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Prospective Study of Distribution of Different Causes of Pathological Unconjugated Hyperbilirubinemia Risk Factor and Outcome

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ABSTRACT
The distribution of various pathological unconjugated hyperbilirubinemia causes and their consequences among neonates presenting to the pediatrics department of a tertiary care teaching hospital in Gujarat, India, were evaluated in the current study. The effects of pathological unconjugated hyperbilirubinemia on neonates presenting to the pediatrics department of a Gujarat, India tertiary care teaching hospital were evaluated. After obtaining permission from the institutional ethics committee, 81 neonates presenting or referred to the NICU of the department of Pediatrics of the study institution with a diagnosis of unconjugated neonatal hyperbilirubinemia were recruited into the study. It was observed that the mean hemoglobin level was 15.5±3.2 gm/dl, mean total leukocyte count was 10.3±4.9 X10^3/cm^3, total platelet count was 2.1±1.1 lakh/cm^3, mean CRP was 17.6±40.3 and mean hematocrit was 46.3±10.8 respectively in the participants at the time of their admission. The most frequent causes of unconjugated neonatal hyperbilirubinemia in the neonates were sepsis and ABO incompatibility. The condition was effectively managed with a significant reduction in levels of indirect and transcutaneous bilirubin levels and a high survival rate. The distribution of causes did not differ significantly between male and female neonates.

INTRODUCTION

It has been observed that during the first week of life, nearly 60% of all term newborns exhibit significant clinical hyperbilirubinemia, manifesting as jaundice[1]. Recent reports of kernicterus in otherwise healthy new borns highlight the serious public health concern associated with neonatal jaundice. This is regrettable, though, because the majority of kernicterus cases-especially those involving near-term and term new borns-can be prevented if they are promptly detected and treated[2]. Research has shown that 84% of newborns admitted to hospitals exhibit some form of abnormality in their serum bilirubin levels. Moreover, it has been discovered that the most frequent reason for hospital readmission during the neonatal period is hyperbilirubinemia. It has been noted that hospitalized newborns with hyperbilirubinemia have a higher chance of developing a variety of ailments, including metabolic complications, infections that can arise in both the community and hospital and other issues. Furthermore, the newborn's repeated readmissions to hospitals place an excessive financial strain on the family and the healthcare system. Neonatal hyperbilirubinemia (NHB) is a medical condition that is largely preventable, but if left untreated, it can have serious consequences. In addition to the potentially lethal kernicterus, NHB raises the chance of developing major illnesses such cerebral palsy, apnea, seizure disorders, sensorineural deafness and learning disabilities. For a newborn to be healthy, early NHB detection and treatment are therefore essential. The American Academy of Paediatrics (AAP) states that within 24 hours of delivery, newborns should be routinely checked for any abnormalities in bilirubin levels in their blood samples. Nevertheless, these guidelines are frequently ignored in resource-constrained environments like those found in India, which results in a sizable fraction of subclinical NHB cases going undetected. In addition, the general public's ignorance of NHB and its negative effects causes parents to overlook the condition's warning signs, which exacerbates the issue.

