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Clinical evaluation of factors responsible for neonatal hyperbilirubinemia in by estimation of 24 hour serum bilirubin levels

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Abstract
The new born needs the utmost care for all the neonatal problems for its better outcome in the future and neonatal hyperbilirubinemia is one of them; with its timely detection and management a good prognosis can be predicted. Discharging healthy term babies from the hospital after delivery at increasingly earlier postnatal ages has recently become a common practice for medical, social and economic reasons. However, it has been seen that newborns whose post-delivery hospital stay is less than 72 hours are at a significantly greater risk for readmission than those whose stay is >72 hours. Hyperbilirubinemia is the most commonly reported cause of readmission during the early neonatal period. Hence based on above findings the present study was planned for Clinical Evaluation of Factors Responsible for Neonatal hyperbilirubinemia in by Estimation of 24 Hour Serum Bilirubin Levels.

The prospective study conducted at District Female Hospital, Basti during the Period January 2016 to December 2017 in Paediatrics Department and total 2019 full term neonates were enrolled in the present study. Cord Serum Bilurubin and Albumin levels were evaluated in all enrolled cases. Blood samples were drawn by venipuncture into a micro-capillary, which was centrifuged in RM 12 C micro-centrifuge, at the rate of 10000 rpm for 5 min. Bilirubin estimation was done spectrophotometrically using twin beam method (455 and 575 nm wave lengths) and analyzed by Wako Bilirubin Tester Model SE 101 DII. Wako Bilirubin Tester requires only 0.05 ml of serum that can be analyzed directly in the capillary tube after whole blood sample in the micro-capillary has been centrifuged.

The most of the cases have developed the significant Neonatal hyperbilurubinemia. 67.9% cases had albuin level more than 2.8 gm/dl. An influencing effect of early discharge on morbidity and mortality of newborns has not been established yet. Making policies against early discharge will not be practical in the present scenario where there are economic constraints, few hospital beds and a very large patient load.

Keywords: neonatal hyperbilirubinemia, total serum bilirubin, etc

Introduction

Neonatal physiologic jaundice results from simultaneous occurrence of the following two phenomena [1]: Bilirubin production is elevated because of increased breakdown of fetal erythrocytes. This is the result of the shortened lifespan of fetal erythrocytes and the higher erythrocyte mass in neonates [2, 3].

Hepatic excretory capacity is low both because of low concentrations of the binding protein ligandin in the hepatocytes and because of low activity of glucuronyl transferase, the enzyme responsible for binding bilirubin to glucuronic acid, thus making bilirubin water soluble (conjugation).

Bilirubin is produced in the reticuloendothelial system as the end product of heme catabolism and is formed through oxidation-reduction reactions. Approximately 75% of bilirubin is derived from hemoglobin, but degradation of myoglobin, cytochromes, and catalase also contributes. In the first oxidation step, biliverdin is formed from heme through the action of heme oxygenase, the rate-limiting step in the process, releasing iron and carbon monoxide. The iron is conserved for reuse, whereas carbon monoxide is excreted through the lungs and can be measured in the patient's breath to quantify bilirubin production.

Next, water-soluble biliverdin is reduced to bilirubin, which, because of the intramolecular hydrogen bonds, is almost insoluble in water in its most common isomeric form (bilirubin IXα Z, Z). Because of its hydrophobic nature, unconjugated bilirubin is transported in the plasma tightly bound to albumin. Binding to other proteins and erythrocytes also occurs, but the physiologic role is probably limited. Binding of bilirubin to albumin increases postnatally with age and is reduced in infants who are ill.

The presence of endogenous and exogenous binding competitors, such as certain drugs, also decreases the binding affinity of albumin for bilirubin. A minute fraction of unconjugated bilirubin in serum is not bound to albumin. This free bilirubin is able to cross lipid-containing membranes, including the blood-brain barrier, leading to neurotoxicity. In fetal life, free bilirubin crosses the placenta, possibly by a carrier-mediated process [4], and excretion of bilirubin from the fetus occurs primarily through the maternal organism.

