Original Article

Maternal and Neonatal Risk Factors for Neonatal Jaundice and Readmission – An Indian Perspective

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Abstract

Introduction: Neonatal hyperbilirubinemia is a common neonatal ailment and is mostly benign except in few cases where it might progress to kernicterus. Neonatal jaundice is preventable and treatable if detected in time, and therefore, it is crucial to identify risk factors for developing severe hyperbilirubinemia. **Materials and Methods:** A prospective observational study was conducted with the aim to examine the risk factors for significant jaundice and also for readmission to the hospital. **Results:** A total of 1159 neonates were enrolled, of which 11.2% (n = 134) developed significant neonatal jaundice prior to discharge and 2.1% (n = 25) were readmitted with significant jaundice. The maternal risk factors for significant jaundice were primigravida with age range between 23 and 27 years, "O" blood group, conception by *in vitro* fertilization and embryo transfer (IVF-ET), antenatal oxytocin use, and lower segment cesarean section delivery. The neonatal risk factors for significant jaundice were late preterm male neonates born with birth weight between 2 and 2.5 kg and delayed cord clamping (DCC). The maternal risk factors for readmisssion jaundice were young primigravida with "O" blood group hailing from North India with antenatal use of oxytocin and gestational diabetes mellitus. The neonatal risk factors for readmission jaundice were low birth weight, DCC, twin pregnancies, neonates discharged between 48 and 72 h after birth. **Conclusion:** The statistically significant factors ($P < 0.05$) associated with an increased risk of developing significant hyperbilirubinemia requiring readmission included low birth weight, gestational age 35–36 weeks and 6 days, DCC, and IVF-ET conception.

Keywords: Hyperbilirubinemia, kernicterus, neonatal jaundice, phototherapy, preterm

Introduction

Neonatal jaundice in varying degrees is an unpreventable condition in 60%–80% of newborns worldwide.[1,2] In most babies with jaundice, there is no underlying disease, and this early jaundice (termed "physiological jaundice") is generally benign. However, in a proportion of infants, jaundice may become severe, progressing to acute bilirubin encephalopathy or kernicterus with a significant risk of neonatal mortality.[3,4] Surviving infants may acquire long-term neurodevelopmental sequelae such as cerebral palsy, sensorineural hearing loss, intellectual difficulties, or gross developmental delays.[5]

Neonatal hyperbilirubinemia in infants ≥35 weeks' gestational age (GA) is defined as total serum or plasma bilirubin (TB) >95th percentile on the hour-specific Bhutani nomogram.[6] Current evidence suggests that low- and middle-income countries (LMICs) from sub-Saharan Africa and South Asia disproportionately bear the burden with an estimated 1.1 million babies every year developing severe neonatal hyperbilirubinemia.[7]

Failure to initiate and establish proper breastfeeding is one of the important factors among many others which can play an important role in the development of severe jaundice. Significant unconjugated neonatal hyperbilirubinemia continues to be the most common cause of hospital admissions and readmissions in the neonatal population worldwide putting extra burden on the already scarce health infrastructure in LMIC.[8]

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Furthermore, readmission to the hospital leads to anxiety and stress in the family by disrupting the return of the mother–infant pair to the nurturing home environment. Neonatal jaundice is preventable and treatable if detected in time, and therefore, it is imperative to identify the infants at risk for developing severe hyperbilirubinemia.[9]

The purpose of this study is to evaluate risk factors associated with neonatal jaundice and with readmission jaundice in a tertiary care setup.

Materials and Methods

The study design was a prospective observational study conducted in the postnatal ward in a tertiary care set up in Delhi, India, over a period of 1½ years spanning from August 2016 to March 2018. The study commenced after approval from the protocol and ethical committee. Written informed consent was obtained from all the parents/guardians of the enrolled subjects. All neonates with gestation ≥35 weeks with hyperbilirubinemia in phototherapy range according to the AAP guidelines were included in the study.[9]

Inclusion criteria

All intramural term and preterm babies (≥35 weeks) in the postnatal ward who developed unconjugated hyperbilirubinemia and neonates presenting to the well-baby clinic with neonatal jaundice requiring readmission.

