually was not associated with clinical bleed, and thrombocytopenia was transient in nature. Majid Vafaie et al⁸ found in their study that the mean platelet counts before initiation of phototherapy, 24 hours thereafter, at the end of phototherapy, and 48 hours after completion of phototherapy were 2,98,170/ μ L, 2,88,540/ μ L, 2,82,620/ μ L and 2,66,310/ μ L respectively which were statistically significant during time. Results of these studies⁶⁻⁸ showed that phototherapy led to a significant reduction in platelet count in new-borns receiving phototherapy but changes were mostly transient and usually did not lead to clinical bleed.

Sajid A et al⁹ studied with 150 new-borns with a mean age of (3.95 \pm 1.71) days having unconjugated hyperbilirubinemia. After 24 hours of phototherapy, about 8.1% of the patients were having severe thrombocytopenia (platelet count < 50,000/ μ L); this percentage rose to 18.4% after 48 hours and 33.3% after 72 hours of phototherapy. None of the patients developed clinical manifestation of bleeding. The number of patients with normal platelet count (1,50,000/ μ L to 4,00,000/ μ L) after 24 hours of continuous phototherapy was 50%, gradually reducing to 38% after 48 hours and only 33% after 72 hours of completion of phototherapy (p value < 0.05). Khera S et al⁶ and Majid Vafaie et al⁸ also noticed that the degree and incidence of thrombocytopenia increased with increasing duration of phototherapy received. In the present study also differences in mean platelet counts before and just after phototherapy with different durations of phototherapy were statistically significant (p<0.0001). Differences were more marked when duration of PT was longer (Table 4A & Table 4B). Several other researchers¹⁰⁻¹³ also had similar experience like us.

In the present study, mean birth weight of the study population was (2.4725 \pm .4782) kg and mean gestational age was (36.4316 \pm 2.4802) weeks. Ninety (47.4%) neonates were preterm and 100 (52.6%) were full-term. Mean platelet counts before initiation of PT was lower among preterm babies in our study. Corresponding values were also found to be on a lower side just after completion of PT, and 7 days after completion of PT (p<0.0001). This finding tallied with the results obtained in studies conducted by Khera S et al⁶ Sajid A et al,⁹ Kannar V et al¹⁰ and Sonawane P et al.¹¹

Though most of the published studies found thrombocytopenia in association with phototherapy, there are few articles which depicted completely different and interesting findings. Ahmadpour KM et al¹⁴ showed that phototherapy resulted in rise of platelet count but had no significant effect on the WBC and reticulocyte counts. Monsef A et al¹⁵ and Sakha K et al¹⁶ also showed increase in platelet count in their study. Modanlou HD et al¹⁷ observed that none of the infants who received phototherapy developed thrombocytopenia. Abdul Tawab CN et al¹⁸ found statistically significant change in the platelet count amongst term new-borns but not in preterm ones after PT.

The drop in platelet counts following PT may be due to the photochemical reaction in the vascular bed and direct platelet injury by the ultraviolet light of phototherapy leading to reduction in platelet life span and an increase in platelet turnover.⁸⁻¹⁶ Thrombocytopenia is expected to be more marked when bone marrow compensation is inadequate, as in the case of preterm neonates.

Limitations of the study

The notable short comings of this study were: this study was done in a single tertiary care centre thereby limiting the scope for generalisation of the results, and it was conducted predominantly on Bengali population and thus, studies need to be done in other ethnic groups as well for validation of results.

CONCLUSIONS

Phototherapy can be a cause of decrease in platelet count in neonates receiving PT for unconjugated hyperbilirubinemia. In our study, thrombocytopenia was more prominent with increasing duration of PT and in preterm new-borns. Though the fall in platelet counts were statistically significant, it did not affect the new-borns clinically. Moreover, changes were mostly transient, as in most of the cases platelet values returned back to the pre-treatment level 7 days after completion of PT. We would therefore like to emphasise that clinicians need to be aware of this association so that unnecessary elaborate work ups can be avoided and consequent psychological stress on family members and treating physicians can be minimised.

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Author's contribution:

SKS- Concept and manuscript writing; **BB**-Critical revision; **SL, MM**- Manuscript editing; **NS, JA, V, KA, VK, AA, DG, TM**- Review of literature; **PB, SM**-Compilation of records.

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