

**A STUDY ON SENSITIVITY OF CORD BLOOD
BILIRUBIN LEVEL IN PREDICTING
NEONATAL HYPERBILIRUBINEMIA**

Dissertation submitted to

**THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY,
CHENNAI**

With partial fulfillment of the regulations

For the award of the degree of

MD BRANCH IV

PAEDIATRIC MEDICINE

**GOVT.KILPAUK MEDICAL COLLEGE & HOSPITAL,
CHENNAI**



**THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY,
CHENNAI, TAMILNADU**

APRIL 2017

CERTIFICATE

Certified that this dissertation entitled “**A STUDY ON SENSITIVITY OF CORD BLOOD BILIRUBIN LEVEL IN PREDICTING NEONATAL HYPERBILIRUBINEMIA**” is a bonafide work done by **DR. MARY REENA .C**, Postgraduate student of Paediatric Medicine, Government Kilpauk Medical College & Hospital, during academic year 2014-2017.

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I declare that this dissertation entitled “**A STUDY ON SENSITIVITY OF CORD BLOOD BILIRUBIN LEVEL IN PREDICTING NEONATAL HYPERBILIRUBINEMIA**” has been conducted by me at Government Kilpauk Medical College and Hospital. It is submitted in the fulfillment of the award of the degree of M.D (Paediatrics for the April 2017 examination to be held under **The Tamilnadu DR.M.G.R Medical University, Chennai**. This has not been submitted by me for the award of any degree or diploma from any other university.

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A STUDY ON SENSITIVITY OF CORD BLOOD BILIRUBIN IN PREDICTING NEONATAL HYPERBILIRUBINEMIA

INTRODUCTION

Neonatal hyperbilirubinemia is a major concern for both parents and pediatricians. Hence early discharge of healthy term neonates after delivery has become a common practice because of social, medical, economic constraints [1]. But an association between early discharge and the risk of re admission to the hospital has been increased [2]

Neonatal hyper bilirubinemia is the most common cause for readmission during early new born period [3] hence the early recognition, follow-up, and treatment of jaundice has become more important. Severe jaundice requiring exchange transfusions and kernicterus, can occur in some full-term healthy neonates discharged early with no apparent findings of hemolysis [4]. [The American Academy of Pediatrics recommends

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Neonatal hyperbilirubinemia is the most common cause for readmission during early newborn period [3] hence the early recognition, follow-up, and treatment of jaundice has become more important. Severe jaundice requiring exchange transfusions and kernicterus, can occur in some full-term healthy neonates discharged early with no apparent findings of hemolysis [4]. The American Academy of Pediatrics recommends that neonates discharged within 48 hours should have a follow-up visit after 48 to 78 hours to detect early neonatal hyperbilirubinemia [5]. But however this is not possible in our country due to limited followup facilities in the locality. Hence the concept of prediction of neonatal hyperbilirubinemia in early stage is an attractive option.

A reliable and clinically evaluated method for estimation of serum bilirubin dependent brain damage is still lacking [6,7]. Measurement of the serum bilirubin clinically is not reliable [8]. In order to implement early detection, treatment and prevention of bilirubin dependent brain damage, indicates the necessity to predict the risk of jaundice

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INTRODUCTION

Neonatal hyperbilirubinemia is a major concern for both parents and pediatricians. Hence early discharge of healthy term neonates after delivery has become a common practice because of social, medical, economic constraints ^[1]. But an association between early discharge and the risk of re admission to the hospital has been increased ^[2]

Neonatal hyperbilirubinemia is the most common cause for readmission during early new born period ³. Hence the early recognition, follow-up, and treatment of jaundice has become more important. Severe jaundice requiring exchange transfusion and kernicterus, can occur in some full-term healthy neonates discharged early with no apparent findings of hemolysis⁴. The American Academy of Pediatrics recommends that neonates discharged within 48 hours should have a follow-up visit after 48 to 78 hours to detect early neonatal hyper bilirubinemia ⁵. But however this is not possible in our country due to limited followup facilities in the locality . Hence the concept of prediction of neonatal hyper bilirubinemia in early stage is an attractive option.

