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 7 days 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.\(^1\)\(^2\) 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)\(^3\) and Facility Based Newborn Care (FBNC), Ministry of Health and Family Welfare, Government of India guideline (for neonates aged less than 35 weeks);\(^4\) 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, \(n = \frac{z^2pq}{d^2}\) (\(z=\)standard normal variate taken as 1.96 considering 5% type I 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/mm\(^3\) was taken as the definition of thrombocytopenia. Mild, moderate and severe thrombocytopenia were graded when platelet counts were between (100,000 to 150,000)/mm\(^3\), (50,000–100,000)/mm\(^3\) and less than 50,000/mm\(^3\) respectively. Platelet count above 4,50,000/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 predesigned 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 (\(\chi^2\) 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 $2.4725 \pm 0.4782$ kg. Mean gestational age was $36.4316 \pm 2.4802$ weeks. The average age for presentation of phototherapy was $4.5737 \pm 1.5811$ postnatal days (Table 2). Mean haemoglobin level of the neonates was $17.3816 \pm 1.0784$ gm/dl. Mean TSB before initiation of phototherapy, just after completion and 7 days after completion of phototherapy were $17.8595 \pm 3.7034$ mg/dl and $8.1726 \pm 2.2586$ mg/dl and $5.7279 \pm 1.5918$ mg/dl respectively. The mean duration of phototherapy required was $48.1895 \pm 13.6054$ hours (Table 2).

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

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

| Time of analysis | Platelet count | SD | Minimum | Maximum | Median |
|-----------------|---------------|----|---------|---------|--------|
| Before initiation of PT | 2,49,321.0526 | 0.4782 | 1,52,000.0000 | 4,70,000.0000 | 2,25,500.0000 |
| After completion of PT | 2,22,436.8421 | 0.4782 | 1,52,000.0000 | 4,70,000.0000 | 2,25,500.0000 |
| 7 days after completion of PT | 2,46,210.5263 | 0.4782 | 1,52,000.0000 | 4,70,000.0000 | 2,25,500.0000 |

In 187 neonates (97.4%), mean platelet count before initiation of phototherapy were in between $1,50,000/\mu L$ and $4,50,000/\mu L$, and in 3 neonates (1.6%) value was $>450000/\mu L$ (Table 3B).

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 | 100.0 |
| Just after completion of PT | 1000000- <1500000 | 59 | 31.1 |
| | 1500000- 4500000 | 131 | 68.9 |
| | Total | 190 | 100.0 |
| 7 days after completion of PT | 1500000- 4500000 | 188 | 98.9 |
| | >450000 | 2 | 1.1 |
| | Total | 190 | 100.0 |

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. 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.
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).

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/µL and 4,50,000/µL, and in 3 neonates (1.6%) value was >450000/µL (Table 3B). In 59(31.1%) neonates, platelet count just after completion of phototherapy were in the range of 1,00,000/µL to less than 1,50,000/µL and in 131(68.9%) neonates’ values were in between 1,50,000/µL and 4,50,000/µL. Seven days after days of completion of phototherapy, platelet count was in the range of 1,50,000/µL to 4,50,000/µL in 188(98.9%) neonates; and 2 neonates (1.1%) had a count of more than 4,50,000/µL (Table 3B). Among 190 neonates under our study, 59(31.1%) neonates developed

| 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 | 375000.0000 |
| 84 Hours                         | 2                  | 46000.0000 | .0000 | 46000.0000 | 46000.0000 | 46000.0000 |

Table 5: Relationship of thrombocytopenia following phototherapy with gestational age

| 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/µL) just after phototherapy but no bleeding manifestation was there. Khera S et al 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 al 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 Vafaei et al 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/µL, 2,88,540/µL, 2,82,620/µL and 2,66,310/µL respectively which were statistically significant during time. Results of these studies 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 al studied with 150 new-borns with a mean age of (3.95 ± 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/µL); 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/µL to 4,00,000/µL) 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 al and Majid Vafaei et al 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 phototherapy was longer (Table 4A & Table 4B). Several other researchers also had similar experience like us.

In the present study, mean birth weight of the study population was (2.4725± 0.4782) kg and mean gestational age was (36.4316± 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 al, Sajid A et al, Kannar V et al and Sonawane P et al. Though most of the published studies found thrombocytopenia in association with phototherapy, there are few articles which depicted completely different and interesting findings. Ahmadiour KM et al showed that phototherapy resulted in rise of platelet count but had no significant effect on the WBC and reticulocyte counts. Monsef A et al and Sakha K et al also showed increase in platelet count in their study. Modanlou HD et al observed that none of the infants who received phototherapy developed thrombocytopenia. Abdul Tawab CN et al 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. 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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