RESULT AND ANALYSIS

The mean age at admission for the babies was 3.3±2.6 days. The male: female ratio in the present study was 1:0.65.The mean birth weight of the study participants was 2.5±0.6 kg. Most of the study participants were admitted with a weight of between 1.5 and 2.5 kg. The mean weight of the study participants at admission was 2.4±0.6 kg. The mean gestational age of the mothers at birth was 38.5±2.7 weeks. 53.1% of the participants were born to primipara mothers. About 12.3% of the mothers were given anti-D antibodies in their previous pregnancy. 3.7% of the mothers presented with leaking p/v at the time of their presentation for childbirth (Table 1-4). The lower segment cesarean section rate was 30.9%.ABO incompatibility was the most common diagnosis for indirect neonatal hyperbilirubinemia in the sample (61.7%), followed by sepsis (37%), Rh incompatibility (14.8%), G6PD deficiency (8.6%), idiopathic hyperbilirubinemia (6.2%), polycythemia (3.7%) and cephalhematoma (2.5%) respectively (Table 5). It was observed that while the prevalence of ABO incompatibility, sepsis, polycythemia and idiopathic unconjugated neonatal hyperbilirubinemia were higher in female neonates. Most participants were administered double surface phototherapy (DSPT), followed by triple surface phototherapy (TSPT) and single surface phototherapy respectively (SSPT). About 53.1% had to be put on Ryle's tube feeding. 42% of the study participants were given IV fluids and 37% of the participants were administered antibiotics as a part of their management. About 9.9% of the participants required exchange transfusion (Table 6 and 7). The mean hospital stay for the study participants was 5.1±3.3 days and the neonatal death rate was 2.5% (Table 8). At the time of discharge, there was a

Table 1: Distribution of study participants according to the mode of delivery (n = 81)

Mode of delivery	Frequency	Percentage
Spontaneous vaginal delivery	56	69.1
Lower segment caesarean section	25	30.9
Total	81	100

Table 2: Distribution of study participants according to their bilirubin levels at admission (n = 81)

Bilirubin	Mean	SD
Total	17.5	5.1
Indirect	16.6	4.8
direct	0.7	0.8
Transcutaneous bilirubin	19.2	5.1

Table 3: Distribution of study participants according to their final diagnosis of cause of indirect hyperbilirubinemia (n = 81)

Diagnosis	Frequency	Percentage
ABO incompatibility	50	61.7
Sepsis	30	37
Rh incompatibility	12	14.8
G6PD deficiency	7	8.6
Idiopathic	5	6.2
Polycythemia	3	3.7
Cephalhematoma	2	2.5

Table 4: Distribution of study participants according to their final diagnosis of cause of indirect hyperbilirubinemia with regard to their sex (n = 81)

Diagnosis	Males (%)	Female (%)	p-value
ABO incompatibility	28 (57.1)	19 (59.4)	0.975
Sepsis	17 (34.7)	13 (40.6)	0.761
Rh incompatibility	8 (16.3)	4 (12.5)	0.878
G6PD deficiency	4 (8.2)	2 (6.3)	0.911
Idiopathic	3 (6.1)	2 (6.3)	0.654
Polycythemia	1 (2.0)	2 (6.3)	0.704
Cephalhematoma	2 (4.1)	0 (0)	0.671

Table 5: Distribution of study participants according to their hemogram parameters at admission (n = 81)

CBC	Mean	SD
Hemoglobin	15.5	3.2
Total leukocyte count	10.3×10^3	4.9×10^3
Total platelet count	2.1	1.1
CRP	17.6	40.3
Hematocrit	46.3	10.8

Table 6: Distribution of study participants according to phototherapy status (n = 81)

Phototherapy	Frequency	Percentage
SSPT	8	9.9
DSPT	40	49.4
TSPT	33	40.7
Total	81	100

Table 7: Distribution of study participants according to feeding status (n = 81)

Feeding	Frequency	Percentage
Breastfeeding only	22	27.2
Ryles tube feeding only	43	53.1
spoon feeding only	3	3.7
BF+RTF	1	1.2
BF+SF	1	1.2
SF+RTF	11	13.6
Total	81	100

Table 8: Distribution of study participants according to outcome (n = 81)

Outcome	Frequency	Percentage
Discharge	78	96.3
Death	2	2.5
Discharged against medical advice	1	1.2
Total	81	100

statistically significant decrease in the total serum bilirubin (<0.001), direct (0.001) and indirect bilirubin (<0.001) and transcutaneous bilirubin (<0.001) levels in the study participants.

DISCUSSION

Hyperbilirubinemia is a significant complication in newborns. Neonatal hyperbilirubinemia is a condition7 that is particularly common in developing nations like India. This condition is made more complicated by the numerous maternal risk factors that put the neonates at risk of developing altered bilirubin metabolism.

