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The risk factors for unconjugated hyperbilirubinemia and readmission jaundice in intramural neonates ≥ 35 weeks

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Abstract

Background: Neonatal hyperbilirubinemia is a common condition that is typically benign, although in some cases it may progress to kernicterus. Because neonatal jaundice is both preventable and treatable when detected early, identifying risk factors for developing severe hyperbilirubinemia is essential. **Materials and Methods:** A prospective observational study was conducted to examine the risk factors associated with significant neonatal jaundice and hospital readmission for jaundice. **Results:** A total of 600 neonates were enrolled. Among them, 15% (n = 90) developed significant jaundice prior to discharge, and 2.5% (n = 15) required readmission. Maternal risk factors for significant jaundice included primigravida status with maternal age between 23 and 27 years, blood group O, conception by in vitro fertilization and embryo transfer (IVF-ET), antenatal oxytocin use, and lower-segment cesarean section. Neonatal risk factors included late-preterm male infants with birth weight between 2 and 2.5 kg and delayed cord clamping (DCC). Maternal risk factors for readmission included young primigravida women with blood group O from North India, antenatal oxytocin use, and gestational diabetes mellitus. Neonatal risk factors for readmission included low birth weight, DCC, twin pregnancy, and discharge between 48 and 72 hours after birth. **Conclusion:** The statistically significant factors

($P < 0.05$) associated with an increased risk of developing significant hyperbilirubinemia requiring readmission were low birth weight, gestational age of 35–36 weeks, DCC, and conception via IVF–ET

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

Introduction

Hyperbilirubinemia is the most common cause of neonatal hospitalization [1]. Although most newborns with hyperbilirubinemia have a good prognosis [2], approximately 8–11% develop persistently elevated bilirubin levels that may lead to severe complications, including lifelong disabilities such as growth retardation, encephalopathy, autism, and hearing impairment [3–5]. The incidence of pathological jaundice is approximately 1% in infants without risk factors, rising sharply to nearly 59% in those with identifiable risk factors [3].

Neonatal jaundice, in varying degrees, is an almost universal condition, affecting 60%–80% of newborns worldwide [6–7]. In most cases, jaundice is benign and termed “physiological jaundice,” with no underlying pathology. However, a subset of infants may develop severe hyperbilirubinemia that progresses to acute bilirubin encephalopathy or kernicterus, conditions associated with substantial neonatal morbidity and mortality [8–9]. Surviving infants may suffer long-term neurodevelopmental sequelae, including cerebral palsy, sensorineural hearing loss, intellectual impairment, or global developmental delay [10].

In infants born at ≥ 35 weeks of gestational age (GA), neonatal hyperbilirubinemia is defined as a total serum or plasma bilirubin (TB) level > 95 th percentile on the hour-specific Bhutani nomogram [11]. Evidence indicates that low- and middle-income countries (LMICs), particularly in sub-Saharan Africa and South Asia, bear a disproportionate burden, with an estimated 1.1 million infants each year developing severe hyperbilirubinemia [12]. Suboptimal breastfeeding practices are among the significant contributors to severe jaundice, alongside other maternal and neonatal factors. Unconjugated neonatal hyperbilirubinemia remains a leading cause of hospital admissions and readmissions worldwide, placing additional strain on already limited healthcare systems in LMICs [13].

Readmission for jaundice further contributes to parental anxiety and disrupts the early mother–infant bonding process. Since neonatal jaundice is largely preventable and treatable when identified early, it is crucial to recognize infants at increased risk of developing severe hyperbilirubinemia [14].

The present study aims to evaluate the maternal and neonatal risk factors associated with significant neonatal jaundice and jaundice-related readmission in a tertiary care setting.

Materials and Methods

This prospective observational study was conducted in the postnatal ward of the Dr. KNS Memorial Institute of Medical Sciences, Barabanki, Lucknow. The study

commenced after approval from the institutional protocol and ethics committee. Written informed consent was obtained from the parents or guardians of all enrolled neonates. All infants with gestational age (GA) ≥ 35 weeks who developed hyperbilirubinemia within the phototherapy range, as defined by the American Academy of Pediatrics (AAP) guidelines, were included in the study [14].