A reliable and clinically evaluated method for estimation of serum bilirubin dependent brain damage is still lacking [^{6,7}]. Measurement of the serum bilirubin clinically is not reliable ⁸ In order to implement early detection, treatment and prevention of bilirubin dependent brain damage, indicates the necessity to predict the risk of jaundice in initial stage. The present study was conducted in healthy term neonates to find out the sensitivity of cord blood bilirubin in predicting neonatal hyperbilirubinemia.

- 1) To study the sensitivity of cord blood bilirubin level in predicting neonatal hyperbilirubinemia.
- 2) To find out mean cord blood bilirubin level.

DEFINITION

Neonatal Jaundice or Neonatal Hyperbilirubinemia or Neonatal Icterus (*ἰκτερός*)- is defined as yellowish staining of the skin and mucous membranes / sclera by bilirubin.

PREVALANCE OF NEONATAL HYPERBILIRUBINEMIA

About 60% term infants & 80 % preterm neonates develop jaundice during neonatal period⁽¹⁰⁾. The present study showed the incidence of neonatal hyperbilirubinemia was 22.80%. In various studies it was between 13-25%.

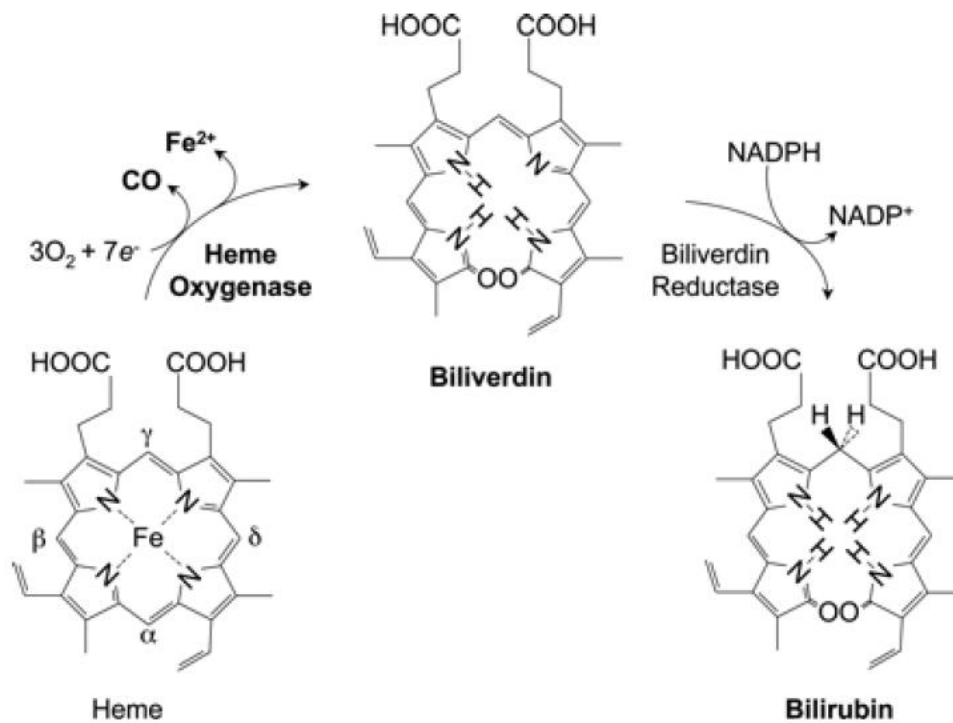
PHYSIOLOGY OF BILIRUBIN PRODUCTION

Bilirubin production

The breakdown product of haeme is bilirubin.⁽¹¹⁾ and it occurs in the phagocytic cells of RES. Heme oxygenase acts on heme and opens up the tetrapyrrole ring of heme to produce biliverdin ,carbon monoxide. The enzyme biliverdin reductase catalyze the conversion of biliverdin to bilirubin.

From non hemoglobin sources 1mg/kg of bilirubin was . produced(cytochromes,myoglobin,catalases).

