ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 02 | February - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

REBOUND BILIRUBIN LEVELS AFTER PHOTOTHERAPY IN NEONATES WITH HYPERBILIRUBINEMIA: INCIDENCE & RISK FACTORS

Paediatric Medicine

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ABSTRACT

Background: To asses the serum bilirubin rebound following discontinuation of phototherapy in near term and term neonates as are only limited studies available in our country and this type of study was not done in our center previously.
Methods: A prospective observational study was conducted on 150 neonates with indirect hyperbilirubinemia who were treated according to standard guidelines. Phototherapy was stopped when one value of serum bilirubin level reached below cut-off line.Serum bilirubin levels were measured at 12 hrs and 24 hrs after discontinuation of phototherapy to see rebound hyperbilirubinemia.
Results: Out of 150 neonates, total 17 neonates(11.33%) developed rebound; among them 10 were male (11.5%) and 7 were female (11.1%). Significant risk factors for rebound: haemolytic disease especially sepsis & G6PD deficiency ,high discharge bilirubin level and short duration of conventional phototherapy. No significant association was found between rebound Hyperbilirubinemia and birth weight of neonates.
Conclusions: SBR should be considered in neonates with hemolysis, suspected sepsis, short duration of conventional phototherapy, and relatively high discharge TSB. These risk factors should be taken into account when planning post-phototherapy follow-up.

KEYWORDS

Conventional phototherapy • Hemolysis • Intensive phototherapy • Neonatal hyperbilirubinemia • Rebound hyperbilirubinemia

INTRODUCTION

Neonatal hyperbilirubinemia is common in first week of life. Nearly 60% of term and 80% of preterm[1] neonates develop jaundice in first week of life. High serum bilirubin level may be toxic to the developing brain and cause neurological impairment.[(1)]

Therefore American Academy of pediatrics recommends that newborn who discharged within 48 hours should have a follow-up visit after 48 to 72 hours for any significant neonatal jaundice.[(2)] These babies may develop jaundice which may be over looked or delay in recognition unless the baby is closely monitored. So it is necessary to measure serum total bilirubin (STB) in all jaundiced infants and ensure follow-up evaluation within 2 days of all infants discharged prior to 48 hours.

In most cases neonatal jaundice is benign and no intervention is required. But around 5-10% of them have clinically significant jaundice which need treatment[(2)]. There are only few options for treatment of neonatal jaundice which are as under : (1) Phototherapy; (2) Exchange transfusion; (3) Drugs like phenobarbitone; (4) IVIG (intravenous immunoglobulin). Treatment of neonatal jaundice by exchange transfusion is costly, relatively invasive, time consuming and associated with complications. Early treatment with phototherapy is simple, effective, cheap and have relatively lessor side effects.

Phototherapy is stopped when the serum bilirubin level is below the phototherapy cut off value as per American academy of paediatric guideline.[(3)]Discontinuation of phototherapy too early may lead to rise of serum bilirubin to an unacceptable level, which may require further reinstitution of phototherapy[2]defined as Significant Bilirubin rebound (SBR)[4].

The need for measurement of Serum bilirubin after stopping phototherapy to see rebound has remained a topic of interest by researchers recently. There are only limited studies available in our country and this type of study was not done in our center previously. So this study was designed to determine the pattern and magnitude of post phototherapy rebound serum bilirubin in neonates requiring phototherapy for hyperbilirubinemia.

AIM & OBJECTIVE

AIM : To asses the serum bilirubin rebound following discontinuation of phototherapy in near term and term neonates.
Primary Objective : To asses the pattern of rebound serum bilirubin at 12 hrs and 24 hrs post phototherapy.
Secondary objective : To asses the risk factors for rebound serum bilirubin.

MATERIAL & METHODS

Study setting :
This study was carried out in the Department of Paediatrics, S.M.S Medical College Jaipur and attached group of hospitals.

Study design : Prospective observational study.

