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Original Research Article

Pathological jaundice in late preterm neonates admitted in a tertiary hospital, Imphal: a prospective cohort study

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ABSTRACT

Background: Approximately 85% of all term and most preterms develop clinical jaundice. Hyperbilirubinrmia is defined as a total bilirubin (TB) >95th percentile on the hour-specific Bhutani normogram. Pathological jaundice implies the onset of jaundice before 24 hours of age, rate of rise in TSB of >0.2 mg/dl/hour and jaundice persisting after 14 days in term and 21 days in late-preterms. The aim of this study was to determine the incidence, progression and the predictors of pathological jaundice among the late preterm infants admitted in Paediatrics ward of a tertiary care centre, Imphal.
Methods: A hospital based prospective cohort study was carried out in paediatrics department, RIMS during a period of 2 years (September 2019 to August 2022) with approval from research ethics board. Sample size was 100 based on consecutive sampling.
Results: Pathological jaundice developed among 65.0% (95% CI: 54.7-74.1%) neonates. The median duration of onset was 47.0 hours. The mean bilirubin at the time of diagnosis of jaundice was 15.5 mg/dl. Three neonates underwent exchange transfusion. Of these 3, one had pre-exchange bilirubin encephalopathy. Male gender, breast feeding, sepsis, infants blood group (B +ve), jaundice among the siblings and birth trauma (birth asphyxia/cephalhematoma) were significantly associated with the development of neonatal hyperbilirubinemia.
Conclusions: Jaundice is condition that is often present and constitutes one of the major risks for neurodevelopmental issues in later life and the risk is further compounded by prematurity. Hence further studies with a larger sample size on a multicentric level could add robustness to our study thereby helping in better understanding and management of the condition.

Keywords: Late-preterm, Pathological jaundice, Total serum bilirubin, Exchange transfusion

INTRODUCTION

Jaundice is the visible manifestation in the skin due to elevated serum concentrations of bilirubin. Hyperbilirubinemia is the most common clinical condition requiring evaluation and treatment in the newborn and a frequent reason for hospital readmission during the first week of life.[1]

Physiologic jaundice is very common in the first week of life which gradually subsides between 10-14 days of life. Jaundice in first week of life occurs approximately in 60% of term infants and 80% of preterm infants.[3] Although generally a benign, postnatal, transitional phenomenon in majority of the neonates, a few neonates develop marked potentially hazardous bilirubin levels that can pose a direct threat of serious brain injury.[4] Late preterm infants are those born at a gestational age of 34 $^{0\backslash7}$ to 36 $^{6/7}$ weeks (239-259 days deliveries during this late preterm period are increasing days. Deliveries since even mild prematurity is now recognized to be associated with adverse health outcomes, it poses healthcare challenges. They present

with inadequate thermoregulation, immature and weak suck and swallow patterns, incomplete adaptation of certain enzyme systems like decreased glucuronyl transferase enzyme activity, and a slower postnatal maturity of hepatic bilirubin uptake and poor immunological and respiratory systems.[5] Late preterm gestation has also been identified as one of the important risk factors for the development of severe jaundice and kernicterus. Jaundice in late preterm infants is more pronounced, more protracted in nature than in their term counterparts.[6] Significant jaundice may indicate underlying disease. High serum unconjugated free bilirubin is neurotoxic and can cause deafness, kernicterus, or athetoid cerebral palsy. Studies indicate that there is no specific bilirubin level that is definitely safe or toxic for all newborns.[7-10]

Significant jaundice is defined as requirement of phototherapy as per hour specific total serum bilirubin normogram of AAP guidelines. Pathological jaundice implies the onset of jaundice before 24 hours of age, an elevation of TB that requires phototherapy, rate of rise in TSB or TcB level of >0.2 mg/dl/hour and jaundice persisting after 14 days in term and 21 days in late-preterm infants.[2] Infants who had initial bilirubin levels above 95th percentile for any time period were significantly more likely to have "significant hyperbilirubinemia" detected in subsequent bilirubin measurement. Significant jaundice may indicate underlying disease. High serum unconjugated free bilirubin is neurotoxic and can cause deafness, kernicterus, or athetoid cerebral palsy.