When it reaches the liver, bilirubin is transported into liver cells, where it binds to ligandin. Uptake of bilirubin into hepatocytes increases with increasing ligandin concentrations. Ligandin concentrations are low at birth but rapidly increase over the first few weeks of life. Ligandin concentrations may be increased by the administration of pharmacologic agents such as phenobarbital.

Bilirubin is bound to glucuronic acid (conjugated) in the hepatocyte endoplasmic reticulum in a reaction catalyzed by

uridine diphospho glucuronosyltransferase (UDPGT). Monoconjugates are formed first and predominate in the newborn. Diconjugates appear to be formed at the cell membrane and may require the presence of the UDPGT tetramer.

Bilirubin conjugation is biologically critical because it transforms a water-insoluble bilirubin molecule into a water-soluble molecule. Water-solubility allows conjugated bilirubin to be excreted into bile. UDPGT activity is low at birth but increases to adult values by age 4-8 weeks. In addition, certain drugs (phenobarbital, dexamethasone, clofibrate) can be administered to increase UDPGT activity.

Infants who have Gilbert syndrome or who are compound heterozygotes for the Gilbert promoter and structural mutations of the UDPGT1A1 coding region are at an increased risk of significant hyperbilirubinemia. Interactions between the Gilbert genotype and hemolytic anemias such as glucose-6-phosphatase dehydrogenase (G-6-PD) deficiency, hereditary spherocytosis, or ABO hemolytic disease also appear to increase the risk of severe neonatal jaundice.

Further, the observation of jaundice in some infants with hypertrophic pyloric stenosis may also be related to a Gilbert-type variant. Genetic polymorphism for the organic anion transporter protein OATP-2 correlates with a 3-fold increased risk for developing marked neonatal jaundice. Combination of the OATP-2 gene polymorphism with a variant UDPGT1A1 gene further increases this risk to 22-fold [5]. Studies also suggest that polymorphisms in the gene for glutathione-S-transferase (ligandin) may contribute to higher levels of total serum bilirubin.

Thus, some interindividual variations in the course and severity of neonatal jaundice may be explained genetically [6]. As the impact of these genetic variants is more fully understood, development of a genetic test panel for risk of severe and/or prolonged neonatal jaundice may become feasible [7].

Once excreted into bile and transferred to the intestines, bilirubin is eventually reduced to colorless tetrapyrroles by microbes in the colon. However, some deconjugation occurs in the proximal small intestine through the action of B-glucuronidases located in the brush border. This unconjugated bilirubin can be reabsorbed into the circulation, increasing the total plasma bilirubin pool. This cycle of uptake, conjugation, excretion, deconjugation, and reabsorption is termed 'enterohepatic circulation'. The process may be extensive in the neonate, partly because nutrient intake is limited in the first days of life, prolonging the intestinal transit time.

In mother-infant dyads who are experiencing difficulties with the establishment of breast feeding, inadequate fluid and nutrient intake often leads to significant postnatal weight loss in the infant. Such infants have an increased risk of developing jaundice through increased enterohepatic circulation, as described above. This phenomenon is often referred to as breastfeeding jaundice and is different from the breast milk jaundice described below.

Certain factors present in the breast milk of some mothers may also contribute to increased enterohepatic circulation of bilirubin (breast milk jaundice). β-glucuronidase may play a role by uncoupling bilirubin from its binding to glucuronic acid, thus making it available for reabsorption. Data suggest that the risk of breast milk jaundice is significantly increased in infants who have genetic polymorphisms in the coding sequences of the UDPGT1A1 [8] or OATP2 genes. Although the mechanism that causes this phenomenon is not yet agreed on, evidence suggests that supplementation with certain breast milk substitutes may reduce the degree of breast milk jaundice

Neonatal jaundice, although a normal transitional phenomenon in most infants, can occasionally become more pronounced. Blood group incompatibilities (eg, Rh, ABO) may increase bilirubin production through increased hemolysis. Historically, Rh isoimmunization was an important cause of severe jaundice, often resulting in the development of kernicterus. Although this condition has become relatively rare in industrialized countries following the use of Rh prophylaxis in Rh-negative women, Rh isoimmunization remains common in low- and middle-income countries (LMICs).

