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Original Research Article

Incidence of thrombocytopenia in neonates receiving phototherapy for indirect hyperbilirubinemia: a prospective cohort study

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ABSTRACT

Background: Thrombocytopenia as a side effect of phototherapy has not been mentioned in the standard literature but was described briefly as isolated case reports after the phototherapy came in vogue in 1958. The purpose of this study was to find the incidence of thrombocytopenia in neonates with uncomplicated indirect hyperbilirubinemia receiving phototherapy in a referral hospital.
Methods: This was a prospective cohort study conducted in a referral hospital over a period of 18 months from June 1, 2013 to November 1, 2014.
Results: A total of 103 babies were enrolled. The overall incidence of post-phototherapy thrombocytopenia was 45.6% while mild, moderate and severe thrombocytopenia was present in 66%, 21.3% and 12.8% of babies respectively. The lowest platelet count observed was 31,000/mm3 but none of the neonates showed bleeding manifestations. The incidence of thrombocytopenia following phototherapy was significantly higher in preterm babies, infants who received double surface phototherapy, babies who received phototherapy for >72 hours and in babies who received phototherapy on day 2 or 3 of life.
Conclusions: Neonates requiring phototherapy for hyperbilirubinemia are at risk of developing thrombocytopenia, hence the treatment should be initiated based on the standard guidelines. Unnecessary use and prolongation of phototherapy should be avoided considering the possible side effects. Platelet count should be monitored particularly in pre-term neonates receiving phototherapy. Neonates receiving double surface phototherapy and those requiring phototherapy for longer duration require more frequent platelet count monitoring.

Keywords: Hyperbilirubinemia, Incidence, Neonates, Phototherapy, Thrombocytopenia

INTRODUCTION

Phototherapy is the most common modality of treatment for jaundice in neonates. Phototherapy though safe, is not free of side effects. Thrombocytopenia as a side effect of phototherapy has not been mentioned in the standard literature but was described briefly as isolated case reports after the phototherapy came in vogue in 1958. In 1966 Zieve et al, demonstrated effects of high intensity white light on human platelet in vitro. Platelets which had been briefly exposed to light following photosensitization by hematoporphyrin lost the ability to aggregate and release potassium, acid phosphatase, serotonin and adenosine

triphosphate. Electron photomicrographs of these altered platelets showed depletion of cytoplasmic materials and smooth membrane contours as compared to controls.[1] Maurer et al, observed Similar kind of platelet abnormalities within 96 hours of exposure in vivo. Phototherapy causes an increase in platelet production possibly secondary to reduction in platelet life span and when bone marrow compensation is inadequate the platelet count may fall.[2] Shortened platelet life span may be the result of sequestration of damaged platelets in the spleen; however, definite proof is lacking. The purpose of this study was to find the incidence of thrombocytopenia in neonates with uncomplicated indirect hyperbilirubinemia receiving phototherapy in a referral hospital.

METHODS

This was a prospective cohort study conducted in a referral hospital in Jharkhand, an eastern state of India, over a period of 18 months from June 1, 2013 to November 1, 2014. All the neonates admitted to Special Newborn Care Unit (SNCU) for phototherapy during this period were screened for enrollment. Consecutively admitted apparently healthy neonates requiring phototherapy for indirect hyperbilirubinemia irrespective of gender, age at onset of jaundice and birth weight, were included while babies with features of severe hemolysis, direct hyperbilirubinemia, sepsis, birth asphyxia, platelet count <1, 50,000 /mm^3 at admission, baby or mother on any drugs causing thrombocytopenia, babies requiring exchange transfusion, babies with hemangiomas or any congenital anomalies, were excluded from this study. Neonates who developed signs suggestive of sepsis during phototherapy were also excluded. The study was approved by institutional ethical committee and informed consent was obtained from the parents. The decision of initiation of phototherapy was based on the guidelines from American Academy of Pediatrics 2004.[3] All neonates received phototherapy using 6 compact fluorescent lamps (Phoenix CFL 101) which provide an intensity of up to 40 µw when positioned 35 cms from the baby's body. Irradiance was checked by a photo radiometer and was maintained at 30 µw/nm/cm^2 at all times. Phototherapy was interrupted only for feeding and nursing for 20 minutes every 2 hours. Platelet count was performed at admission and then at every 24 hours interval as long as phototherapy was given and just after stopping phototherapy by automated coulter LH 750 analyzer based on flowcytometry and electrical impedance principle and reconfirmed by microscopy.