Exclusion criteria

1. Babies who had received intrauterine transfusion in ABO and Rh incompatibility
2. Babies with conjugated hyperbilirubinemia
3. Age of neonate >10 days at the time of detection of jaundice
4. GA <35 weeks.

All intramural newborn babies ≥35 weeks were considered eligible for the study. Babies were assessed for breastfeeding, icterus, change in weight from birth weight, presence of caput, cephalohematoma, and bruising, etc. GA was assessed from maternal dates and early scans and confirmed by clinical examination using the New Ballard method in preterm neonates. Weight of the baby was taken each time using the same weighing scale. Breastfeeding was started within 1 hr of birth in case of normal vaginal delivery and within 6–12 h in case of cesarean section. Mothers were imparted counseling sessions and support regarding breastfeeding twice a day.

At the time of discharge, parents were counselled for warning signs concerning jaundice and were advised to report to the hospital immediately if any such signs develop. Early discharge (≤24 h) is currently not being practiced at our center. The advice for follow-up visits for infants discharged between 24 and 47.9 h of life was at 96 hrs and for those discharged between 48 and 72 h, it was at 120 h.

The clinical assessment of the baby for jaundice was done with the help of Kramer's method. Clinical icterus in relation to postnatal age of the baby warranting estimation of total bilirubin was done by microbilirubinometry using a heel prick sample. As a thumb rule, icterus below the umbilicus was considered an indication to do capillary bilirubin. For any total serum bilirubin result >18 mg/dl on microbilirubinometry, a sample was sent to the laboratory for estimation.[10] Weight loss in percentage and absolute value was assessed and the baby was clinically examined for any signs of dehydration. Blood levels of sodium and creatinine were checked in the laboratory before starting phototherapy for neonates with >8% weight loss, other clinical signs of dehydration, or those readmitted with jaundice. The decision of phototherapy was based on AAP charts for term and preterm babies ≥35 weeks. Phototherapy was given at the bedside using compact fluorescent lamps (CFL) phototherapy units and repeat bilirubin assessments were done by microbilirubinometry. The babies with neonatal jaundice with or without dehydration were managed as per the standard protocol in our center.

Results

The total number of live births at ≥35 weeks during the study period was 1196, of which 37 were excluded (neonatal jaundice due to ABO/Rh setting = 27, conjugated hyperbilirubinemia = 04 and 06 were of age >10 day) and the remaining 1159 neonates were enrolled into the study. The total number of enrolled newborns who were given phototherapy for neonatal jaundice prior to discharge was 134 (11.2%). The number of enrolled newborns readmitted with jaundice for phototherapy during the study period was 25 (2.1%). Nearly 60% of the neonates who had received phototherapy (n = 134) were born by lower segment cesarean section (LSCS) to primigravida mothers by *in vitro* fertilization and embryo transfer (IVF-ET). In the readmission group, majority of mothers were young primigravidas with "O" blood group and had been given antenatal oxytocin [Table 1].

In the neonates who received phototherapy prior to discharge, majority were males (61.2%), late preterms (58.2%) (P = 0.02, odds ratio [OR] =1.9, 95% confidence interval [CI] =1.3–3.1) and with delayed cord clamping (DCC) (98%) (P = 0.04, OR = 1.9, 95% CI = 1.1–3.8). Most of these babies developed jaundice between 48 and 72 h at a mean age of 57 ± 17 h. The average duration of phototherapy requirement in these babies was 26 ± 06 h. The mean age at which discharged from the hospital was 110 ± 14 h [Table 2].