Inclusion Criteria

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

Exclusion Criteria

- Neonates who had received intrauterine transfusion for ABO or Rh incompatibility
- Neonates with conjugated hyperbilirubinemia
- Neonates aged >10 days at the time jaundice was detected
- GA <35 weeks
- All intramural neonates ≥ 35 weeks were screened for eligibility. A detailed assessment was performed, including evaluation of breastfeeding adequacy, presence of icterus, weight change from birth, and detection of caput succedaneum, cephalohematoma, or bruising. Gestational age was determined using maternal dates and early ultrasound findings and confirmed clinically in preterm infants using the New Ballard Score.

Neonatal weight was measured using the same calibrated scale for consistency. Breastfeeding was initiated within 1 hour of birth following a normal vaginal delivery and within 6–12 hours after cesarean section. Mothers received breastfeeding counselling and support twice daily. Before discharge, parents were instructed regarding warning signs of jaundice and advised to seek immediate medical attention if symptoms worsened. Early discharge (≤ 24 hours) is not practiced at this center. Follow-up was scheduled at 96 hours for infants discharged between 24 and 47.9 hours of life and at 120 hours for those discharged between 48 and 72 hours.

Clinical assessment for jaundice was performed using Kramer's method. Total bilirubin estimation was done using microbilirubinometry via heel-prick sampling when clinical icterus, relative to postnatal age, warranted testing. As a general rule, icterus extending below the umbilicus prompted bilirubin measurement. For all microbilirubinometry values >18 mg/dL, a venous sample was sent for laboratory confirmation [15].

Weight loss was assessed both as a percentage and in absolute terms, and infants were evaluated clinically for signs of dehydration. Serum sodium and creatinine were measured in neonates with $>8\%$ weight loss, signs of dehydration, or those readmitted for jaundice. Phototherapy decisions were guided by AAP nomograms for infants ≥ 35 weeks GA. Phototherapy was administered at the bedside using compact fluorescent lamp (CFL) phototherapy units, and bilirubin levels were monitored using microbilirubinometry. Neonates with jaundice, with or without dehydration, were managed according to the standard protocol of the institution.

Results

The total number of live births at ≥ 35 weeks during the study period was 600, of which 25 were excluded (neonatal jaundice due to ABO/Rh setting = 18, conjugated hyperbilirubinemia = 6 and 12 were of age >10 day) and the remaining 600 neonates were enrolled into the study. The total number of enrolled newborns who were given phototherapy for neonatal jaundice prior to discharge was 90 (15%). The number of enrolled newborns readmitted with jaundice for phototherapy during the study period was 15 (2.5%). Nearly 60% of the neonates who had received phototherapy ($n = 90$) 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].

Table 1: Maternal characteristics

		Maternal characteristics of neonates who received phototherapy ,		Maternal characteristics of neonates with readmission for jaundice	
		(n=90)	n (%)	(n=15)	n (%)
Maternal age (years)	18-22	25	27.8	7	46.7
	23-27	38	42.2	4	26.7
	28-32	21	23.3	2	13.3
	33-37	15	16.7	1	6.7
	≥ 38	1	1.1	1	6.7
Parity	Paimi	50	55.6	8	53.3
	Para2	18	20	3	20
	Para3	15	16.7	2	13.3
	Para4	7	7.8	2	13.3
Blood group	O	46	51.1	8	53.3
	A	20	22.2	4	26.7
	B	27	30	1	6.7
	AB	7	7.8	2	13.3
Ethnic background	North-eastern India	15	16.7	2	13.3
	North India	55	61.1	9	60
	Central India	4	4.4	2	13.3
	West India	4	4.4	1	6.7
	Central India	12	13.3	1	6.7
Pregnancy related illnesses	GDM	25	27.8	7	46.7
	PIH	20	22.2	1	6.7
	Both	15	16.7	6	60
	None	30	33.3	1	6.7
Oxytocin used for induction antenatally	Yes	73	81.1	10	66.7
	No	17	18.9	5	33.3
History of	Yes	12	13.3	3	20

previous infant with jaundice	No	78	86.7	12	80
Conception	Spontaneous	35	35.9	7	46.7
	IVF-ET	55	61.1	8	53.3
Mode of delivery	NVD	40	44.4	0	0
	AVD	2	2.2	0	0
	LSCS	48	53.3	0	0
Employment	Homemaker	41	45.6	0	0
	Employed	49	54.4	0	0