Thrombocytopenia was defined as platelet count <150,000/mm^3. Mild, moderate and severe thrombocytopenia were defined as platelet counts between 100,000-150,000/mm^3; 50,000-100,000/mm^3 and <50,000/mm^3, respectively.[4] Neonates were then divided in two groups viz those with thrombocytopenia and those without thrombocytopenia. Variables like duration as well as the type of phototherapy and demographic factors such as sex, birth weight, gestational age, neonatal age and severity of thrombocytopenia were studied and compared in the two groups.

Statistical analysis

Data is shown in mean with standard deviation (SD). Chi-square test was used for categorical variables. Student t test was used to compare more than two groups for significance in difference. Statistical analysis was done by using SPSS version 17 (statistical package for social sciences). p value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, 148 babies were enrolled out of which 45 were excluded because of the exclusion criteria. Of the 103 neonates, 54.4% (n=56) were male neonates, 58.3% (n=60) were born at term gestation while 41.7% (n=43) were preterm babies. Mean gestational age and birth weight was 37.9 weeks (SD±3.1) and 2.6 kgs (SD±0.5) respectively. Single Surface Phototherapy (SSPT) was administered to 72.8% (n=75) while 27.2% (n=28) of the babies received Double Surface Phototherapy (DSPT). Of the 28 neonates who received DSPT, 17 were preterm babies. Most of the babies (85.4%; n=88) received phototherapy within 5 days of birth while mean duration of phototherapy was 49.6 hours (SD±30.8). Out of 103 enrolled babies, 45.6% (n=47) developed thrombocytopenia out of which 66% (n=31), 21.3% (n=10) and 12.8% (n=6) had mild, moderate and severe thrombocytopenia respectively. The minimum platelet count in the cohort following phototherapy was 31,000/mm^3 but none of the neonates developed bleeding manifestations.

Incidence of thrombocytopenia based on gender

Among male neonates (n=56), 46.4% (n=26) developed thrombocytopenia with mild, moderate and severe thrombocytopenia observed in 61.5% (n=16), 23.1% (n=6) and 15.4% (n=4) respectively. In female babies (n=47), 44.7% (n=21) developed thrombocytopenia out of them mild, moderate and severe thrombocytopenia was observed in 71.4% (n=15), 19.1% (n=4) and 9.5% (n=2) respectively. There was no statistically significant difference in the incidence of thrombocytopenia based on gender (male 46.4% vs female 44.7%, p> 0.05) (Table 1).

Incidence of thrombocytopenia based on gestational age

Out of 43 preterm neonates, 58.1% (n=25) had thrombocytopenia of which 52% (n=13), 28% (n=7) and 20% (n=5) had mild, moderate and severe thrombocytopenia respectively. Among term neonates (n=60), 36.7% (n=22) developed thrombocytopenia out of them 81.8% (n=18), 13.6% (n=3) and 4.5% (n=1) had mild, moderate and severe thrombocytopenia respectively. Incidence of thrombocytopenia was more in

preterm than term babies (58.1% vs 36.7%), which was statistically significant (p< 0.05) (Table 1).

Incidence of thrombocytopenia based on birth weight:

Depending upon the birth weight, 43.7% (n=45) of babies belonged to low birth weight (LBW) group with none of the babies below 2000 grams. Among these LBW neonates, 53.3% (n=24) developed thrombocytopenia out of which mild, moderate and severe thrombocytopenia was observed in 79.2% (n=19), 12.5% (n=3) and 8.3% (n=2) respectively. In babies with birth weight >2500 grams (n=58), 46.6% (n=27) had thrombocytopenia out of which 44.4% (n=12), 26% (n=7) and 14.8% (n=4) developed mild, moderate and severe thrombocytopenia respectively. Incidence of thrombocytopenia was more in LBW group (53.3% vs 46.6%) however, it was not statistically significant (p>0.05) (Table 1).

Incidence of thrombocytopenia based on type of phototherapy given

SSPT and DSPT was given to 72.8% (n=75) and 27.2% (n=28) of the babies. Among SSPT group, 30.7% (n=23) had thrombocytopenia out of which 91.3% (n=21) had mild thrombocytopenia and 8.7% (n=2) had moderate thrombocytopenia while none had severe thrombocytopenia.