Out of 25 babies readmitted for jaundice, 48% of babies were low birth weight, 52% were late preterms, and DCC was done in 96%. Majority (60%) of babies readmitted for jaundice had significant weight loss (>8%). Out of 25 babies, 15 were from twin pregnancies, majority were second of twins. Both the twins were readmitted in 2 cases. 60% of babies got readmitted with jaundice at an age >120 h at a mean age of 120 ± 33.6 h. About 68% of these babies who were readmitted had been discharged at an age <72 h [Table 3].

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Table 1: Maternal characteristics

	Maternal characteristics of neonates who received phototherapy ($n=134$), *n* (%)	Maternal characteristics of neonates with readmission for jaundice ($n=25$), *n* (%)
Maternal age (years)		
18-22	38 (28.3)	12 (48)
23-27	51 (38.1)	6 (24)
28-32	26 (19.4)	4 (16)
33-37	18 (13.4)	1 (4)
≥38	1 (0.7)	2 (8)
Parity		
Primi	79 (59.0)	14 (56)
Para 2	27 (20.1)	7 (28)
Para 3	21 (15.5)	2 (8)
Para 4	7 (5.2)	2 (8)
Blood group		
O	57 (42.5)	15 (60)
A	32 (23.5)	6 (16)
B	37 (27.6)	3 (12)
AB	8 (5.9)	1 (4)
Ethnic background		
North-eastern India	22 (16.4)	5 (20)
North India	80 (59.7)	15 (60)
Central India	8 (5.9)	4 (16)
West India	8 (5.9)	1 (4)
South India	16 (11.9)	0
Pregnancy related illnesses		
GDM	34 (25.4)	12 (48)
PIH	26 (19.4)	2 (8)
Both	18 (13.4)	9 (36)
None	56 (41.8)	2 (8)
Oxytocin used for induction antenatally		
Yes	76 (56.7)	16 (64)
No	58 (43.3)	9 (36)
History of previous infant with jaundice		
Yes	26 (19.4)	7 (28)
No	108 (80.6)	18 (72)
Conception		
Spontaneous	53 (39.6)	12 (48)
IVF-ET	81 (60.4)	13 (52)
Mode of delivery		
NVD	53 (39.5)	
AVD	3 (2.2)	
LSCS	78 (58.2)	
Employment		
Homemaker	53 (39.6)	
Employed	81 (60.4)	

GDM: Gestational diabetes mellitus, PIH: Pregnancy-induced hypertension, IVF-ET: *In vitro* fertilization-embryo transfer, NVD: Normal vaginal delivery, AVD: Assisted vaginal delivery, LSCS: Lower segment cesarean section

Discussion

The incidence of significant jaundice in the current study was 11.56% compared to 5%–10% in the general population.[11] This relatively higher incidence could be explained by the large number of high-risk pregnancies including preterm deliveries at our center. Our study showed a higher preponderance for jaundice in male neonates akin to previous studies.[12]

Preterm birth is a recognized risk for neonatal jaundice and the same was affirmed in the current study too, in which 58.2% of babies who developed significant hyperbilirubinemia requiring phototherapy were born <37 weeks. The possible explanation for the increased incidence of NNJ in preterm babies is delayed maturation as well as lower concentration of Uridine diphospho-glucuronosyltransferase, immature gastrointestinal function, and feeding difficulties that predispose them to

an increase in enterohepatic circulation, decreased stool frequency, dehydration, etc.[13-16]

The incidence of readmission due to jaundice was 2.2% in our study was. Majority (52%) of the babies who were readmitted

Table 2: Neonatal characteristics.