Unconjugated hyperbilirubinemia has several different underlying diagnoses that are linked to its development, suggesting a diverse causative pathway. Furthermore, because of the innate demographic and geographic variations, the precise epidemiology of these conditions varies from place to place and population to population. Thus, in the current study, 81 neonates who were either born at or referred to a tertiary care referral hospital in Gujarat, India, were used as a sample and the various causes of pathological neonatal hyperbilirubinemia and its consequences were investigated. The neonates in the current study had a mean age of 3.3±2.6 days at admission, with the majority of them being admitted 1-2 days after birth. According to the results of this study, pathological unconjugated neonatal hyperbilirubinemia typically manifests itself within 72 hours of birth. Kulkarni *et al*.[3] and Ajay *et al*. both noted in their studies on the subject that the majority of newborns who presented with neonatal hyperbilirubinemia did so within the first three days of life[3].

In the current investigation, the incidence of unconjugated neonatal hyperbilirubinemia was found to be disproportionately male. The pertinent literature has extensively documented the increased risk of neonatal hyperbilirubinemia in male babies[4]. Male neonates were more likely than female neonates to be affected by the condition, according to studies by Khairy *et al*. and Mishra *et al*. Olusanya *et al*.[5] conducted a systematic review of the literature on neonatal hyperbilirubinemia and found that most studies on neonates in the Indian subcontinent suggested that males were more likely to have the condition[6,7]. Similar results were reported by Ajay *et al*., Devi *et al*. and Kassa *et al*.[8] when they studied neonates born to mothers in developing nations[4]. This can be explained by the population characteristics in each geographical region as well as the fact that certain conditions, like G6PD deficiency, are more common in men and cause unconjugated neonatal hyperbilirubinemia.

The majority of study participants had a mean birth weight of 2.5±0.6 kg, which is within the normal range for newborns. However, there was a high prevalence of low birth weight (43.3%), with 8.6% of participants having a very low birth weight (<1.5 kg). Wong *et al*. found no evidence of a significant correlation between the neonates' birth weight and the development of neonatal hyperbilirubinemia in their study." Still, other authors who have written about the subject, like Mostafa *et al*. and Boksabadi *et al*. revealed results resembling those of the current investigation, noting that neonates with low birth weights had a high prevalence of pathological neonatal hyperbilirubinemia." Olysanya *et al*. noted in their systematic review that a risk factor for the development of neonatal hyperbilirubinemia was low birth weight, which was significantly correlated with the condition[5].

It was found in this study that 53.1% of the participants were primi mothers at birth. Afroze *et al*.[6] reported similar findings to the current study, noting that more than 50% of the mothers whose neonates developed neonatal hyperbilirubinemia were primi mothers, despite the observation that there was no significant association between the parity of mothers and the development of neonatal hyperbilirubinemia in their neonates[6]. About 12.3% of the moms reported using anti-D during a prior pregnancy, suggesting that they had experienced Rh incompatible pregnancies previously. This was a significant finding because unconjugated neonatal hyperbilirubinemia is frequently caused by ABO incompatibility. According to this research, women who have previously experienced ABO incompatibility are more likely to experience complications during a subsequent pregnancy, which raises the possibility that their unborn child may experience neonatal hyperbilirubinemia. Certain groups, including

Devi *et al*. and Boksabadi *et al*., have reported that cesarean section deliveries provide protection against neonatal hyperbilirubinemia[7]. That was not, however, the case in the current investigation. The study's prevalence of newborns delivered via lower segment cesarean section (30.9%) was comparable to the country as a whole, which was reported to be 32.7% by the nationally representative National Family Health Survey 5 (NFHS-5).