Among DSPT group, 85.7% (n=24) developed thrombocytopenia and out of them 35.7% (n=10), 28.6% (n=8) and 21.4% (n=6) had mild, moderate and severe thrombocytopenia respectively. Incidence of thrombocytopenia was higher in DSPT group (85.7% vs 30.7%) which was statistically significant (p<0.05) (Table 1).

Table 1: Incidence of post- phototherapy thrombocytopenia in the study cohort.

Variable	Babies with Thrombocytopenia n (%)	Babies without Thrombocytopenia n (%)	p Value
Gender			
Male	26 (46.4)	30 (53.6)	>0.05
Female	21 (44.7%)	26 (55.3%)	
Gestational age			
≥ 37 weeks	22 (36.7)	38 (63.3)	<0.05
< 37 weeks	25 (58.1)	18 (41.9)	
Birth weight			
≥ 2500 grams	27 (46.6)	31 (53.4)	>0.05
<2500 grams	24 (53.3)	21 (46.7)	
Type of phototherapy			
SSPT	23 (30.7)	52 (69.3)	<0.05
DSPT	24 (85.7)	4 (14.3)	
Duration of phototherapy			
24 hrs	2 (11.1)	16 (88.9)	<0.05
24-48 hrs	10 (22.2)	35 (77.8)	
48-72 hrs	16 (76.2)	5 (23.8)	
>72 hrs	19 (100)	0 (0)	
Hours of life phototherapy started			
24-48	33 (54.1)	28 (45.9)	<0.05
49-72	12 (44.4)	15 (55.6)	
>72	2 (13.2)	13 (86.8)	

Incidence of thrombocytopenia in relation to duration of phototherapy

Out of 103 neonates, 17.5% (n=18) received phototherapy for 24 hours, 43.7% (n=45) received phototherapy for 24-48 hours, 20.4% (n=21) received phototherapy for 48-72 hours, 10.7% (n=11) for 72-96 hours and 7.8% (n=8) for >96 hours. Out of the 18 neonates who received phototherapy for 24 hours, mild thrombocytopenia was observed in 11.1% (n=2) while none of the babies developed moderate or severe thrombocytopenia. Of the 45 neonates who received phototherapy for a duration of 24-48 hours, 22.2% (n=10) developed thrombocytopenia out of which 80% (n=8) had mild thrombocytopenia and 20% (n=2) had moderate thrombocytopenia while none of the neonates had severe thrombocytopenia. Of the 21 neonates who received phototherapy for 48-72 hours, 76.2% (n=16) had thrombocytopenia out of which mild thrombocytopenia

was present in 93.8% (n=15) and severe thrombocytopenia in 6.2% (n=1). All the neonates (n=19) who received phototherapy for >72 hours had thrombocytopenia out of which mild, moderate and severe thrombocytopenia was seen in 31.6% (n=6), 42.1% (n=8) and 26.3% (n=5) respectively. The incidence of thrombocytopenia was higher as the duration of phototherapy increased beyond 72 hours which was statistically significant ($p<0.05$) (Table 1).

Incidence of thrombocytopenia based on the day of life at which phototherapy was started

In 59.2% (n=61) neonates, phototherapy was initiated between 24-48 hours after birth out of which 54.1% (n=33) developed thrombocytopenia. Among them 57.6% (n=19) had mild thrombocytopenia, 30.3% (n=10) had moderate thrombocytopenia and 12.1% (n=4) had severe thrombocytopenia. In 26.2% (n=27) of neonates phototherapy was started between 49-72 hours after birth, 44.4% (n=12) neonates had thrombocytopenia. Out of these 12 neonates, 91.7% (n=11) had mild thrombocytopenia and 8.3% (n=1) had severe thrombocytopenia. Of the 15 neonates admitted beyond 72 hours after birth for phototherapy, 2 neonates (13.3%) had thrombocytopenia, out of which, 50% (n=1) had mild thrombocytopenia and 50% (n=1) had severe thrombocytopenia. The incidence of thrombocytopenia was higher if the phototherapy was initiated within 72 hours of birth than beyond that, which was statistically significant ($p<0.05$) (Table 1).