Nonimmune hemolytic disorders (spherocytosis, G-6-PD deficiency) may also cause increased jaundice, and increased hemolysis appears to have been present in some of the infants reported to have developed kernicterus in the United States in the past 15-20 years. The possible interaction between such conditions and genetic variants of the Gilbert and UDPGT1A1 genes, as well as genetic variants of several other proteins and enzymes involved in bilirubin metabolism, is discussed above. More recently, 3 novel mutations in genes encoding either alpha or beta spectrin (SPTA1 or SPTB) were found in 3 unrelated neonates with nonimmune hemolytic jaundice. These discoveries also highlight the challenges involved in the common use of the terms physiologic jaundice and pathologic jaundice. Although physiologic jaundice is a helpful concept from a didactic perspective, applying it to an actual neonate with jaundice is more difficult.

Consider the following metaphor: Think of total serum bilirubin in neonatal jaundice as a mountain covered by a glacier. If a measurement of the height of the mountain is taken when standing on the summit, the amount of rock and the amount of ice that comprise this measurement is unclear. The same is true for many total serum bilirubin values obtained in neonatal jaundice. An underpinning of physiologic processes and pathological process (eg, Rhesus incompatibility) may clearly contribute to the measurement. However, how much of the measured total value comes from each of these components is unclear. Also, because genetic variants in bilirubin metabolism are only exceptionally pursued in the diagnostic work-up of infants with jaundice, their possible contribution to the measured total serum bilirubin is usually unknown.

Physiologic jaundice is caused by a combination of increased bilirubin production secondary to accelerated destruction of erythrocytes, decreased excretory capacity secondary to low levels of ligandin in hepatocytes, and low activity of the bilirubin-conjugating enzyme uridine diphospho glucuronosyltransferase (UDPGT).

Pathologic neonatal jaundice occurs when additional factors accompany the basic mechanisms described above. Examples include immune or nonimmune hemolytic anemia, polycythemia, and the presence of bruising or other extravasation of blood. Decreased clearance of bilirubin may play a role in breast feeding jaundice, breast milk jaundice, and in several metabolic and endocrine disorders.

An estimated 50% of term and 80% of preterm infants develop jaundice, typically 2-4 days afer birth [3]. Neonatal hyperbilirubinemia is extremely common because almost

every newborn develops an unconjugated serum bilirubin level of more than 30 µmol/L (1.8 mg/dL) during the first week of life. Incidence figures are difficult to compare because authors of different studies do not use the same definitions for significant neonatal hyperbilirubinemia or jaundice. In addition, identification of infants to be tested depends on visual recognition of jaundice by health care providers, which varies widely and depends both on observer attention and on infant characteristics such as race and gestational age [9].

With the above caveats, epidemiologic studies provide a frame of reference for estimated incidence. In 1986, Maisels and Gifford reported 6.1% of infants with serum bilirubin levels of more than 220 µmol/L (12.9 mg/dL) [10]. In a 2003 study in the United States, 4.3% of 47,801 infants had total serum bilirubin levels in a range in which phototherapy was recommended by the 1994 American Academy of Pediatrics (AAP) guidelines, and 2.9% had values in a range in which the 1994 AAP guidelines suggest considering phototherapy [11]. In some LMICs, the incidence of severe neonatal jaundice may be as much as 100 times higher than in higher-income countries [12].

Incidence varies with ethnicity and geography. Incidence is higher in East Asians and American Indians and lower in Africans. Greeks living in Greece have a higher incidence than those of Greek descent living outside of Greece. Incidence is higher in populations living at high altitudes. In 1984, Moore *et al.* reported 32.7% of infants with serum bilirubin levels of more than 205 µmol/L (12 mg/dL) at 3100 m of altitude [13].