[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]

Table 2: Neonatal characteristics. Neonates who received phototherapy prior to discharge, n=90, n (%)

		N	Percentage (%)
Birth weight	≥ 4000 gm	1	1.1
	3500 - 3999 gm	8	8.9
	3000 - 3499 gm	21	23.3
	2500 - 2999 gm	20	22.2
	2500 - 2999 gm	35	38.9
	1500 - 1999 gm	5	5.6
Birth weight	≥41 weeks	11	12.2
	37 weeks-40 weeks6 days	25	27.8
	35-36 weeks6 days	54	60
Birth-weight status	AGA	19	21.1
	SGA	27	30
	LGA	44	48.9
Delayed cord clamping	Yes	89	98.9
	No	1	1.1
Cephalohematoma/Caput	Yes	14	15.6
	No	76	84.4
Age in hours at appearance of Jaundice	24 - 48 hours	18	20
	48 - 72 hours	23	25.6
	72 - 96 hours	35	38.9
	> 96 hours	14	15.6
Duration of Phototherapy	12-24 hr	18	20
	24- 48 hr	56	62.2
	48-60 hr	12	13.3
	61-72 hr	4	4.4
	> 96 hr	0	0
Additional therapy (other than phototherapy)	EBM suppl	19	21.1
	EBM suppl	14	15.6
	IV Fluids	00	0
	Not given	67	74.4
Phototherapy	Rash	18	20

side-effects	Diarrhoea	4	4.4
	Fever	3	3.3
Duration of hospitalization	48-72 hr	62	68.9
	72-96 hr	18	20
	96-120 hr	4	4.4
	> 120 hr	6	6.7

In the neonates who received phototherapy prior to discharge, majority were males(60%), late preterms(60%) and with delayed cord clamping (DCC) (98.9%). Most of these babies developed jaundice between 72 and 96 h at a mean age of 38.9 h. The average duration of phototherapy requirement in these babies was 27 h. The mean age at which discharged from the hospital was 114 h [Table 2].

Table 3: Neonatal characteristics. Neonates with readmission for jaundice, n=25

		N	Percentage (%)
Birth weight	≥ 4000 gm	0	0
	3500 - 3999 gm	1	6.7
	3000 - 3499 gm	3	20
	2500 - 2999 gm	4	26.7
	2500 - 2999 gm	6	40
	1500 - 1999 gm	1	6.7
Birth weight	≥41 weeks	1	6.7
	37 weeks-40 weeks6 days	6	40
	35-36 weeks6 days	8	53.3
Birth-weight status	AGA	9	60
	SGA	5	33.3
	LGA	1	6.7
Delayed cord clamping	Yes	14	93.3
	No	1	6.7
Cephalohematoma/Caput	Yes	6	40
	No	9	60
Age in hours at appearance of Jaundice	72 - 96 hours	2	13.3
	96 - 120 hours	3	20
	> 120 hours	10	66.7
Duration of Phototherapy	12-24 hr	0	0
	25- 48 hr	0	0
	48-60 hr	4	26.7
	61-72 hr	10	66.7
	> 96 hr	1	6.7
Additional therapy (other than phototherapy)	EBM suppl	1	6.7
	EBM suppl	2	13.3
	IV Fluids	3	20
	Not given	9	60
Phototherapy side-effects	Rash	2	13.3
	Diarrhoea	1	6.7
	Fever	1	6.7

