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Original Research Article

Risk Factors for Unconjugated Hyperbilirubinemia and Readmission for Jaundice in Neonates: A Case-Control Study

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Abstract

Background: About 60% of term and 85% of preterm neonates experience hospital readmission due to hyperbilirubinemia, which is a common condition in newborns. Although it is frequently a benign condition, it can have neurological consequences like bilirubin induced encephalopathy and the kernicterus spectrum of disorders. We sought to assess the neonatal and maternal risk factors for hyperbilirubinemia as well as to pinpoint those that may be changed.

Methods: From September 2021 to February 2022, an observational case-control study was conducted in the paediatrics department of the SKMCH in Muzaffarpur, Bihar. Neonates without hyperbilirubinemia were used as controls, while neonates with hyperbilirubinemia levels within the phototherapy range as defined by age and gestation by the American Academy of Paediatrics were used as cases. All neonates included in the study underwent thorough prenatal, perinatal, family history, and physical examinations. Risk factors such as the presence of maternal illness, intrauterine growth retardation (IUGR), premature rupture of the membranes (PROM), prematurity, ABO and Rh incompatibility, prior phototherapy use in siblings, breastfeeding issues, and birth asphyxia were also assessed.

Results: Neonatal hyperbilirubinemia has been associated significantly with IUGR (P value 0.01), prematurity (P value 0.002), ABO incompatibility (P value 0.009), breastfeeding difficulties (P value 0.001), birth asphyxia (P value 0.05), and the presence of PROM (P value 0.05) in multivariate logistic regression studies of collected data.

Conclusion: Rapid care and early detection of neonatal hyperbilirubinemia minimise the morbidity and death linked to this widespread illness.

Keywords: Jaundice of Neonate, Neonatal Jaundice, Icterus Neonatorum.

Introduction

The most typical reason for a newborn's hospital readmission is neonatal hyperbilirubinemia. About 60% of term and 80% of preterm neonates are affected by it [1]. The yellowish colouring of the skin, sclera, and mucous membranes is known as

jaundice and is a symptom of hyperbilirubinemia, or elevated serum bilirubin levels.

However, in some cases, it may have significant mortality and morbidity due to neurological sequelae like bilirubin induced encephalopathy and kernicterus spectrum of disorders. Usually, it is a benign condition that resolves without any sequelae. Due to the immature blood-brain barrier (BBB) in the early stages of life, neonates are more susceptible to developing these sequelae.

Therefore, early intervention and prevention of complications related to neonatal hyperbilirubinemia depend on prompt identification and monitoring of the neonates at risk for developing significant hyperbilirubinemia.

There are many things that have been linked to newborn hyperbilirubinemia. These may include maternal conditions like anaemia, hypothyroidism, TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) infections, diabetes mellitus, hypertension, poor obstetric history, ABO and Rh incompatibility, breastfeeding difficulties, foetal conditions like IUGR, oligohydramnios or polyhydramnios, neonatal conditions like prematurity [1-4],

As there were few studies defining the common causes of hyperbilirubinemia, this study was carried out to determine the various risk factors, both maternal and foetal, associated with neonatal hyperbilirubinemia and identify the modifiable risk factors that were predominant in the population included in this study.

Material and Methods

From September 2021 to February 2022, an observational case-control study was carried out in the paediatrics department of the Sri Krishna Medical College and Hospital in Muzaffarpur, Bihar. After calculating two-sided confidence levels ($1 - \alpha = 95$), a sample of 55 cases and 55 controls were selected.

The study covered cases of neonates who needed phototherapy for their hyperbilirubinemia. Neonatal patients were those whose serum bilirubin levels met the criteria for phototherapy under the National Institute for Health and Clinical Excellence (NICE) Guidelines for neonates under 35 weeks of gestation or according to the Bhutani Nomogram Charts for neonates >35 weeks of gestation. In a 1:1 age and sex matched ratio, controls were newborns without transcutaneous bilirubin (TcB) levels high enough to require phototherapy.

