International Journal of Medical and Health Sciences

Journal Home Page: http://www.ijmhs.net ISSN:2277-4505

Original article

Phototherapy Induced Thrombocytopenia –A Comparative Study among Breastfed Term And Preterm Neonates With Hyperbilirubinemia

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ABSTRACT

Introduction: There are reports which attribute phototherapy with acquired thrombocytopenia during early neonatal period. Present study is been planned to assess the difference in the phototherapy induced thrombocytopenia between breastfed preterm neonates and full term neonates with unconjugated hyperbilirubinaemia. **Material and Methods**: It is a tertiary care teaching hospital based prospective study over a period of 2 years. 25 breastfed full term neonates and 25 breastfed preterm neonates with unconjugated hyperbilirubinemia requiring phototherapy for at least 48 hours were selected for the study. Pathologic hyperbilirubinemia requiring phototherapy was defined as per 2004 American Academy of Pediatrics hyperbilirubinemia treatment guidelines. Platelet count and total serum bilirubin levels, before and after 48 hours of phototherapy were estimated**.** **Results:** After the phototherapy, term neonate showed statistically significant change in the platelet count (2.7 ± 0 .83lakhs/per ml,) when compared to pretreatment levels platelet count 2.0± 0.69(lakhs/per ml) (T=3.4 to 11.4, p=0.0001).After the phototherapy, it was observed that preterm neonates did not show a statistical difference in the platelet count between pretreatment and post treatment levels (T=1.55, p=0.125) . There was no association between the gestational age (term/preterm) and the incidence of thrombocytopenia (Chi square =0.035,p=0.85) as assessed by chi square test with Yates correction. **Conclusion**: Gestational age of neonate is not the factor associated with incidence of thrombocytopenia in children receiving phototherapy. Studies with larger sample size will give more definitive results on this issue.

KEYWORDS: Phototherapy, Thrombocytopenia ,Term, Preterm, Hyperbilirubinemia

INTRODUCTION

Neonatal jaundice is a problem, observed in approximately 60% full-term and 80% pre-term neonates[1, 2] in their first week of neonatal life. The treatment options available for neonatal jaundice include phototherapy, exchange transfusion, and drugs like phenobarbitone, intravenous immunoglobulin, metalloporphyrin. Phototherapy is the first line of treatment of unconjugated hyperbilirubinemia to reduce the serum level of unconjugated bilirubin levels[3,4]. Animal and human studies suggest that hyperbillirubinemia and phototherapy may lead to thrombocytopenia. Maurer et al found that rabbits exposed to phototherapy had decreased platelet counts and increased platelet turnover[5,6].

Maurer et al [5,6] and Pishwa et al [7] observed that neonates exposed to phototherapy suffers from thrombocytopenia but phototherapy is still an issue which is inadequately addressed. There are reports which attribute phototherapy with the acquired thrombocytopenia during early neonatal period. Majority of studies implicate cytomegalovirus acquired through breast feeding as the dominant case of the acquired thrombocytopenia but a few studies have also reported autoimmune thrombocytopenia [7-9] in breast fed neonates. There are very few studies examining the effect of phototherapy on the platelet count of breast fed babies[7-12].Present study is been planned to assess the difference in the of phototherapy induced thrombocytopenia between breastfed preterm neonates and full term neonates with unconjugated hyperbilirubinemia.

MATERIALS AND METHODS

The study was performed in accordance with Declaration of Helsinki[13].This was a tertiary care teaching hospital based, prospective study done in the Department of Pediatrics at Yenepoya Medical College hospital over a period of 2 years- from October 2012 to October 2014. Conjugated hyperbilirubinemia (CH) was defined as direct bilirubin value greater than 1.0 mg/dl if total bilirubin is less than 5 mg/dl or direct bilirubin more than 20% of the total bilirubin if the total bilirubin is greater than 5 mg/dl [14].

Preterm birth defined as delivery before 37 completed weeks and after the completed 34 weeks of gestation [15,16].Term birth defined as delivery after 37 (>37 weeks) completed weeks of gestation[15,16].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; < 50,000/mm^3, respectively. Neonates showing a fall of platelet count were recorded.