Duration of hospitalization	48-72 hr	7	46.7
	72-96 hr	5	33.3
	96-120 hr	3	20
	> 120 hr	0	0
Age at time of initial discharge	<48 hours	0	0
	48- 72 hrs	10	66.7
	72-96 hrs	5	33.3
Percentage weight loss since birth	< 5%	2	13.3
	5-7%	3	20
	7-10%	4	26.7
	> 10%	6	40
TSB at readmission	15-18	3	20
	19-22	11	73.3
	23-26	1	6.7
	27-30	0	0
	≥ 31	0	0
Serum sodium at readmission	130-135	8	53.3
	136-140	3	20
	141-145	2	13.3
	151-156	2	13.3

[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]

Out of 15 babies readmitted for jaundice, 40% of babies were low birth weight, 53.3% were late preterms, and DCC was done in 98.9%. Majority (60%) of babies readmitted for jaundice had significant weight loss (>8%). Out of 15 babies, 15 were from twin pregnancies, majority were second of twins. Both the twins were readmitted in 2 cases. 66.7% of babies got readmitted with jaundice at an age >120 h at a mean age of 122 h. About 66.7% of these babies who were readmitted had been discharged at an age <72 h [Table 3].

Discussion

The incidence of significant jaundice in the present study was 15%, higher than the 5%–10% reported in the general population [16]. This increased incidence may be attributed to the relatively large number of high-risk pregnancies and preterm deliveries at our center. A higher prevalence of jaundice among male neonates was noted, consistent with previous studies [17]. Preterm birth is a well-established risk factor for neonatal jaundice, and this was reaffirmed in our study, where 60% of neonates who required phototherapy were born at <37 weeks of gestation. The increased susceptibility of preterm infants to neonatal jaundice can be explained by delayed hepatic maturation, lower activity of uridine diphospho-glucuronosyltransferase, immature gastrointestinal function, and feeding difficulties, all of which predispose them to hyperbilirubinemia [22].

Delayed cord clamping (DCC) emerged as a significant risk factor for both in-hospital jaundice requiring phototherapy and jaundice necessitating readmission. This

association may be related to the routine practice of DCC (45–60 seconds) in term infants at our center. Furthermore, 60% of small-for-gestational-age (SGA) newborns developed significant jaundice, a finding consistent with Singla et al. [22] and attributable to increased bilirubin load, reduced hepatic uptake, and impaired conjugation mechanisms [17,23].

An interesting observation in the current study was that most mothers of neonates with significant jaundice and readmission-related jaundice were aged 23–27 years. Literature on maternal age as a risk factor remains scarce, and the reason behind this association is unclear. Given that this is a socioeconomically productive age group, further research is warranted. Additionally, 60% of neonates with significant jaundice and 56% of those readmitted were born to primigravida mothers, contrasting with the findings of Mesic et al., which showed no significant association between birth order and jaundice [24]. Antenatal oxytocin use for induction and conception via IVF–ET also emerged as significant risk factors, aligning with earlier studies [25–26].

In our study, 68.9% of neonates readmitted for jaundice had been discharged between 48 and 72 hours of life. Almost all were exclusively breastfed, except for two infants who received supplemental feeds at home. According to the American Academy of Pediatrics, early and very early discharge occur at 48 and 24 hours, respectively, after uncomplicated vaginal delivery. Our findings align with previous research showing that infants discharged within the first two days of life are more likely to be readmitted for jaundice compared with those remaining hospitalized for ≥ 3 days [27]. This observation is particularly relevant in the context of increasing early discharge practices driven by medical, social, and economic factors.

The strengths of our study include inclusive eligibility criteria, allowing for a more representative and clinically relevant sample, and systematic, objective assessments with emphasis on preventive strategies such as twice-daily breastfeeding counselling. However, limitations include a relatively small sample size, single-center tertiary care setting, and lack of long-term follow-up. Future studies with larger cohorts and extended surveillance, including neurodevelopmental assessments, are essential to validate and expand upon these findings.

Conclusion

A higher risk of significant neonatal jaundice was associated with primigravida mothers, those from North India, and maternal risk factors such as gestational diabetes mellitus and antenatal oxytocin use. Neonatal risk factors included preterm male infants with birth weight between 2 and 2.5 kg and delivery by lower-segment cesarean section.

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