We excluded congenitally malformed neonates, infants whose parents refused to participate in the trial, and newborns whose records of pregnancy and delivery were insufficient.

All newborns delivered in our hospital were checked for hyperbilirubinemia twice day through physical examination and transcutaneous bilirubinometer use.

All parents of neonates included in the study received a thorough information sheet outlining the study's methodology. Each neonate who participated in the study had their physical examination.

The prenatal, perinatal, and family history information was gathered. A variety of risk variables presence was evaluated. The maternal records were examined for information on maternal sickness, prenatal screenings, and labour or delivery specifics. According to hospital standards, breastfeeding was encouraged for all newborns, and residents and staff regularly evaluated residents feeding needs and their breastfeeding difficulties. Mothers whose secretions were insufficient were recommended to supplement their infants diets with donor milk from an on-site human milk bank.

The neonates case files contained information about the birth occurrences. All cases included in the study underwent laboratory testing such as complete blood count (CBC) with peripheral smear, septic screen, serum bilirubin levels, blood grouping, thyroid levels, and glucose - 6 - phosphate dehydrogenase (G6PD) levels.

The thyroid levels of control neonates were not measured because standard thyroid screening was not performed on all newborns. Until the serum bilirubin levels were below the range for phototherapy as defined by the American Academy of Paediatrics as per age and gestation, all cases included in this study underwent phototherapy while having their levels of bilirubin continuously monitored. In this investigation, there were no patients that needed exchange transfusions or pharmacologic treatment.

Excel 2021 was used to enter all of the acquired data, and STATA 10.0 was used to study and assess each variable. For the connection of a risk factor with neonatal hyperbilirubinemia, an ODDS ratio > 1 was deemed significant, and a P value <0.05 was deemed statistically significant. Through multivariate logistic regression analysis, the risk factors that were determined to be statistically significant were again examined.

Results

3 neonates were eliminated from the study because they had congenital heart problems, bringing the total number of neonates involved in the study to 58. There was also a 1:1 matched control group (N = 55) for sex and age. All of the infants that we studied were of Indian descent. The ratio of men to women was 1.13:1. Between the study groups, there was no correlation between gender, head circumference, length, and weight (OR 0.74 and P value 0.070).

The various risk factors considered in our study.

Table 1: Risk Factor in Maternal Illness

Risk Factors	Cases (Total 55) n%	Controls (Total 55) n%	OR (95%CI)	p-value
Gestational Diabetes Mellitus/Diabetes Mellitus	5(9.09%)	2(3.63%)	12.625(0.77-186.32)	0.00321
Hypertension/Pregnancy induced hypertension	9(16.36%)	5(9.09%)	1.35(0.12-7.72)	0.7125
Preeclampsia/Eclampsia	3(5.45%)	1(1.82%)	13.25(0.17-289.98)	0.0148
TORCH Infections	2(3.63%)	1(1.82%)		0.8289
Hypothyroidism	2(3.63%)	1(1.82%)		0.8474
Anemia	9(16.36%)	4(7.27%)	3.6(0.49-20.53)	0.0837
PROM	5(9.09%)	3(5.45%)	9.7(1.10-79.51)	0.0029

Table 2: Risk Factor in Maternal Factors

Risk Factors	Cases (Total 55) n%	Controls (Total 55) n%	OR (95%CI)	p-value
Bad Obstetric History	5(9.09%)	3(5.45%)		0.4760
ABO Incompatibility	15(27.27%)	6(10.91%)	8.46(2.06-40.42)	0.0002
Rh Incompatibility	5(9.09%)	1(1.82%)	0.64(0.013-5.55)	0.6747
Breast Feeding Problem	19(34.54%)	6(10.91%)	7.1(1.59-42.75)	0.0018