Determining the various causes of pathological unconjugated neonatal hyperbilirubinemia in the study population was the main goal of the current investigation. ABO incompatibility was found to be the most frequent cause of the condition among the patients (61.7%), with sepsis (37%), Rh incompatibility (14.8%), G6PD deficiency (8.6%), polycythemia (3.7%) and cephalhematoma (2.5%) following in order of prevalence. According to numerous reports, one of the most frequent causes of unconjugated neonatal hyperbilirubinemia is ABO incompatibility. Exaggerated hemolysis is the main pathophysiological mechanism causing hyperbilirubinemia in neonates incompatible with ABO. 42 Maternal anti-A and anti-B antibodies of the immunoglobulin G subclass in mothers with blood group O cross the placental barrier and cause hemolysis in newborns with blood types A, B, or AB in immune-mediated hemolysis, such as in ABO incompatibility. Unconjugated neonatal hyperbilirubinemia is the resultant condition. ABO incompatibility is widespread in India, as the results of this study clearly show. Authors like Malik *et al*., Mostafa *et al*. and Kassa *et al*.[8] made similar observations in which they discovered that the most common cause of unconjugated neonatal hyperbilirubinemia was ABO incompatibility[8]. Another significant factor contributing to unconjugated neonatal hyperbilirubinemia is sepsis. Unconjugated neonatal hyperbilirubinemia is the result of non-immune mediated hemolysis, which is brought on by sepsis, particularly severe forms of it. An excess of free radicals is also produced in the bodies of neonates in septic states, which causes oxidative damage to red blood cells, hemolysis and an elevation of the unconjugated bilirubin load." Many authors have reported on the prevalence of sepsis as a cause of neonatal hyperbilirubinemia, including Devi *et al*. and Malik *et al*. Sabzehi *et al*. and Kumar and Batcha evaluated the causes and risk factors of neonatal hyperbilirubinemia and found that sepsis resulting from a urinary tract infection was the most frequent cause of unconjugated neonatal hyperbilirubinemia in the neonates in their study sample[9]. Still a leading cause of neonatal death in developing nations like India is sepsis. The results of this investigation confirm its significance as a risk factor for the emergence of additional severe adverse neonatal conditions, like unconjugated neonatal hyperbilirubinemia.

The incompatibility of the mother's Rh factor with her unborn child is another significant immune system-mediated hemolytic jaundice in the newborn. 48 This condition involves the development of antibodies against Rh antigen in a Rh-negative mother who has previously been exposed to Rh positive RBCs from a previous pregnancy, whether it was viable or not. Although the antigens at first belong to the IgM subclass and cannot pass through the placental barrier, in later pregnancies, IgG antibodies begin to be produced. These antibodies can pass through the placental barrier and cause RBC hemolysis in the fetus whose blood type is Rh positive." Due to the high immunogenicity of Rh antigen, hemolytic diseases are typically severe and frequently result in the death of the fetus, a condition known as hydrops fetalis. Despite having a 6% incidence in the general Indian population, Rh incompatibility is a major contributing factor to unconjugated hyperbilirubinemia, as demonstrated by the results of the current study, which showed that 14.8% of cases had this diagnosis. The results of earlier research on the subject of unconjugated neonatal hyperbilirubinemia in neonates, including studies by Bedi *et al*., Arwa *et al*., Aygun *et al*. and Routay *et al*., were consistent with the current investigation. It was noted that although Rh incompatibility was not the primary cause of hemolytic jaundice in the neonates, it was a significant contributing factor, accounting for a significant percentage of unconjugated neonatal hyperbilirubinemia among the patients evaluated in those investigations[10].

Studies have shown that, aside from sepsis, G6PD deficiency is one of the most frequent causes of non-immune mediated hemolytic disease in neonates, which results in unconjugated hyperbilirubinemia. The most prevalent RBC enzyme defect is G6PD enzyme deficiency, which affects 1.6% of Indians overall.The X-linked recessive trait that causes this condition is an inborn lack of the enzyme glucose-6 phosphatase dehydrogenase, which shields red blood cells from oxidative damage by converting nicotinamide adenine dinucleotide phosphate (NADP) to nicotinamide adenine dinucleotide phosphate hydrogenase (NADPH)[11].