Neonates who received phototherapy prior to discharge, *n*=134, *n* (%)	
Birth weight	***n* (%)**
≥ 4000 gm	02 (1.5%)
3500 - 3999 gm	10 (7.5%)
3000 - 3499 gm	32 (23.9%)
2500 - 2999 gm	31 (23.1%)
2000 - 2499 gm	53 (39.6%)
1500 - 1999 gm	06 (4.5%)
Gestational age	
≥41 weeks	15 (11.2%)
37 weeks-40 weeks6 days	41 (30.6%)
35-36 weeks6 days	78 (58.2%)
Birth-weight status	
AGA	30 (22.4%)
SGA	92 (68.7%)
LGA	13 (9.7%)
Delayed cord clamping	
Yes	132 (98.5%)
No	02 (1.5%)
Cephalohematoma/Caput	
Yes	19 (14.2%)
No	95 (85.8%)
Age in hours at appearance of Jaundice	
24 - 48 hours	26 (19.4%)
48 - 72 hours	36 (26.9%)
72 - 96 hours	47 (35.1%)
> 96 hours	25 (18.6%)
Duration of Phototherapy	
12-24 hr	26 (19.4%)
24-48 hr	79 (58.9%)
48-72 hr	21 (15.6%)
72-96 hr	09 (6.7%)
> 96 hr	00 (0.0%)
Additional therapy (other than phototherapy)	
EBM suppl	28 (20.9%)
FSL suppl	18 (13.4%)
IV Fluids	00 (0.0%)
Not given	88 (65.7%)
Phototherapy side-effects	
Rash	26 (19%)
Diarrhoea	06 (4.4%)
Fever	04 (2.9%)
Duration of hospitalization	
48-72 hr	82 (61.1%)
72-96 hr	25 (18.7%)
96-120 hr	11 (8.2%)
> 120 hr	16 (11.9%)

AGA-Appropriate for gestational age, SGA-Small for gestational age, LGA-Large for gestational age, EBM-Expressed breast milk, FSL-Full strength lactogen.

Table 3: Neonatal characteristics.

Neonates with readmission for jaundice, *n*=25	
Birth weight	***n*(%)**
≥ 4000 gm	0 (0.0%)
3500 - 3999 gm	02 (08%)
3000 - 3499 gm	04 (16%)
2500 - 2999 gm	05 (20%)
2000 - 2499 gm	12 (48%)
1500 - 1999 gm	02 (08%)
Gestational age	
≥41 weeks	01 (04%)
37 weeks-40 weeks6 days	11 (44%)
35-36 weeks6 days	13 (52%)
Birth-weight status	
AGA	15 (60%)
SGA	08 (32%)
LGA	02 (08%)
Delayed cord clamping	
Yes	24 (96%)
No	01 (04%)
Cephalohematoma/Caput	
Yes	09 (36%)
No	16 (64%)
Age in hours at appearance of Jaundice	
72 - 96 hours	04 (16%)
96-120 hours	06 (24%)
>120 hrs	15 (60%)
Duration of Phototherapy	
<12 hrs	0 (0%)
12-24 hr	0 (0%)
24-48 hr	06 (24%)
48-72 hr	18 (72%)
72-96 hr	01 (04%)
Additional therapy (other than phototherapy)	
EBM suppl	02 (08%)
FSL suppl	03 (12%)
IV Fluids	04 (16%)
Not given	
Phototherapy side-effects	
Rash	04 (16%)
Diarrhoea	02 (08%)
Fever	02 (08%)
Duration of hospitalization	
3-4 days	11 (44%)
5-6 days	08 (32%)
7-8 days	06 (24%)
Age at time of initial discharge	
<48 hours	0 (0.0%)
48-72hrs	17 (68%)
72-96hrs	08 (32%)

Contd...

Table 3: Contd...

Neonates with readmission for jaundice, *n*=25	
Birth weight	***n*(%)**
Percentage weight loss since birth	
< 5%	04 (16%)
5-7%	06 (24%)
8-10%	07 (28%)
> 10%	08 (32%)
TSB at readmission	
15 - 18	06 (24%)
19 - 22	17 (68%)
23 - 26	02 (8.0%)
27 - 30	00
≥ 31	00
Serum sodium at readmission	
130-135	10 (40%)
136-145	07 (28%)
146 - 150	04 (16%)
151 - 156	04 (16%)

GA: Gestational age, AGA: Appropriate for GA, SGA: Small for GA, LGA: Large for GA, EBM: Expressed breast milk, FSL: Full-strength lactogen, IV: Intravenous, TSB: Total serum bilirubin,

for jaundice within the first 10 days were delivered between 35–36 weeks and 6 days period of gestation (preterms).