METABOLISM OF HEME TO BILIRUBIN



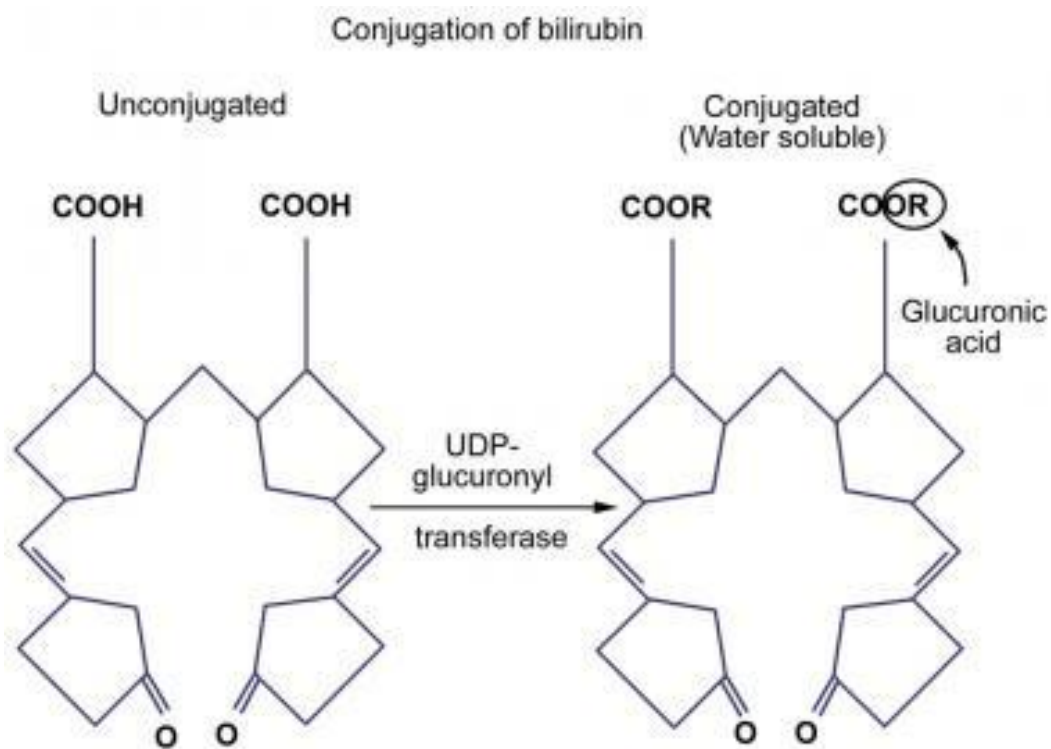
In intrauterine life the fetus requires a good haemoglobin concentration to take oxygen effectively from maternal blood and to get delivered to the fetal tissues. Immediately after delivery, with a good supply of oxygen from their own lungs, the requirement of oxygen is dropped significantly. The red blood cell of neonates have reduced life span of about 90 days compared to adults.³. Following delivery, a significant proportion of neonates may have additional haemoglobin to dispose of as a result of bruising or other losses.

Cytokines can induce heme oxygenase which causes increased breakdown of heme.⁵ In preterm infants already suffering from respiratory distress syndrome, there will be additional load of bilirubin due to cytokine release.⁶

Forms of bilirubin found in plasma

An unravelled product of haem is bilirubin, which has a three-dimensional structure, and hence in the metabolism of bilirubin the amount of exposed reactive groups is significant.⁷ Due to internal hydrogen bonding, the predominant form in neonates is ZZ bilirubin, which is a three-dimensional structure having the mirror image as the ring structure of the parent heme molecule (Figure 2).

STRUCTURE OF BILIRUBIN



ZEbilirubin and EZ-bilirubin (cyclobilirubin) are produced as the result of rotation involving pyrrole rings which accounts for about 14% and <1%, respectively, of circulating bilirubin in neonates⁸ ZE bilirubin and EZ bilirubin isomers have a more open configuration. The reactive groups are exposed so they are readily soluble. These type of bilirubin is formed as a result of phototherapy..