Study period : September 2018 to December 2019

Sample Size
Sample size was calculated at 95% confidence level, alpha error of 0.05 assuming 11.3% rebound in total Serum Bilirubin measured after 24hrs of discontinuation of phototherapy in neonates ≥ 35 weeks of gestational age admitted for hyperbilirubinemia in neonatal ward as per the referance article.[(5)]

At 5% of absolute allowable error in the rebound of total serum bilirubin the required sample size was 150 neonates.

Inclusion Criteria
Near term (35 – 36 6/7 week)[1] and term (37- 42 week) [1] neonates with hyperbilirubinemia receiving phototherapy for first time. (As per AAP guideline).

Exclusion Criteria
- Neonate with gestational age <35 wks and >42 wks.
- Critically sick babies requiring mechenical ventilation.
- Babies undergone for exchange transfusion or received IVIG.
- Direct hyperbilirubinemia.
- Negative consent for the study.

Methadology:
Neonates (Between 35-42 weeks) with hyperbilirubinemia and requiring phototherapy according to the AAP guidelines were enrolled in the study. Written Informed Consent, detailed history regarding the onset, symptoms and risk factor for neonatal jaundice were obtained. General physical examination was done. Gestational age was assessed by Modified bellard score.

LED phototheapy with atleast 8-10 microwatt/cm^2/nm spectral irradiance at infants level (as measured with flux meter), 430-490 nm, at 20cm distance from baby was used.Phototherapy was stopped when one value of serum bilirubin level reached below cut-off line.Serum bilirubin levels were measured at 12 hrs and 24 hrs after discontinuation of phototherapy to see rebound hyperbilirubinemia.

OBSERVATIONS & RESULT:

In our study there were 150 neonates with neonatal jaundice, out of them 83 (55.3%) were near term and 67 (44.7%) were term gestation. Mean gestational age of neonates was 36.96 + 1.71 weeks. Out of 150 neonates; among which 87 neonates (58%) were male and 63 neonates

(42%) were female and the sex ratio was 1.38 : 1, showing male sex predominance. Fifty five neonates (36.7%) had birth weight 2.0 - 2.499 kg, 63 neonates (42%) had 2.500-2.999 kg, 26 neonates (17.3) had 3.0 - 3.499 kg, 5 neonates (3.3%) had 3.500 -3.999 kg, 1 neonate (0.6%) had > 4.0 kg. Birth weight ranged from 2000g to 4200g with median birth weight was 2.5 Kg. Mean birth weight was 2.63 Kg + 0.39 Kg. Out of 150 neonates, in 86 neonates (57.3%) no rebound, 47 neonates (31.3%) developed insignificant rebound, 10 neonates (6.7%) developed significant rebound at 12 hrs of discontinuation of phototherapy, and 7 neonates (4.7%) developed significant rebound at 24 hrs of discontinuation of phototherapy.

Table 1: Various variables and risk factors among study subjects:

Gestational age (weeks)	Total	Rebound Hyperbilirubinemia			
		No/insignificant		Significant	
		N	%	N	%
35-36 6/7 weeks (Near term)	83	71	85.5	12	14.5
37-42 weeks (Term)	67	62	92.5	5	7.5
Gender	**Total**	**Rebound hyperbilirubinemia**			
		No/Insignificant		Significant	
		N	%	N	%
Male	87	77	88.5	10	11.5
Female	63	56	88.9	7	11.1

Birth weight (Kg)	Total	Rebound Hyperbilirubinemia			
		No/insignificant		Significant	
		N	%	N	%
2.0- 2.499 Kg	55	50	90.9	5	9.1
2.500 – 2.999 Kg	63	54	85.7	9	14.3
3.0-3.499 kg	26	24	85.7	2	7.7
3.500 -3.999 kg	5	4	80	1	20
> 4.0 kg	1	1	100	0	0