The aim of this study was to determine the incidence, progression and the predictors of pathological jaundice among the late preterm infants admitted in paediatric ward of a tertiary care centre, Imphal.

METHODS

A hospital based prospective cohort study, in paediatrics department, RIMS for a period of two years (September 2019 to August 2021) with approval from research ethics board. Sample size was 100 assuming the prevalence as 10.1 from previous study conducted by Lavanya et al with absolute allowable error of 5% at 45% confidence interval. It was based on consecutive sampling.

Data was entered in IBM statistical package for the social sciences (SPSS) statistics version 21 for windows (IBM Corp. 1995, 2012). For categorical variables: Chi-square test or Fisher's exact probability test was used and for continuous variable, analysis of variance (ANOVA) test was used.

Study variables

Independent/predictor variables: These include age of the neonate in hours, gender of the neonate, birth weight in kg, serum bilirubin, and age of onset of jaundice in hours.

Dependent/outcome variables

These include: proportion of neonates with pathological Jaundice, and association of pathological jaundice with independent predictors.

Inclusion criteria

All consenting inborn late preterm neonates with post-menstrual age of 34 $^{0/7}$ to 36 $^{6/7}$ weeks were eligible for inclusion.

Exclusion criteria

Late preterm neonate, discharged before 48 hours of life, and with major congenital malformations were excluded.

Study procedure

After obtaining permission from the institute ethics committee and informed consent from the legal guardians of the neonates, a pre-designed proforma was used to collect the socio-demographic and the natal characteristics of the neonates. The neonates were followed up for the appearance of significant jaundice using necessary blood investigations. Relevant maternal, perinatal and neonatal variables were prospectively recorded. TSB was measured in all enrolled neonates at 0-12, 12-24, 25-36, 36-48 hours of life and when indicated clinically thereafter. Neonates were followed up during the hospital stay and after discharge till completion of the 14th postnatal day. The key outcome was significant hyperbilirubinemia defined as need of phototherapy on the basis of American academy of paediatrics guidelines.

RESULTS

A total of 100 late preterms admitted in paediatric ward were included in the study. Of them, 47%, 42% and 11% were 36, 35 and 34 weeks respectively. Their mean birth weight was 2303.2 grams while the median birth weight was 2400 grams with a minimum of 1300 grams and a maximum of 3400 grams. The majority (91.0%) of the neonates were appropriate for gestational, three were large for gestational age while six were small for gestational age. Majority of the neonates (61.0%) were exclusively breast fed. 18.0% and 21.0% were formula fed and mixed fed respectively. More than half of the mothers were of O +ve blood group. A +ve mothers comprise 20.0% while 16% were B +ve. Majority (41.0%) of the neonates were of B +ve blood group followed by A +ve (24.0%), while O +ve and AB +ve blood groups was noted in 19% and 16% respectively.

Table 2 shows that pathological jaundice developed among 65.0% (95% CI: 54.7-74.1%) neonates. The median duration of onset was 47.0 (44.0-132.0) hours with a minimum of 18 hours and a maximum of 288 hours.

Table 1: Demography of the neonates studied.

Gender		Gestation (weeks)			Blood group of the neonate				Birth weight			Type of feed		
M	**F**	**34**	**35**	**36**	**O +ve**	**B +ve**	**A +ve**	**AB +ve**	**LGA**	**AGA**	**SGA**	**BF**	**FF**	**MF**
66	34	11	42	47	19	41	24	16	3	91	6	61	18	21

Table 2: Pathological jaundice among the neonates (N=100).

Pathological jaundice	Frequency (n)	Percentage (95% CI)
Yes	65	65.0 (54.7-74.1)
No	35	35.0 (25.9-45.3)

Table 3 shows that four neonates developed pathological jaundice within 24 hours. Jaundice developed at 25-48 hours and >48 hours among 28 and 33 neonates respectively.

The mean bilirubin at the time of diagnosis of pathological jaundice was 15.5 (3.0) mg/dl. The mean level of maximum bilirubin among the neonates with pathological jaundice was 15.5 (3.0) mg/dl.

Table 3: Pathological jaundice by time of onset (N=100).