A study from Turkey reported significant jaundice in 10.5% of term infants and in 25.3% of near-term infants. Significant jaundice was defined according to gestational and postnatal age and leveled off at 14 mg/dL (240 µmol/L) at 4 days in preterm infants and 17 mg/dL (290 µmol/L) in the term infants. Severe neonatal jaundice is 100-fold more frequent in Nigeria than in industrialized countries. In Denmark, 24 in 100.000 infants met exchange transfusion criteria, while 9 in 100.000 developed acute bilirubin encephalopathy.

Studies seem to suggest that some of the ethnic variability in the incidence and severity of neonatal jaundice may be related to differences in the distribution of the genetic variants in bilirubin metabolism discussed above [14].

The incidence of neonatal jaundice is increased in infants of East Asian, American Indian, and Greek descent, although the latter appears to apply only to infants born in Greece and thus may be environmental rather than ethnic in origin. African infants are affected less often than non-African infants. For this reason, significant jaundice in an African infant merits a closer evaluation of possible causes, including G-6-PD deficiency. In 1985, Linn *et al.* reported on a series in which 49% of East Asian, 20% of white, and 12% of black infants had serum bilirubin levels of more than 170 µmol/L (10 mg/dL).

The possible impact of genetic polymorphisms on ethnic variation in incidence and severity should be recognized. Thus, in a study of Taiwanese infants, Huang *et al.* reported that neonates who carry the 211 and 388 variants in the UGT1A1 and OATP2 genes and who are breastfed are at particularly high risk for severe hyperbilirubinemia. Risk of developing significant neonatal jaundice is higher in male infants. This does not appear to be related to bilirubin production rates, which are similar to those in female infants.

Brain damage due to kernicterus remains a true risk, and the apparent increased incidence of kernicterus in recent years may be due to the misconception that jaundice in the healthy full-term infant is not dangerous and can be disregarded.

The incidence of kernicterus in North America and Europe ranges from 0.4-2.7 cases per 100,000 births. Death from physiologic neonatal jaundice per se should not occur. Death from kernicterus may occur, particularly in countries with less developed medical care systems. In one small study from rural Nigeria, 31% of infants with clinical jaundice tested had G-6-PD deficiency, and 36% of the infants with G-6-PD deficiency died with presumed kernicterus compared with only 3% of the infants with a normal G-6-PD screening test result. Parents should be educated about neonatal jaundice and receive written information prior to discharge from the birth hospital. The parent information leaflet should preferably be available in several languages.

A novel 2-color icterometer (Bilistrip) appears to have the potential to facilitate early maternal detection of clinically significant jaundice and help them in decision making to seek medical treatment. In a study that trained mothers in a maternity hospital to use the icterometer on the blanched skin of their infant's nose to determine absence (light yellow) or presence (dark yellow) of significant jaundice, there was a 95.8% sensitivity and 95.8% negative predictive value for detecting infants requiring phototherapy [15]. Of the 2,492 mother-infant pairs in the study, 347 (13.9%) selected dark yellow; the 2-color icterometer missed only 1 of the 24 neonates who required phototherapy.

The new born needs the utmost care for all the neonatal problems for its better outcome in the future and neonatal hyperbilirubinemia is one of them; with its timely detection and management a good prognosis can be predicted. Discharging healthy term babies from the hospital after delivery at increasingly earlier postnatal ages has recently become a common practice for medical, social and economic reasons. However, it has been seen that newborns whose post-delivery hospital stay is less than 72 hours are at a significantly greater risk for readmission than those whose stay is >72 hours. Hyperbilirubinemia is the most commonly reported cause of readmission during the early neonatal period. Hence based on above findings the present study was planned for Clinical Evaluation of Factors Responsible for Neonatal hyperbilirubinemia in by Estimation of 24 Hour Serum Bilirubin Levels.