Etiological Diagnosis	Total	Rebound hyperbilirubinemia				P value
		Absent		Significant		
		N	%	N	%	
Cephalhematoma	11	9	81.8	2	18.2	0.802
Asphyxia	20	17	85	3	15	0.859
Sepsis	22	15	68.2	7	31.8	0.004
G6PD deficiency	4	1	25	3	75	0.001
ABO incompatibility	35	28	80	7	20	0.113
Rh incompatibility	11	7	63.6	4	36.4	0.026
DCT positive	5	2	40	3	60	0.005
Hypothyroidism	5	5	100	0	0	0.923

Age at onset of hyperbilirubinemia	Total	Rebound hyperbilirubinemia			
		No/Insignificant		Significant	
		N	%	N	%
< 24 hrs	0	0	0	0	0
25- 48 hrs	29	24	82.8	5	17.2
49-72 hrs	38	32	84.2	6	15.8
73-96 hrs	28	25	89.3	3	10.7
97-120 hrs	18	16	88.9	2	11.1
121-144 hrs	16	15	93.7	1	6.3
≥ 145 hrs	21	21	100	0	0

Age at discontinuation of phototherapy	Total	Rebound Hyperbilirubinemia			
Hours		No/insignificant		Significant	
		N	%	N	%
< 24	0	0	0	0	0
25-48	0	0	0	0	0
49-72	2	2	100	0	0
73-96	23	18	78.3	5	21.7
97-120	42	36	85.7	6	14.3
121-144	27	25	92.6	2	7.4
145-168	17	15	88.2	2	11.8
> 169	39	37	94.9	2	5.1

Duration of phototherapy	Total	Rebound hyperbilirubinemia			
		No/Insignificant		Significant	
		N	%	N	%
<12 hour	0	0	0	0	0
12 - 23 hrs	23	22	95.6	1	4.4
24 - 35 hrs	33	30	90.9	3	9.1
36 – 47 hrs	46	39	84.8	7	15.2
48 – 59 hrs	22	19	86.4	3	13.6
60 -71 hrs	23	20	87	3	13
≥ 72 hrs	3	3	100	0	0

Table 2 : Serum bilirubin at 12& 24 hours among study subjects

Rebound Hyperbilirubinemia (12 hours)	N	Mean	Std. Deviation	P value
No/Insignificant	140	12.6	2.3	<0.001 (S)
Significant	10	16.0	1.6	
Rebound hyperbilirubinemia(24 hours)				
No / Insignificant	143	13	2.6	
Significant	7	17.9	2.0	

DISCUSSION:

In the current study, rebound hyperbilirubinemia occurred in 11.33% of neonates, the majority of whom developed rebound hyperbilirubinemia as a result of hemolytic disease and sepsis, mostly ABO incompatibility. Few studies have systematically investigated the phenomenon of post-phototherapy bilirubin rebound. Previous reports in the international literature have indicated that SBR is rare and therefore it is unnecessary to keep an infant in the hospital after phototherapy has been discontinued to check for SBR [4,6-10]. A cohort study on 226 neonates with indirect hyperbilirubinemia excluding those with a history of exchange transfusion and evidence of sepsis noticed are bound rate of 6.2% [11]. Also Bansal et al. reported a rebound rate of 7.3% in their samples [12]. In addition, other studies [6, 8, 13], with fewer numbers and different inclusion criteria, reported lower incidence of rebound than our study (4.3 and 5.1% respectively). The high rate of bilirubin rebound in our study may be due to increased incidence of hemolytic etiology, different inclusion criteria applied in other studies, and the fact that our hospital is considered a tertiary center concerned with high and critical levels of hyperbilirubinemia. On the other hand, Jodiery et al. found no significant differences between mean TSB at the time of termination of phototherapy and 24–48 h after stopping the phototherapy [16].