Onset (in hours)	Frequency (n)	Percentage
≤24	4	4.0
25-48	33	33.0
>48	28	28.0
Absent	35	35.0

Table 4 shows that pathological jaundice was higher among the neonates who were delivered at 34 weeks of gestation when compared to others but it was not found to be statistically significant (p=0.107).

Table 4: Association of period of gestation with pathological jaundice (N=100).

Gestational age (weeks)	Pathologic jaundice		P value
	Yes, n (%)	No, n (%)	
34	10 (90.9)	1 (9.1)	0.107
35	28 (66.7)	14 (33.3)	
36	27 (57.4)	20 (42.6)	

Table 5 shows that pathological jaundice was found to be higher among the neonates who were exclusively breast fed (73.8%) when compared to formula feeding (55.6%) and mixed feeding (47.6%) but it was found to be statistically significant (p=0.046).

Table 6 shows that there was a significant association for positive urine culture and sensitivity and positive sepsis screening with pathological jaundice (p<0.05).

Table 5: Association of type of feeding with pathologic jaundice (N=100).

Type of feeding	Pathologic jaundice		P value
	Yes, n (%)	No, n (%)	
Breast feeding	45 (73.8)	16 (26.2)	0.046
Formula feeding	10 (55.6)	8 (44.4)	
Mixed feeding	10 (47.6)	11 (52.4)	

Table 6: Association of urine culture and sensitivity and sepsis screening with pathological jaundice (N=100).

Parameters	Pathologic jaundice		P value
	Yes, n (%)	No, n (%)	
Urine culture and sensitivity			
Positive	7 (100.0)	0	0.044*
Negative	58 (62.4)	35 (37.6)	
Sepsis screening			
Positive	21 (100.0)	0	<0.001
Negative	44 (55.7)	35 (44.3)	

*Fisher's exact test

Table 7 shows that pathological jaundice was higher among the neonates with B +ve blood group when compared to others and it was found to be statistically significant (p=0.001).

Table 7: Association of blood group of the neonate with pathological jaundice (N=100).

Blood group of the neonate	Pathologic jaundice		P value
	Yes, n (%)	No, n (%)	
O +ve	6 (31.6)	13 (68.4)	0.001
B +ve	34 (82.9)	7 (17.1)	
A +ve	17 (70.8)	7 (29.2)	
AB +ve	8 (50.0)	8 (50.0)	

Table 8 shows that the pathological jaundice was higher among the neonates with a history of jaundice among the siblings (87.3% versus 37.8%) and it was found to be statistically significant (p<0.001).

Table 8: Association of history of jaundice among the siblings with pathologic jaundice (N=100).

Jaundice among the siblings	Pathologic jaundice		P value
	Yes, n (%)	No, n (%)	
Yes	48 (87.3)	7 (12.7)	<0.001
No	17 (37.8)	28 (62.2)	

Table 9 shows that the pathological jaundice was higher among the neonates with birth trauma (100.0% versus 60.2%) and it was found to be statistically significant (p=0.007).

Table 9: Association of birth trauma with pathologic jaundice (N=100).

Birth trauma (birth asphyxia/ cephalhematoma)	Pathologic jaundice		P value
	Yes, n (%)	No, n (%)	
Yes	12 (100.0)	0	0.007
No	53 (60.2)	35 (39.8)	

*Fisher's exact test

DISCUSSION

Pathologic jaundice developed among 65% (95% CI: 54.7-74.1%) neonates. The median duration of onset was 47.0 (44.0-132.0) hours with a minimum of 18 hours and a maximum of 288 hours. Four neonates developed pathological jaundice within 24 hours. Jaundice developed at 25-48 hours and >48 hours among 28 and 33 neonates respectively. The mean bilirubin at the time of diagnosis of pathological jaundice was 15.5 (3.0) mg/dl. The mean level of maximum bilirubin among the neonates with significant hyperbilirubinemia was 15.5 (3.0) mg/dl. Three neonates underwent exchange transfusion out of which 1 had pre-exchange bilirubin encephalopathy.