50 Cases were included in the study.25 breastfed full term neonates and 25 breast fed preterm neonates with unconjugated hyperbilirubinemia requiring phototherapy for at least 48 hours were selected for the study. Early demise (first days of admission), Apgar of less than 7 at 5 minutes, IUGR, birth asphyxia, respiratory distress, hemolytic anemia, sepsis, congenital malformations, infants of diabetic mothers, maternal hypertension and infants undergoing exchange transfusion were excluded. Parents declining to participate in the study or failure to give a written consent were also excluded from the study.

Predesigned proforma was used to document studied variables in the both groups. Besides routine investigation, platelet count and total serum bilirubin levels, before and after 48 hours of phototherapy were estimated. The laboratory studies such as total and direct bilirubin levels, liver transaminases, prothrombin and partial thromboplastin time, gamma-glutamyltranspeptidase levels, complete blood count, thyroid function tests, and urine analyses were evaluated in selected patients. TORCH (toxoplasmosis, rubella, cytomegalovirus (CMV), herpes virus, syphilis) were done in selected cases.

Pathologic hyperbilirubinemia requiring phototherapy was defined per 2004 American Academy of Pediatrics hyperbilirubinemia treatment guidelines [16].Phototherapy was performed according to AAP guidelines[16,17]. All neonates received intensive phototherapy using 8 special blue tube lamps (Philips TL 20 W/52) positioned within 15 to 20 cm of the patient's body. Irradiance was checked by a photo radiometer to maintained approximately 20 µw/nm/cm^2 at all times. Phototherapy was interrupted only for feeding and nursing for 20 minutes every 2 hours.

Statistical analysis: The data obtained were analyzed using SPSS software version 17.0 for Windows (SPSS, Chicago, IL). Numerical variables were compared between the two groups by using the independent student's test. Welch alternate test was used to assess difference in the platelet count between term and preterm babies. P values of less than 0.05 were considered as statistically significant.

RESULTS

A total of 50 neonates breastfed full term neonates and breastfed preterm neonates were enrolled in the study. There was no difference in the sex (pre-term, M: F=17:8 Vs full-term M:F =10:15), of the studied groups. Among the neonatal factors, gestational age, APGAR score and Ballard score were statistically different (p=0.00 to 0.007). Blood groups and pre treatment serum bilirubin, serum calcium and platelet counts were not statistically different in two groups different (p=1.00 to 0.14) as shown in table 1.

Table : 1 Neonatal parameters of study subjects

Variable		Term	Preterm	t value	P value*
Gestational Age (weeks)		39.1±1.0	36.3±1.4	8.543	0.000
Sex (M:F)		17:8	10:15	N.A	0.47
Birth Weight (gm)		3113.6±408.5	2365.6±390.3	6.620	0.000
Apgar Score (At 1 Min)		7.9±0.3	7.6±0.6	2.385	0.021
Apgar Score (At 5 Min)		9.0±0.0	8.9±0.3	1.809	0.077
New Ballard Score (Week)		38.9±0.9	35.4±0.7	15.701	0.000
Blood Group	O^+	7	12	19	0.462
	A^+	8	5	13	
	B^+	9	6	15	
	B^-	0	1	1	
	AB^+	1	1	2	
Serum Billirubin(mg/dL)		16.2±2.0	15.3±2.4	1.502	0.140
Platelet(lakhs/per ml)		2.7 ± 0 .83	2.2 ± 0.69	1.108	.283

*Unpaired t test

There was no statistical difference in the studied maternal parameters like maternal age, parity, mode of delivery and maternal blood group different (p=1.00 to 0.84) as shown in table 2. Similarly there was no statistical difference in the studied phototherapy parameters in two groups like hour of initiation of phototherapy, duration of phototherapy and the complication observed with phototherapy different (p=0.89 to 0.21) as shown in table 3.