Table 3: Risk Factor in Type of delivery

Risk Factors	Cases (Total 55) n%	Controls (Total 55) n%	OR (95%CI)	p-value
Normal vaginal delivery	28(50.91%)	12(21.82%)	0.63(0.22-1.74)	0.3338
Lower segment caesarean section	24(43.64%)	44(80.00%)	0.99(0.36-2.80)	0.9941
Instrumental delivery	4(7.27%)	1(1.82%)		0.7667

Table 4: Risk Factor in Fetal outcome

Risk Factors	Cases (Total 55) n%	Controls (Total 55) n%	OR (95%CI)	p-value
IUGR	21(38.8%)	10(18.18%)	14.72(3.67-83.12)	0.0001

Table 5: Risk Factor in Neonatal

Risk Factors	Cases (Total 55) n%	Controls (Total 55) n%	OR (95%CI)	p-value
Prematurity	23(41.82%)	11(20.00%)	4.91(1.58-16.82)	0.0015
Birth Asphyxia	8(14.55%)	3(5.45%)	1(1.82%)	0.0097
Cephalohaematoma	2(3.64%)	0		
Polycythaemai	2(3.64%)	0		
Sepsis	7(12.73%)	0		
Breast milk Jaundice	1(1.82%)	0		

Table 6: Risk Factor in Family history

Risk Factors	Cases (Total 55) n%	Controls (Total 55) n%	OR (95%CI)	p-value
History of sibling who received phototherapy	3 (5.45%)	1 (1.82%)	8.66 (0.12-181.72)	0.0481
History of jaundice in (1^{st}, 2^{nd}, 3^{rd}) degree relatives	2 (3.64%)	1 (1.82%)		0.8663

ABO incompatibility (P = 0.002), breastfeeding difficulties (P = 0.0018), the presence of IUGR (P = 0.001), prematurity (P = 0.0015), birth asphyxia (P = 0.0097), and family history of sibling who received phototherapy (P = 0.0481) were all associated with neonatal factors that were significantly related to neonatal outcomes, according to a univariate analysis.

Some neonatal factors, such as polycythaemia, sepsis, cephalohematoma, and breast milk jaundice, were only discovered in cases, making it impossible to comment on their relationship with neonatal hyperbilirubinemia.

Table 7: Analysis of Multivariate Regression

Risk Factors	OR (95%CI)	p-value
IUGR	2.48(1.24-4.95)	0.010
Prematurity	2.81(1.44-5.48)	0.0025
ABO Incompatibility	2.83(1.29-6.23)	0.0092
Breast feeding problems	3.89(1.81-9.20)	0.0013
Birth asphyxia	2.97(0.99-8.93)	0.051
History of sibling who received phototherapy	1.16(0.23-5.73)	0.854
Mothers with diabetes mellitus	188(0.47-7.54)	0.368

Mothers with eclampsia	1.83(0.34-9.89)	0.480
Presence of PROM	3.02(0.98-9.29)	0.065

Discussion

Neonatal hyperbilirubinemia (NNH), a disease that is common in newborns, can have serious consequences for morbidity and mortality. The quick identification of neonates at risk has become crucial for lowering the difficulties related to the illness due to the availability of non-invasive and efficient treatments like phototherapy. Through this study, an effort was made to pinpoint any potentially modifiable risk factors for hyperbilirubinemia in the study's participant population. Similar to studies by Mostafa SA *et al* [6] and by Xavier R *et al* [7], this study found breastfeeding to be a significant risk factor associated with hyperbilirubinemia (P value 0.0013 and OR 3.89), despite the fact that Kuzniewicz MW *et al* [8]. found no significant association between breastfeeding difficulties and NNH (P value 1) in their study.

Numerous studies have examined ABO incompatibility [9,10]. and Rh incompatibility [11]. some have found no association between either factor and a significant risk for NNH [12,16]; however, this study establishes a significant association with ABO incompatibility, with a P value of 0.0092, whereas Rh incompatibility was not found to have a significant association. Better antenatal care and timely Anti-D factor medication may be to blame for this.