A study by Lavanya et al had shown a similar higher incidence of significant hyperbilirubinemia (57.0%) among the late preterm neonates.[12] Similarly, the incidence of significant jaundice was 59% in a study by Bansal et al and also with other studies by Aziz et al and Algameel et al.[14,17,19]

Our study showed that significant hyperbilirubinemia was higher among the male child when compared to the female child (74.2% versus 47.1%) and it was found to be statistically significant (p=0.007), which is consistent to the study results of Gupta et al, where the study had reported that males were found to have significantly higher incidence of jaundice when compared to the females among the late preterm group; similar association had been reported by studies conducted elsewhere.[13,21,22] A study by Bansal et al along with other studies have failed to show such association.[14,52,59]

A study by Lavanya et al showed that large for gestation, gestational age, birth trauma and previous sibling with severe jaundice are the clinical variables significantly associated with significant jaundice.[12] Similar findings were reported by studies conducted by Keren et al, Bansal et al, Aziz et al and Knupfer et al, where lower gestation age (34 and 35 weeks), large for gestation age (LGA), ABO incompatibility and previous sibling with jaundice were significantly associated with significant hyperbilirubinemia.[11,14,17,24] A study by Bhutani et al also have concluded that large for gestational age and late preterm infants disproportionately developed kernicterus as compared with those who were appropriate for gestational age and term.[15] In a study by Aynalem et al, Rh incompatibility (p=0.002), ABO incompatibility, perinatal asphyxia and sepsis were significantly associated with hyperbilirubinemia.[16] Caesarean delivery was significantly associated with neonatal jaundice in a study by Ozdemirci et al.[18] Our study results have shown that male gender, breast feeding, sepsis, infants blood group (B +ve), jaundice among the siblings and birth trauma (birth asphyxia/cephalhematoma) were significantly associated with the development of neonatal hyperbilirubinemia. However, decreasing gestational age, birth weight, mode of delivery, abnormal thyroid and liver function tests and G6PD deficiency were not significantly associated. However, due to smaller sample size, the results should be interpreted with caution and it is always better to interpret in accordance with clinical significance.

Limitations

Limitations of the study was the smaller sample size and hence the issue of generalizability to a larger population. However, the study results could be extrapolated to the population of the similar setting, since a representative sample size was calculated. Secondly, use of different diagnostic and management criteria for pathological jaundice could have affected the study comparisons. Moreover, the cord bilirubin level which is an important predictor of hyperbilirubinemia could have added more strength to the study, if it had been measured. Hence further studies with a larger sample size on a multicentric level could add robustness to our study results thereby helping in better understanding and management of the condition.

CONCLUSION

Jaundice is a clinical condition that is often present and constitutes one of the major issues during the neonatal period and the risk is further compounded by prematurity. It is always imperative to rule out the possible causes of readmission of the mother-infant dyad before they are discharged. Concern about neonatal hyperbilirubinemia is imperative, given the inherent risk of subsequent development of kernicterus. Late preterm neonates are usually treated and managed no differently from those of term neonates with respect to diagnosis, treatment and follow-up of hyperbilirubinemia. Over the years several studies had been conducted to determine the predictors of significant hyperbilirubinemia among the neonates. Considering the fact that the chances of the condition to be higher among the late preterm neonates, it is of utmost importance to determine the burden and the predictors of significant hyperbilirubinemia among this subgroup of neonates so that the unnecessary hospital admissions could be avoided. Hence this study was conducted among the late preterm neonates in a tertiary care centre, to determine the incidence and course of significant hyperbilirubinemia and the predictors of jaundice for better understanding on

the efficient management of these neonates. The study showed that male gender, breast feeding, sepsis, infants blood group (B +ve), jaundice among the siblings and birth trauma (birth asphyxia/cephalhematoma) were significantly associated with the development of neonatal hyperbilirubinemia. However, decreasing gestational age, birth weight, mode of delivery, abnormal thyroid and liver function tests and G6PD deficiency were not significantly associated. The incidence of pathological jaundice is higher among the late preterm neonates which highlights a need for the early recognition and screening of jaundice in this age group. Hence further studies with a larger sample size on a multicentric level could add robustness to our study results thereby helping in better understanding and management of the condition.

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