In our study significant hyperbilrubinemia was seen more in neonates with age at onset of hyperbilrubinemia at 24 – 48 hours (17.2%), followed by those with age at onset of hyperbilrubinemia at 97 – 144 hours (14.3%) and 49 – 96 hours (10.8%) but no significant association was however found between age at onset of hyperbilrubinemia and rebound hyperbilrubinemia (p=0.349). Also rebound Hyperbilirubinemia was maximum in neonates with birth weight 3.500 -3.999 kg (20%) followed by those with birth weight 2.500 – 2.999 Kg (14.3%). No significant association was found between rebound Hyperbilirubinemia and birth weight of neonates (p=0.797) in our study. Bansal et al' study that reported birth weight < 2000 g and onset of jaundice at < 60 h of age as risk factors for SBR[8]. This may be due to increased plasma bilirubin in relation to weight and immaturity of liver and liver enzymes responsible for binding and conjugation of bilirubin [14].

In our study significant association was seen between rebound hyperbilirubinemia and Sepsis (p=0.004), G6PD deficiency (p=0.001), Rh incompatibility (P=0.026),DCT (p=0.005). So Rebound hyperbilirubinemia was significantly higher in neonates with hemolyic disease especially G6PD deficiency and sepsis. These results were comparable to the study done by Arakhita swain et al (2017); Al-Saedi et al (2002).It was found that SBR was observed mainly in presence of risk factors and rare in absence of risk factors. Similar observation made by Al Saedi et al (2002), Arakhita swain et al (2017); Richa soni et al (2017).

Short duration of conventional phototherapy was found to be a risk factor for SBR, which was in concordance with studies by Kaplan et al. and Berkwitt et al. [11, 13], as phototherapy may be discontinued early while the rise in bilirubin level will continue, concomitant with immaturity of the bilirubin conjugation process [15]. Also, higher TSB at discharge relative to phototherapy threshold was considered as a significant risk in the current study and this was similarly reported by Berkwitt et al. and Chang et al. [11, 16]. On the other hand, Niknafs and colleagues stated that discontinuation of phototherapy at lower bilirubin levels would not prevent bilirubin rebound [3]. Suspected sepsis was found to be a risk factor for SBR in our study, in consistent with Valinjkar et al.[17], which may be related to rapid hemolysis of neonatal erythrocytes and increased catabolism of heme to bilirubin in relation to sepsis [18].

There was also a statistically significant relation between exposure to

intensive phototherapy and SBR, which was similarly reported by other studies [12, 17] and was explained by rapid decline in the TSB level with intensive than conventional phototherapy; it is possible that a greater rebound might occur because of the underlying alteration in bilirubin production and excretion may persist and cause bilirubin rebound after stopping phototherapy [12]. The AAP subcommittee on hyperbilirubinemia recommends follow-up bilirubin level within 24 h of cessation of phototherapy for those with hemolytic diseases, initiated early, or discontinued before the infant is 3–4 days old. The committee considers SBR among neonates who had rehospitalized for hyperbilirubinemia to be a rare occurrence and suggests a bilirubin measurement or clinical evaluation after 24 h in these infants as a clinical opinion [2].

In the light of the present data, our recommendation is to assess different proven risks in selecting neonates to be tested for rebound hyperbilirubinemia. Neonates with hemolytic causes suspected sepsis, exposure to intensive phototherapy, short duration of conventional phototherapy, and relatively high discharge TSB should be regarded as high-risk factors. Delay in discharge of these infants may be considered if their follow-up cannot be ensured. The limitations of this study include the presence of many confounding variables such as hemolysis, high admission TSB, and treatment with intensive phototherapy which have linked effects, inability to do routine glucose-6-phosphate dehydrogenase test in all neonates, and high percentage of neonates with undiagnosed cause of bilirubin rebound. In conclusion, there are several risk factors should be taken into account when planning post-phototherapy followup, especially those with hemolysis, suspected sepsis, short duration of conventional phototherapy, exposure to intensive phototherapy, and relatively high discharge TSB.

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