Table 2: Maternal parameters of studied patients

Variable		term	Preterm	t value	P value*
Maternal Age (years)		25.5±4.1	25.5±3.8	0.000	1.000
Parity	Primi Para	8	6	N.A	0.529
	Multi Para	17	19		
Mode of Delivery	FTND	9	12	N.A	0.390
	LSCS	16	13		
Mothers Blood Group	O^+	7	14	N.A	0.084
	O^-	3	0		
	A^+	7	4		
	A^-	0	1		
	B^+	5	5		
	AB^+	3	0		
	AB^-	0	1		

FTND=*Full Term Normal Delivery, LSCS=Lower segment Cesarian section,*. *Unpaired t test ^chi square test with Yates correction

Table 3: Phototherapy parameters of studied patients

Variable		Term	Preterm	t value*	P value*
Hours of Life at Initiation of Phototherapy(hr)		78.0±17.9	77.6±17.6	0.072	0.360
Total Hours of Phototherapy(hr)		50.1±3.2	50.2±2.9	-0.139	0.890
Complications of Phototherapy	Dehydration	1	4	N.A	0.217
	None	22	17		
	Rashes	2	1		
	Rash With Dehydration	0	2		
	Loose Stool	0	1		

*Unpaired t test

Table 4: Changes in platelet count before and after phototherapy.

Variable	Term	t & p value	Preterm	t & p value
Serum Billirubin Before Phototherapy(mg/dL)	16.2±2.0	T=11.4, P=0.0001*	15.3±2.4	T=10.077, p=0.0001*
Serum Billirubin After Phototherapy(mg/dL)	10.5±1.5		9.7±1.4	
Platelet Count Before Phototherapy(lakhs/per ml)	2.7 ± 0 .83	T=3.24, p=0.002*	2.2 ± 0.69	T=1.55, p=0.125*
Platelet Count After Phototherapy(lakhs/per ml)	2.0± 0.69		1.9 ± 0.67	
Incidence of thrombocytopenia before Phototherapy	0		0	
Incidence of thrombocytopenia after Phototherapy	23.1%		33.3%	

***Welch alternate t test**

After the phototherapy, it was observed that term neonate showed statistically significant change in the serum bilirubin (10.5±1.5mmol/l) and platelet count (2.7 ±0 .83lakhs/per ml,) an compared to pretreatment levels (full-term serum bilirubin16.2±2.0mmol/l, platelet count 2.0± 0.69lakhs/per ml) (T=3.4 to 11.4, p=0.0001)

After the phototherapy, it was observed that pre term neonate showed statistically significant change in the serum bilirubin (pre-term, 9.7±1mmol/l.) as compared to pretreatment levels (serum bilirubin pre-term, 15.3±2.4mmol/l) (T=10.07, p=0.0001) but preterm neonate did not show a statistical difference in the platelet count between pretreatment and post treatment levels (T=1.55, p=0.125) .There was no association between the gestational age (term/preterm) and the incidence of thrombocytopenia (Chi square =0.035,p=0.85) as assessed by chi square test with Yates correction as shown in table 4.

DISCUSSION

Thrombocytopenia is one of the most common haematological problems encountered in the neonatal period presenting in 1-5% of newborns at birth. Neonatal thrombocytopenia is defined as a platelet count of less than 150,000/mm^3. The hallmark of platelet disorders is petechiae, purpura, however newborns may present more severely with, mucocutaneous bleeding and intra- cranial hemorrhages. There are many neonatal and maternal factors that are associated with thrombocytopenia of the newborn. The majority of newborns with thrombocytopenia are born prematurely after pregnancies complicated by placental insufficiency and/or fetal hypoxia (ie maternal pre-eclampsia and intra-uterine growth retardation of the fetus). These pre-term infants with early-onset thrombocytopenia have impaired megakaryocytopoeisis and platelet production.

An increase in platelet consumption and/or sequestration to the spleen and other organs is the mechanism in 25-35% of cases of neonatal thrombocytopenia. Transplacental passage of maternal platelets alloantibodies and auto antibodies account for 15-20% of thrombocytopenia present at birth. Placental transfer of maternal immunoglobulin G (IgG) directed against fetal platelet antigens is known to be the underlying mechanism. Since breast milk contains IgG it is theoretically possible that breast feeding of these infants could cause thrombocytopenia. But there are report shows that an infant with neonatal alloimmune thrombocytopenia may be safely breast fed, even when the breast milk contains the platelet specific antibody (HPA-1a)[18].