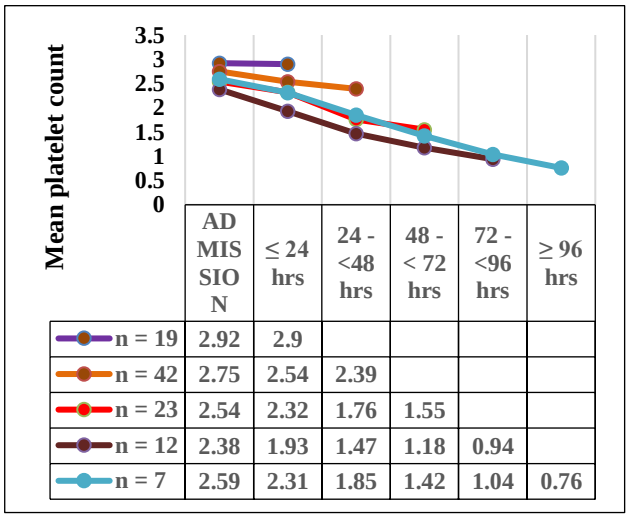
DISCUSSION

This study was an attempt to find the incidence of thrombocytopenia in babies receiving phototherapy in a referral hospital in eastern part of India. The overall incidence of thrombocytopenia in babies who received phototherapy was 45.6%, out of which 66%, 21.3% and 12.8% of infants had mild, moderate or severe thrombocytopenia respectively. In the study conducted majority of neonates had mild thrombocytopenia (74%), moderate and severe thrombocytopenia was seen in 23% and 3% cases respectively.[5] In another study conducted 86.4% of neonates had mild thrombocytopenia while moderate and severe thrombocytopenia was seen in 14.6% of babies.[6] Our study didn't observe any significant difference in incidence of thrombocytopenia as far as gender was concerned which is comparable to the study.[5]

This study observed that preterm babies who received phototherapy had significantly higher incidence of thrombocytopenia than term babies which was in comparison with the study.[7] However the results were in contrast, where they have shown that term babies had higher incidence of thrombocytopenia, but the results were not statistically significant.[5] The incidence of post-phototherapy thrombocytopenia was higher in LBW babies in this study, though it was not significant statistically. This finding was in contrast to a study by Observed thrombocytopenia more in babies weighing >2500 grams.[5] The effects of phototherapy on platelet counts in low birth weight neonates and concluded that in 38.7% of babies' platelet count fall below 1, 50,000/ mm^3 and the lowest count was 52,000/mm^3.[2]

Babies who received DSPT have significantly higher incidence of thrombocytopenia as compared to those who received SSPT. The incidence of mild, moderate and severe thrombocytopenia was also observed in DSPT group. Further, among the neonates who received DSPT, incidence of thrombocytopenia was more in preterm babies (≤37 weeks). Conducted similar studies and found a higher incidence of thrombocytopenia in babies who had received DSPT, but the results were not significant.[5,8]

Our study observed that the incidence of thrombocytopenia was directly proportional to the duration of phototherapy received. All the babies who received phototherapy for more than 72 hours developed thrombocytopenia while one-fourth of them had severe thrombocytopenia. The fall in mean platelet count in relation to duration of phototherapy showed a steady decline in the mean platelet count with increasing duration of phototherapy. The fall in mean platelet count was more at phototherapy duration of 24-48 hours (Figure 1).



	ADMISSION	≤ 24 hrs	24 - <48 hrs	48 - < 72 hrs	72 - <96 hrs	≥ 96 hrs
n = 19	2.92	2.9				
n = 42	2.75	2.54	2.39			
n = 23	2.54	2.32	1.76	1.55		
n = 12	2.38	1.93	1.47	1.18	0.94	
n = 7	2.59	2.31	1.85	1.42	1.04	0.76

Figure 1: Fall in mean platelet count based on duration of phototherapy.

The mean platelet counts have increased in neonates who received phototherapy for 48-72 hours which is contrary to our study.[9] Thrombocytopenia was seen in maximum number of cases during the first 24 hours of phototherapy, and similar findings were noted in a study.[5,2] That rate of fall of platelet count was more in the first 24 hours of phototherapy which is in contrast to our finding.[8] The incidence of thrombocytopenia was observed to be inversely proportional to the age of the neonate at which phototherapy was started. The incidence

was significantly more in neonates who received phototherapy on day 2 or 3 of life. This finding was in contrast to the studies; however, their results were not statistically significant.[5,6,7,8]

CONCLUSION

Neonates requiring phototherapy for hyperbilirubinemia are at risk of developing thrombocytopenia, hence the treatment should be initiated based on the standard guidelines. Unnecessary use and prolongation of phototherapy should be avoided considering the possible side effects. Platelet count should be monitored particularly in pre-term neonates receiving phototherapy. Neonates receiving double surface phototherapy and those requiring phototherapy for longer duration require more frequent platelet count monitoring.

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