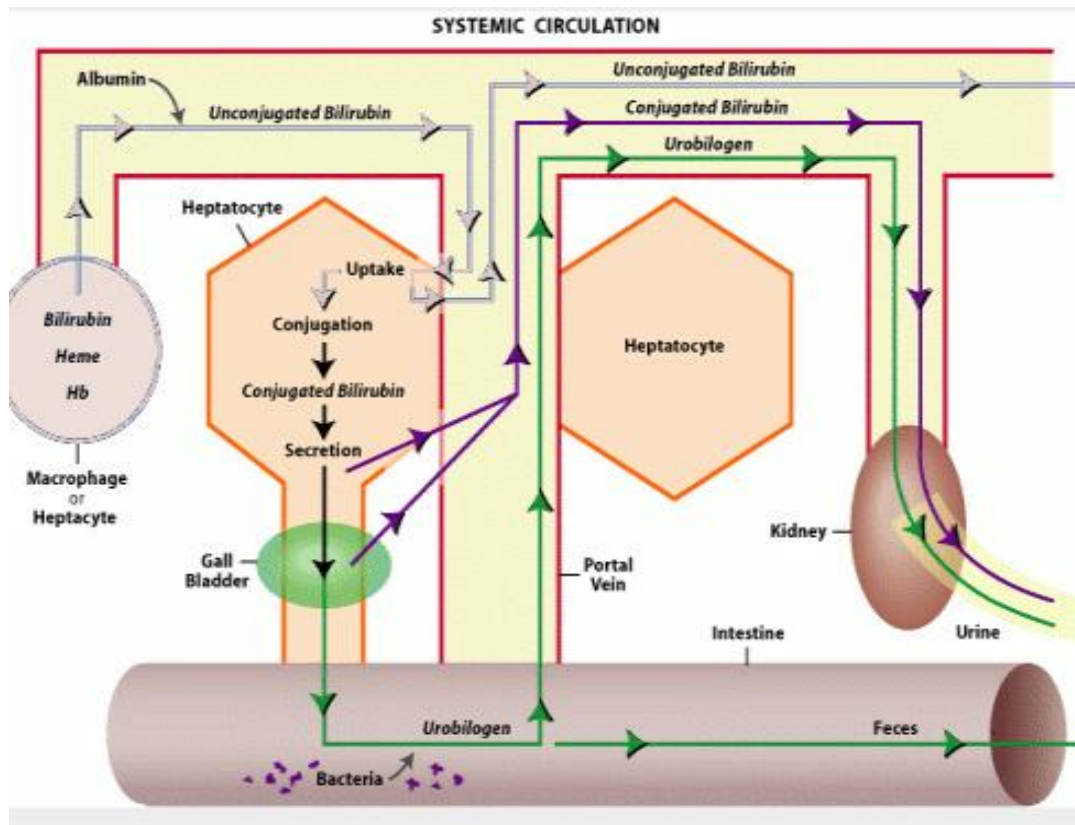
Albumin bound unconjugated bilirubin with the binding affinity of 10^M is transported in plasma. which is non toxic and does not cross the blood brain barrier. Bilirubin can bind with other proteins such as lipoproteins, alpha-fetoprotein and ligandin. Lysine plays a major role in in binding of bilirubin to ligandin and albumin . Recent studies suggest that modulation in bilirubin toxicity is due to lysine.

Bilirubin dissociated from albumin is taken up by facilitated diffusion into the hepatocytes and bind with cytosolic glutathione-s- transferase (ligandin) which keeps it soluble and prevents its efflux. Bilirubin conjugation is essential for efficient biliary excretion and glucuronidation of bilirubin is catalysed by isoform of Uridinediphoshoglucuronate Glucuronyl Transferase, termed UGT1A1. Direct bilirubin is not absorbed in the intestine and secreted in to second part of duodenum after being stored in gall bladder.

Direct bilirubin is reduced to stercobilinogen by gut bacteria and it is excreted in feces. The newborn gut is devoid of gut bacteria and the enzyme glucuronidase converts the conjugated bilirubin into unconjugated bilirubin which gets reabsorbed into the systemic circulation and it is known as Enterohepatic circulation. Glucuronidase enzyme is destroyed by intestinal bacteria. Bilirubin is also present in the meconium of which half of this is unconjugated bilirubin and it is reabsorbed. Indirect bilirubin in the fetus is removed by crossing the placenta or fetal liver.