Methodology

The prospective study conducted at District Female Hospital, Basti during the Period January 2016 to December 2017 in Paediatrics Department and total 2019 full term neonates were enrolled in the present study. Cord Serum Bilurubin and Albumin levels were evaluated in all enrolled cases. Blood samples were drawn by venipuncture into a micro-capillary, which was centrifuged in RM 12 C micro-centrifuge, at the rate of 10000 rpm for 5 min. Bilirubin estimation was done spectrophotometrically using twin beam method (455 and 575 nm wave lengths) and analyzed by Wako Bilirubin Tester Model SE 101 DII. Wako Bilirubin Tester requires only 0.05 ml of serum that can be analyzed directly in the capillary tube after whole blood sample in the micro-capillary has been centrifuged.

All the patients were informed consents. The aim and the

objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Infants with Gestational age ≥ 35 weeks (based on last Menstrual Period) and neonatal assessment by expanded New Ballard Score. Absence of significant illness – Requiring NICU admission for >12 hours. Absence of major congenital malformations. d. Residing at Patna or nearby whose parents agree to come for follow up.

Exclusion Criteria: All sick newborn babies and babies with Rh incompatibility were excluded from the study.

Results & Discussion

NEONATAL hyperbilirubinemia is a cause of concern for the parents as well as for the pediatricians. It occurs in 5-10% of healthy term infants [16, 17] and is the most common reason for readmission after early hospital discharge [18]. Concerns regarding jaundice have increased after reports of bilirubin induced brain damage occurring in healthy term infants, even without hemolysis [19]. Total serum bilirubin (TSB) in infants discharged within 48 hr of age generally shows an increasing trend and some of these infants later develop hyper-bilirubinemia. In a cohort of 500 healthy term infants, Alpay, *et al.* found that hyper-bilirubinemia (serum bilirubin 17mg/dl) occurred only after 72 hr of age. The American Academy of Pediatrics recommends that newborns discharged within 48 hours should have a follow-up visit after 2-3 days to detect significant jaundice and other problems [20]. This recommendation is not possible in our country due to limited follow up facilities in the community.

Although there has been a decrease in the length of postdelivery hospital stay for newborns, there is still much controversy about early or late discharge of mother baby dyad. Opponents of early discharge suggest many associated risk factors like hyperbilirubinemia, breast feeding difficulties, missed identification of congenital anomalies, maternal post-partum cognitive deficits [21, 22]. In various studies from different countries investigating the predictive value of first day serum bilirubin measurement on predicting the later development of significant hyperbilirubinemia has been reported to be between 1.7% to 12%. Bhutani *et al.* have prospectively followed term newborns over the first 5 days of life by measuring serum bilirubin levels daily [21, 22]. In their series of 1097 newborns, no infant who had a bilirubin level of hours of life [23].

Table 1: Demographic Details

Parameters	No. of Cases
Total Cases Enrolled	209
Gender	
Males	110
Females	99
Birth Weight (gm)	2410 – 3150
Gestational Weeks	35 – 40
Delivery Mode	
Vaginal	145
Caesarean	64
APGAR Score	8
Feeding	
Breast Feeding	184
Formula Feed	25
Gestational Acquired Disease	
Yes	10
No	199
Enclosed Haemorrhage	
Yes	0
No	209

Table 2: Clinical Jaundice & Hyperbilurubinemia

Parameters	No. of Cases
Total Cases Enrolled	209
Clinical Jaundice	135
Significant Neonatal hyperbilurubinemia	67.9%
Total Serum Bilirubin	
Less than 6 mg/dl	67
More than 6 mg/dl	142

In another study from India, a TSB value >3.99mg/dl at 18-24 hour was found to predict the subsequent hyperbilirubinemia (>15mg/dl) with sensitivity and 6 specificity of 67%. Both studies opined that a large scale study would be needed before one could mean it as 6, 12 a recommendation/ protocol for Indian population [24]. Study done at IGMC, Shimla on similar lines in 2003 (228 full term babies) concluded that 24±6 hour TSB value >6.4 mg/dl has the best combination of SN (87.5%), NPV (97.9%) & SP (80.1%). The incidence of hyperbilirubinemia was 12%. But higher mean TSB values may reflect the effect of high altitude & ethnic factor. But this relied heavily on clinical assessment which may be inaccurate [25].