Preterm infants are at risk of acquiring human cytomegalovirus (CMV) infection through breast milk transmission, possibly leading to serious symptoms, as suggested by previous studies. Over a period of 8.5 years, Neuberger P et al [19] compared infants infected postnatally with CMV with non infected controls to determine whether CMV infection transmitted through breast milk poses serious acute risks.CMV-infected infantswhichmet the study criteria had lower minimal platelet and neutrophil counts and a higher frequency of C-reactive protein (CRP) elevations to 10 to 20 mg/L than their matched controls (P < or = .001). Neonatal symptoms related to postnatal CMV infection were transient and had no affect on neonatal outcome in these infants, in contrast with uncontrolled reports.

Thrombocytopenia as a definite side effect of phototherapy has not been accepted in consensus and few isolated case reports have brought the issue in attention. Studies have demonstrated that platelets which had been briefly exposed to light showed depletion of cytoplasmic materials and smooth membrane contours as compared to controls. Maurer et al [5] observed similar kind of platelet abnormalities within 96 hours of exposure in vivo. It causes decrease in blood riboflavin level and alters the excretory pattern of tryptophan metabolites, both of which are photosensitive. The phototherapy causes an increase in platelet production rate possibly secondary to reduction in platelet life span and when bone marrow compensation is inadequate the platelet count may fall [5]. .Shortened platelet life span may be the result of sequestration of damaged platelets in the spleen; however, definite proof is lacking. Ultraviolet light may increase platelet turnover and injury during phototherapy by an unknown mechanism. Phototherapy light is transmitted through living tissue to a degree which may lead to photochemical reactions to occur in the vascular bed [20].

50 Cases (n=25) breastfed full term neonates and (n=25) preterm neonates with unconjugated hyperbilirubinaemia given phototherapy were selected for the study. Both the study groups were comparable in maternal and phototherapy parameters but cases did differ in certain neonatal parameters birth weight, APGAR score and Ballard score beside of-course gestational age. In our study, the incidence of thrombocytopenia after 48 hours in pre term and term was 33.3% and 23% respectively, which is comparable to previously reported incidence of 38.7% and 49% by Pishwa et al [7] and KheraS et al[8] respectively.

The platelet counts before phototherapy was 16.2±2.0 and 15.3 ± 2.4 in term and preterm neonates. Term had higher platelet counts as compared to pre-term as expected. However, similar facts were not observed by Maurer et al [5]and KheraS et al [8]. After phototherapy the term neonate showed a statistically significant fall in the platelet count. Similar observations were seen by Pishwa et al [7]and Khera S et al [8]in their study. Rashes and dehydration were the complications observed in the study. None of the neonates with thrombocytopenia, in our as well as in the Pishwa et al [7]and KheraS et al [8]studies had clinical manifestations of bleeding. The reason for the same could be the fact that thrombocytopenia was transient and rarely found to be severe in all the three studies.

The incidence of thrombocytopenia after phototherapy in the term group was found to be 23% as against no case before phototherapy. Similarly the incidence of thrombocytopenia after phototherapy in the pre term group was found to be 33.3% as against no case before phototherapy. Though the pre term group was having the higher incidence of thrombocytopenia after phototherapy as compared to term

neonate, the there was no statistical association between gestational age group and the incidence of thrombocytopenia as assessed by chi square test with Yates correction. Similar analysis was not done in previous studies and this could be attributed to smaller sample size of patients in the present study. The mean platelet count showed a significant fall in the term group but not in pre term group. This may be explained by the fact the preterm had lower pre treatment platelet count and transient nature of thrombocytopenia due to phototherapy. Strength of the study was the presence of a comparable cohort of term and preterm neonate for assessment of the effect of phototherapy on platelet count. A small sample size of the studied patients was the major limitation.