They developed unconjugated neonatal hyperbilirubinemia as a result of G6PD deficiency. Other studies also found similar results. According to Sabzehi *et al*.'s research, 5% of people have G6PD deficiency. About 5.4% was the prevalence reported by Wong *et al*. However, writers such as Arwa *et al*. (2%), Routay *et al*. (3.3%) and Malik *et al*. (1.7%) noted a lower prevalence but concluded that, in the neonates they evaluated for their research, it was a significant

cause of unconjugated neonatal hyperbilirubinemia[12]. The study sample's comparatively high prevalence of the condition can be explained by the fact that the population they belong to has a higher prevalence of the same condition, since the rates of mutations causing G6PD deficiency have been found to differ significantly between populations and geographic areas." Unconjugated neonatal hyperbilirubinemia frequently has more idiopathic, or unidentified, causes than known ones. This is seen in studies by Kulkarni *et al*. and Ajay *et al*., which found that idiopathic neonatal hyperbilirubinemia was the most common diagnosis in their study sample. Idiopathic neonatal hyperbilirubinemia, on the other hand, was found to be less common in the current study, affecting 6.2% of the neonates. Cephalhematoma and polycythemia are rare causes of non-immune mediated unconjugated neonatal hyperbilirubinemia because they cause the neonate's body to produce a significant amount of bilirubin, which causes jaundice. Three (3.7%) and two (2.5%) of the participants in the current study had polycythemia, respectively and cephalhematoma. The incidence of cephalhematoma and polycythemia was lower than that of Arwa *et al*. (8%) and Routay *et al*. (5.4%). This could be attributed to the study population's physiological makeup as well as the care that the attending physicians provided during labor and the post-natal period at the study institution[13].

Upon analyzing the sex distribution of the different causes of unconjugated neonatal hyperbilirubinemia, it was found that although the prevalence of sepsis, idiopathic unconjugated neonatal hyperbilirubinemia, ABO incompatibility and polycythemia was higher in female neonates, the differences did not reach statistical significance. Conversely, there was a higher incidence of Rh incompatibility and cephalhematoma in male neonates; however, the differences did not reach statistical significance upon analysis. As an X-linked disorder, G6PD deficiency was naturally more common in male patients; however, the non-significant difference suggests that there are mutations in the study population that also predispose female neonates to have the condition. These results are consistent with the condition's epidemiology and with research conducted by Ullah *et al*. and Boksabadi *et al*. The results suggest that new-borns with unconjugated neonatal hyperbilirubinemia are nearly equally likely to be male or female[14].