DCC has favorable developmental outcomes in term infants due to increased hemoglobin and iron stores in the initial few months after the birth. However, it does increase the incidence of neonatal jaundice because of the extra blood volume being received by the neonate. Despite this increased incidence of neonatal jaundice, it is recommended that DCC should be practiced where facilities for monitoring and treating neonatal jaundice exist.[17] DCC emerged as an important risk factor for both significant jaundice requiring phototherapy prior to discharge and readmission to the hospital due to jaundice in the current study. This could be attributable to the practice of DCC (45–60 s) in term infants in our tertiary care center.

The current study found higher rates (67.9%) of significant jaundice in SGA newborns (P = 0.04) which is consistent with previous studies by Singla *et al*.[17] and is possibly due to increased bilirubin load in the hepatocyte, decreased hepatic uptake of bilirubin from plasma, and/or defective conjugation.[12,18]

An interesting finding of the current study is that the most common age group of mothers of babies with significant jaundice and readmission jaundice was 23–27 years. We could not find any possible explanation for the same as data available in the literature pertaining to the same is scarce. However, this warrants further research considering that in the current socioeconomic situation, this age group is the most productive age group. Another finding of the current study was that 59% of babies with significant jaundice and 56% of readmitted neonates were born to primigravida mothers. This was in contrast to a study by Mesic *et al.* which showed no statistically significant association between the birth order and the occurrence of jaundice.[19]

Antenatal oxytocin use for induction and conception by IVF-ET also emerged as significant risk factors for the development of significant jaundice in the current study in concurrence with previous studies.[20,21]

In our study, 68% of the neonates readmitted for jaundice were discharged between 48 and 72 h. All the infants readmitted with jaundice were on exclusive breastfeeding except for 3 babies who were given top feeds at home. The American Academy of Pediatrics defines early and very early discharge as 48 and 24 h, respectively, after an uncomplicated vaginal delivery. The trend of readmission for jaundice as shown in the current study is consistent with various studies which have shown that infants discharged from the hospital in the first 2 days of life were more likely to be readmitted for jaundice compared with infants who stayed ≥3 days.[22] This observation merits attention as early discharges of the newborns from the hospital after delivery has recently become a common practice for medical, social, and economic reasons.

The strength of this study is that inclusion criteria for the study were not restrictive leading to more realistic recruitment of subjects and also making the findings of the study more generalizable in real-time clinical practice. Second, meticulous and objective clinical assessment with special emphasis on preventive measures such as twice a day counseling sessions and support regarding breastfeeding were given to the mothers.

The limitations of the study are a relatively smaller sample size in a tertiary care setup without any long-term follow-up. Considering the limitations of the study, larger studies with longer periods of observation to measure periodic and sustained neurodevelopmental follow-up assessments need to be done.

Conclusion

A higher risk of significant jaundice was seen with primigravida mothers, hailing from North India with antenatal risk factors such as gestational diabetes mellitus and antenatal use of oxytocin. The neonatal risk factors included preterm male neonates weighing between 2 and 2.5 kg and delivered by LSCS.

Risk of readmission jaundice was higher in babies with young mothers (18–22 years) discharged before 72 h, low birth weight, GA 35–36 weeks and 6 days, DCC, and IVF–ET conception. Babies readmitted for jaundice required a longer duration of phototherapy (44 ± 08 h) as compared to babies who were given phototherapy prior to discharge (26 ± 06 h).

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Conflicts of interest
There are no conflicts of interest.

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