Polar compounds such as Conjugated bilirubin is unable to penetrate the placental membrane. But non polar compounds can diffuse easily. The

transplacental gradient between fetus and mother is 5:1 to 10:1. Around 12th week of gestation, Bilirubin is present in amniotic fluid but after 36 to 37 weeks of gestation it disappears. Fetus also swallows some amount of bilirubin from amniotic fluid. Biliverdin does not cross the placenta, so biliverdin gets converted into bilirubin¹²



PHYSIOLOGIC HYPERBILIRUBINEMIA ¹²

Neonates are more prone for hyperbilirubinemia due to the following factors:

1. Increased bilirubin production due to decreased RBC survival and increased RBC volume per kg, Increased ineffective erythropoiesis and increased turn over of non hemoglobin heme proteins.
2. Increased entero-hepatic circulation by high levels of beta-glucuronidase, Decreased intestinal bacteria, Decreased gut motility with poor excretion of meconium.
3. Defective uptake of bilirubin from plasma by decreased ligandin and binding of anions to ligandin.
4. Defective conjugation due to decreased uridine diphosphogluconurate glucuronosyl transferase.
5. Decreased hepatic excretion of bilirubin

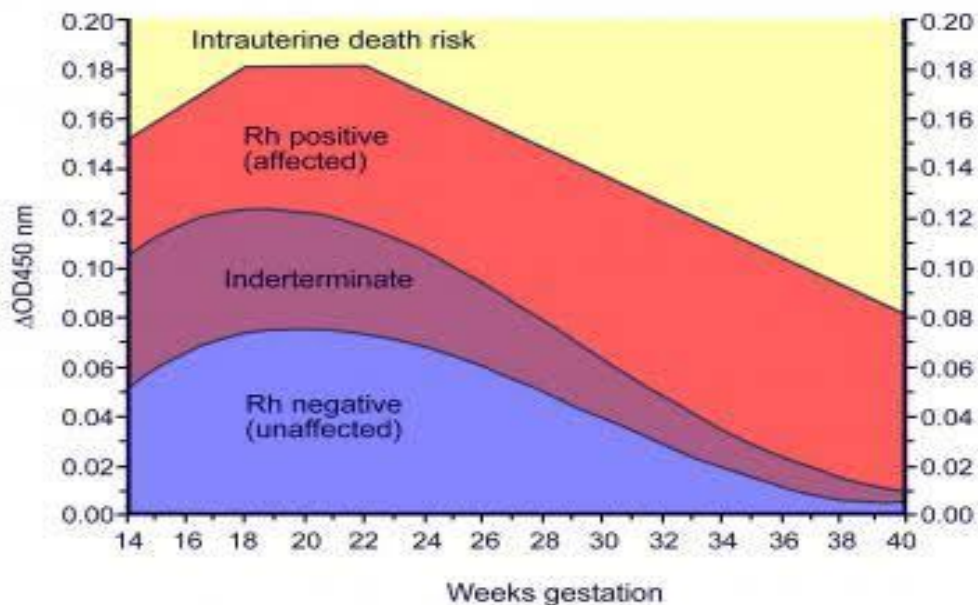
ETIOLOGY OF PATHOLOGICAL HYPERBILIRUBINEMIA:

- I) Increased bilirubin load – Hemolytic Jaundice

Hemolysis occurs due to either immune or non-immune mechanisms. In this case, unconjugated bilirubin levels will be increased.

- i) Immune mediated hemolysis(RH incompatibility and ABO incompatibility)

1) Rh is an antigen carried only on RBCs. When a Rh negative woman carries a Rh positive fetus, she develops antibodies to the fetal Rh antigen on fetal RBCs. Maternal exposure may occur through blood transfusions, fetomaternal hemorrhage, amniocentesis or abortion. Once sensitized, there will be transplacental passage of Immunoglobulin IgG against the fetal antigens resulting in immune destruction of fetal RBCs. Modified liley's chart can be used for the antenatal prediction of Rh isoimmunisation. In this chart optical density difference is plotted against gestational age.



MODIFIED LILEY'S CHART

2) ABO incompatibility

A and B are two major erythrocyte membrane antigens. The cause of hemolysis is due to the reaction of maternal anti-A or anti-B antibodies directed against fetal antigens. It is usually seen in babies having A or B blood group born to O blood group mothers.

ii) Non immune mediated hemolysis

1. RBC Enzyme Defects

i) G6PD Deficiency: X linked mode of inheritance leading to defect in NADPH production. This defect makes RBCs more vulnerable to lysis under oxidative stress conditions

ii) Pyruvate Kinase Deficiency: This enzyme deficiency prevents ATP formation causing cellular death and hemolysis.