The participants' admission values were as follows: mean hemoglobin level: 15.5±3.2 g dL^{-1}, mean total leukocyte count: 10.3±4.9 X103/cm^3, mean total platelet count: 2.1±1.1 lakh/cm^3, mean CRP: 17.6±40.3 and mean hematocrit: 46.3±10.8. As expected given the hemolytic nature of the disorders, the hemoglobin, platelet count and hematocrit were generally lower than normal in the patients with ABO incompatibility, Rh incompatibility and G6PD deficiency than in the majority of the neonates. Participants' total leukocyte counts were also elevated, particularly in those who had been diagnosed with sepsis and infections. The majority of the conditions that cause unconjugated neonatal hyperbilirubinemia also cause inflammation, which is why the study participants' mean CRP values were high and the participants' CRP levels were also found to be generally high. The increase in unconjugated bilirubin levels in a new-born's serum is known as unconjugated hyperbilirubinemia. The current study found that the mean levels of total serum bilirubin were 17.5±5.1 mg dL^{-1} and indirect bilirubin were 16.6±4.8 mg/dl. The study only included patients with unconjugated hyperbilirubinemia, thus the mean direct bilirubin level was 0.7±0.8 mg dL^{-1}. One of the cornerstones of the diagnosis of unconjugated hyperbilirubinemia is the estimation of transcutaneous bilirubin. Unconjugated hyperbilirubinemia in neonates can be effectively diagnosed using this non-invasive bilirubin estimation method. The average transcutaneous bilirubin level was 19.2±5.1 mg dL^{-1} when the research subjects were admitted. The results of this investigation are consistent with those published in previous studies by authors like Kulkarni *et al*. (17.6±4.1 mg $dL^{-}1$) and Afroze *et al*.[6] (16.6±4.6 mg dL^{-1}). When it comes to treating neonatal hyperbilirubinemia, phototherapy is the preferred modality. Double and triple surface phototherapy has been shown in randomized controlled trials to be highly beneficial in lowering the bilirubin levels of neonates with unconjugated neonatal hyperbilirubinemia[15]. Therefore, these two types of phototherapies are primarily performed in the study institution, with single surface phototherapy being used in comparatively milder cases. Given that 96.3% of the patients were released in good health, it was evident that the treatments were successful in reducing the effects of neonatal hyperbilirubinemia. In addition to phototherapy, the majority of the patients in this study needed additional care for their specific conditions. The most frequent intervention was a change in feeding habits. While in certain cases it is advised to breastfeed exclusively to a neonate experiencing jaundice, this is not always the case[16]. These circumstances include serious illnesses like sepsis or massive haemolysis, as well as situations where breastfeeding is the reason for the jaundice. Most of the patients in this study arrived at the research facility in a critically sick state. Several of them needed to be switched to alternate feeding techniques, like spoon and Ryle's tube feeding, while they were in this state. Nonetheless, breastfeeding was

practiced whenever it was feasible, with about one-third of the participants continuing to receive breast milk during their time at the research facility. IV fluid supplementation was one of the additional cares given to the neonates, which was necessary for 42% of the patients. Antibiotic management was administered, particularly in cases where the neonates had sepsis (37% of the patients). The first method of treating neonatal jaundice that was ever successfully employed was exchange transfusion. When phototherapy fails, it is currently the second line of treatment for severe unconjugated hyperbilirubinemia. Exchange transfusion quickly eliminates haemolysis and bilirubin, which results in the removal of antibodies from the bloodstream. In the study institution, a double volume exchange blood transfusion (160-180 mL kg^{-1}) was administered to 8 patients whose phototherapy had failed. Intravenous (IV) immunoglobulin (IVIG) was used for two Rh incompatibility patients who did not respond to standard care. As previously mentioned, the neonates' results in this study demonstrate that the management of unconjugated neonatal hyperbilirubinemia was successful. It was noted that 96.3% of the patients were released from the research facility in good health. Due to multiorgan dysfunction syndrome (MODS) brought on by severe sepsis, only 2 neonates perished. The participants' average hospital stay was 5.1±3.3 days. This was either the same as or less than what other authors, like Kassa *et al*.[8] (5.4±1.1 days), Arwa *et al*. (7.2±2.2 days) and Routay *et al*., had reported. Both Afroze *et al*.[6] (6.6±1.6 days) and (5.9±4.4 days) in their investigations. These results show that the study institution's treatment protocol was successful in treating the patients' unconjugated neonatal hyperbilirubinemia. The participants' lower serum bilirubin levels upon discharge provide additional proof of this. The mean total serum bilirubin was found to be 10.5±2.3, 10.1±2.2 mg dL^{-1} for indirect bilirubin, 0.6±0.9 mg dL^{-1} for direct bilirubin and 12.3±2.4 mg dL^{-1} for transcutaneous bilirubin at the time of discharge. These levels were found to be significantly lower by statistical analysis than what the study participants had when they were admitted to the study institution.

CONCLUSION

We conclude that, the most frequent causes of unconjugated neonatal hyperbilirubinemia in the neonates were sepsis and ABO incompatibility. The condition was effectively managed with a significant reduction in levels of indirect and transcutaneous bilirubin levels and a high survival rate. The distribution of causes did not differ significantly between male and female neonates.

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