Bhutani *et al.* showed in a large cohort that infants who develop hyperbilirubinemia have serum bilirubin levels, which are in higher percentiles soon after birth. The authors created percentile charts of serum bilirubin level at different postnatal ages in near-term and term infants who were direct Coombs test negative. They found that 6.1% of neonates had pre-discharge serum bilirubin 95th percentile; 32.1% of these infants showed hyperbilirubinemia sub-sequently. Neonates with pre-discharge TSB levels in the low risk zone (< 40th percentile) did not show hyperbilirubinemia subsequently. However, there was an important source of bias in this study. Out of around 13,000 neonates,

subsequent bilirubin estimation could be done in only around 25%. The infants included those who came for follow up or were referred by their primary physicians. A large number of infants were thus not included. It is likely that infants without significant problems were not included while developing these percentile charts [26].

Alpay *et al.* in 2000 by a similar prospective study in Turkey concluded that use of 6mg/dl as critical value at 24 hours of life predicted nearly all term neonates (SN of 90% & NPV of 97.9%) with subsequent risk of significant hyperbilirubinemia (>17mg/dl) & will determine all those requiring phototherapy later on. Only 2.05% babies with 24 hour TSB < 6 mg/dl developed significant jaundice but none needed any treatment. Study did not include near term babies [28]. Similarly in study series including 1075 neonates Seidman *et al.* found 5 mg/dl as a better cut off value for predicting significant hyperbilirubinemia with low sensitivity (45.5%), high specificity (91.9%) & high negative predictive value (99%) for risk prediction [27].

Routine obstetric and neonatal hospital stays have decreased markedly in the world during past 15-20 yr, In India, stays of 12 to 24 hr are now common practice. Several studies suggest that neonatal hyperbilirubinemia is the most common cause for readmission of healthy term babies discharged early [29, 30]. Such babies require followup within 48 hours which is not possible in our setup because of difficult geographical terrain [31]. Here comes the role of prediction of neonatal hyperbilirubunemia. There have been reports of a correlation between bilirubin values on day one of life and subsequent hyperbilirubinemia. There has been a paucity of studies on this hypothesis from India. Moreover, high altitude is an independent risk factor for higher serum bilirubin levels.

Hyperbilirubinemia is one of the most common clinical sign encountered in newborns and in most cases a benign problem. If untreated, severe unconjugated hyperbilirubimenia is potentially neurotoxic. Neonatal jaundice is seen in two thirds of entirely healthy term newborn and in a greater proportion of preterm's (80%), in the first week of life. The non-physiological or pathological hyperbilirubinemia in 5-10% of healthy term newborn is the most common reason for readmission of neonates in the first week of life in the current era of early postnatal discharge from the hospital.

Early discharge of healthy term newborn after delivery has become a common practice because of medical, social and economical reasons. The most common cause for readmission during the early neonatal period is hyperbilirubinema. Such readmissions besides involving extra expenses for both family and institution, also exposes a healthy newborn to the hospital environment in addition to causing emotional problems. Universal follow up within 1-2 days of early discharge, umbilical cord bilirubin concentration at birth, routine predischarge bilirubin [32], transcutaneous bilirubin measurement as well as universal clinical assessment of risk factors for developing Jaundice are various strategies to predict significant hyperbilirubinema.

Early identification of high risk newborn is important to institute early treatment and prevention of bilirubin induced neurological dysfunction. Kernicterus although infrequent has atleast 10% mortality and atleast 70% [9] long term morbidity. Studies showed that phototherapy had an absolute risk reduction rate of 10% to 17% for prevention of serum bilirubin levels higher than 20mg/dl in healthy infants with jaundice. There is no evidence to suggest that phototherapy for neonatal hyperbrilirubinemia has any long term adverse neurodevelopmental effects [33].

Conclusion

The most of the cases have developed the significant Neonatal hyperbilurubinemia. 67.9% cases had albuin level more than 2.8 gm/dl. An influencing effect of early discharge on morbidity and mortality of newborns has not been established yet. Making policies against early discharge will not be practical in the present scenario where there are economic constraints, few hospital beds and a very large patient load.

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