CONCLUSION

Gestational age of the neonate is not the factor associated with incidence of thrombocytopenia in children receiving phototherapy. Studies with larger sample size will give more definitive results on this issue.

REFERENCES

1. Plazza A, Stoll B. The fetus and the neonatal infant. Digestive system disorders. In: Nelson Textbook of Pediatrics 18th ed. Kliegman R, Behrman R, Jenson H, Stanton B, eds. Philadelphia: Saunders Elsevier, 2007;756–761.
2. Martin CR, Cloherty JP. Neonatal hyperbilirubinemia. In: Manual of Neonatal Care 6th ed. Cloherty JP, Eichenwald EC, Stark AR, eds. Philadelphia: Lippincott Williams & Wilkins, 2008;181–212.
3. Lucey J, Ferriero M, Hewitt J. Prevention of hyperbilirubinemia of prematurity by phototherapy. Pediatrics 1968; 41;1047–1054.
4. Maisels MJ. Jaundice. In: Neonatology: Pathophysiology and Management of the Newborn 4th ed. Avery GB, Fletcher MA, MacDonald MG, eds. Philadelphia: Lippincott-Raven Pubs, 1994;630–708.
5. Maurer HM, Fratkin M, McWilliams NB, et al. Effects of phototherapy on platelet counts in low-birth weight infants and on platelet production and life span in rabbits. Pediatrics 1976; 57; 506–512.
6. Maurer HM, Haggins JC, Still WJ. Platelet injury during phototherapy. Am J Hematol1976;1; 89–96.
7. Pishva N, Pishva H. Incidence of thrombocytopenia in hyperbilirubinemic neonates during phototherapy. ActaMedicaIranica2000; 38:7–9.
8. Khera S, Gupta R. Incidence of thrombocytopenia following phototherapy in hyperbilirubinemic neonates Medical Journal Armed Forces India -2011; 67(4); 329-332.
9. Kroll H, Bein G. Neonatal autoimmune thrombocytopenia. CurrOpinPediatr. 2006;18(1); 48-52.
10. Buxmann H, Miljak A, Fischer D, Rabenau HF, Doerr HW, Schloesser RL. Incidence and clinical outcome of cytomegalovirus transmission via breast milk in preterm infants before 31 weeks. J Matern Fetal Neonatal Med. 2012;25; 3:57-62.
11. HaÿsS.Cytomegalovirus, breast feeding and prematurity. Acta Paediatr. 2009;98(2); 270-6.
12. Neuberger P, Hamprecht K, Vochem M, Maschmann J, Speer CP et al. Case-control study of symptoms and neonatal outcome of human milk-transmitted cytomegalovirus infection in premature infants. Arch Pediatr. 2007; 14;1:S2-4.
13. World Medical Association Declaration of Helsinki. Ethical principles for medical Research involving human subjects. http://www.wma.net/e/policy/b3.htm,
14. Moyer V, Freese DK, Whitington PF, et al. Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J PediatrGastroenterolNutr 2004; 39; 115-28.
15. Lucey J, Ferriero M, Hewitt J. Prevention of hyperbilirubinemia of prematurity by phototherapy. Pediatrics 1968; 41; 1047–1054.
16. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004; 114(1); 297–316.
17. Kaplan M, Hammerman C. American Academy of Pediatrics guidelines for detecting neonatal hyperbilirubinaemia and preventing kernicterus. Archives of Disease in Childhood. 2005; 90(6); F448–F449
18. Reese J, Raghuveer TS, Dennington PM, Barfield CP. Breast feeding in neonatal alloimmune thrombocytopenia. J Paediatr Child Health. 1994; 30(5); 447-9.
19. Case-control study of symptoms and neonatal outcome of human milk-transmitted cytomegalo virus infection in premature infants. Neuberger P, Hamprecht K, Vochem M, Maschmann J, Speer CP, Jahn G, Poets CF, Goelz R. J Pediatr. 2006;148(3); 326-31.
20. Sisson TRC, Wickler M. Transmission of light through living tissue. Pediatr Res 1973; 7:316.

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