However, multivariate regression studies did not find a significant association as described by studies by Mojtahedi SY *et al* [16] and Boskabadi H *et al* [19,20]. This study demonstrated a significant association of diabetes mellitus and pre-eclampsia with NNH through univariate analysis, similar to studies by Tavakolizadeh R *et al* [17]. and Devi DS *et al* [18].

In contrast to earlier research, this one did not find a favourable link between maternal anaemia or hypothyroidism and NNH.In this investigation, there was no evidence that maternal TORCH infections were significantly associated with the presence of NNH.

Similar to prior studies done in the US [21] and India [2], this study discovered a significant connection between PROM and NNH (P value 0.065). Although a number of studies [22-24]. claimed that the method of delivery had a significant association with NNH, this study found no evidence of such a relationship. According to a Swedish study, [25] planned LSCS carries a lower risk of hyperbilirubinemia. This might be explained by the prolonged hospital stay and effective breastfeeding practises in this group.

The neonates of primigravida women included in this study had the highest prevalence of hyperbilirubinemia (47.79%; n = 27). Although a meta-analysis by Olusanya BO *et al* [26] did not discover any correlation between parity and the presence of NNH, this was comparable to a study by Meng KH *et al*.

IUGR was discovered to have a substantial correlation with NNH (P value 0.010), which is consistent with findings from earlier studies done in India [2-18-27]. Although it has been suggested that being a man increases the risk of neonatal hyperbilirubinemia [28,28,29], no such association was discovered in this study (P value 0.7). Contrarily, Garosi E *et al* [30] found a greater risk of hyperbilirubinemia in newborn females.

Contrary to research by Singla *et al*.32 and Huang *et al* [15], this study, along with a

number of other studies [8-21-31]., indicated that preterm was a risk factor for NNH (P value 0.0025).

In contrast to a study conducted in Taiwan, birth asphyxia in our study had a significant connection with NNH (P value 0.051), just like other studies carried out in India [2], Iran [16], and China [33].

While other studies [8-16-32]. did not find a significant association, some [33,34]. have shown a positive correlation between the presence of cephalohaematoma and polycythaemia and NNH.

Neonatal infections like sepsis and UTI are common. It might be challenging to identify UTI in newborns. Numerous studies [24-28-31-33-35]. claim that infection is a risk factor for NNH, but Huang M-J *et al* [15] did not discover a statistically significant correlation between the two in their study.

The association could not be discussed in this study because only the cases included in it had cephalohaematoma, polycythaemia, and sepsis.

Only the cases included in this study had G6PD testing sent. The only preterm neonate with a substantial result was lost to follow-up, nevertheless. The prevalence of G6PD in this study population was not significant enough to propose the routine screening of all neonates for G6PD deficiency in the group considered for this investigation, hence the relationship between the condition and the disease cannot be remarked on through this study. A substantial correlation between neonatal hyperbilirubinemia and G6PD deficiency was discovered in a study by Sinha R *et al* [36].

This study didn't include any newborns who had hypothyroidism. Breast milk jaundice was identified as the most frequent cause of infant hyperbilirubinemia by Agarwal SK *et al* [37] in their investigation. One newborn was found to have jaundice from breast milk. The diagnosis was made by excluding other possibilities because the baby in question had persistent jaundice with no obvious explanations.

Although other studies [24-27,28-37]. showed a significant association between a history of sibling with hyperbilirubinemia and NNH, this study found no evidence of such an association. Among family history, the history of a sibling with hyperbilirubinemia requiring phototherapy and positive family history for hyperbilirubinemia were taken into consideration. The impact of different aetiologies was not taken into account in this investigation; only the most common one was.

Conclusion

In the population we studied, this study highlights breastfeeding issues as the most prevalent modifiable risk factor linked to neonatal hyperbilirubinemia. With the right prenatal treatment, risk factors like IUGR, PROM, and preterm may be able to be modified.

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