2. RBC Membrane Defects

Hereditary spherocytosis, Elliptocytosis, Stomatocytosis, Pyknocytosis –
In all these conditions RBC with abnormal shape are trapped in the spleen.

3. Hemoglobinopathies

Alpha Thalassemia involves the production of abnormal globin rings that destroy the RBCs.

II) INCREASED BILIRUBIN LOAD-NONHEMOLYTIC CAUSES

It maybe due to polycythemia,breakdown of extravascular blood,increased enterohepatic circulation.

A) POLYCYTHEMIA- (Hematocrit more than 65%)

Causes include preeclampsia of mother, Twin to twin transfusion, delayed cord clamping, Placental red cell transfusion, maternal to fetal transfusion, cord stripping, baby holding below the mother at delivery, forceful uterine contractions before cord clamping.

B) PLACENTAL INSUFFICIENCY

Intrauterine growth retardation, post term infants, mother suffering from heart disease, pulmonary disease, maternal smoking, mother's living in high altitude

C) LUCEY-DRISCOLL SYNDROME

It occurs due to the transfer of glucuronyl transferase inhibiting substance from the mother. Rarely it produces severe unconjugated hyperbilirubinemia.⁷⁵

D) MISCELLANEOUS CAUSES

Infant of diabetic mother, large for gestational age, congenital adrenal hyperplasia, beckwith widemann syndrome, neonatal thyrotoxicosis, congenital hypothyroidism, trisomy21, trisomy13, trisomy18, maternal use of propanolol, sepsis.

III) INCREASED ENTEROHEPATIC CIRCULATION

swallowed blood, cysticfibrosis, Pyloric stenosis, hirschprung disease, meconium ileus, meconium plug syndrome, paralytic ileus, intestinal atresia.

C) EXTRAVASCULAR BLOOD

Cephal hematoma, subgaleal hematoma, extensive bruising.

CEPHALHEMATOMA

It occurs as a result of birth injury. There is collection of blood below the periosteum as a result of rupture of superficial veins. The swelling is fluctuant in nature which is limited by suture lines. There may be change in the color of the skin over the swelling. Most commonly seen over the parietal region. Appears immediately after birth or after one to two days. It disappears after few days or few weeks depending on their size. Incision is required when the cephalohematoma is infected or it is the main cause of severe hyperbilirubinemia.

SUBGALEAL HAEMORRHAGE

Vacuum extraction is the main cause for subgaleal hemorrhage. There is collection of blood in the galea aponeurotica layer of scalp. The haemorrhage can extend into entire calvarium, resulting in ecchymosis, periorbital edema. To stop further bleeding pressure dressing can be used.

III) IMPAIRED BILIRUBIN CONJUGATION ⁽¹⁰⁾

A) CRIGLER NAJJAR SYNDROME TYPE I

This Autosomal recessive disorder occurs due to absence of glucuronyl transferase(UGT1A1) activity. severe unconjugated hyperbilirubinemia occurs in the first week of life and passage of pale yellow stools. Hemolysis is not present in this syndrome.

DIAGNOSIS

Increased bilirubin levels, absence of hemolysis and there will be decreased amount of bilirubin in bile. Definitive diagnosis is by measuring hepatic glucuronyl transferase activity by closed biopsy.

B) CRIGLER NAJJAR SYNDROME TYPE 2

This Autosomal recessive disorder occurs due to partial glucuronyl transferase deficiency. unconjugated hyperbilirubinemia occurs in first 3 days of life. Kernicterus do not occur usually.stool color is normal. hemolysis is not present.

DIAGNOSIS

Increased bilirubin levels, absence of hemolysis, liver enzymes and liver synthetic function tests are normal.

C) GILBERT SYNDROME

Due to mildly reduced activity of UDP-GLUCORONYL TRANSFERASE activity. Relatively common form of unconjugated hyperbilirubinemia during periods of illness or stress.It is a risk factor for pigment gallstones.

D) CONGENITAL HYPOTHYROIDISM

Hyperbilirubinemia occurs due to impaired gut motility, delayed maturation of glucuronide conjugation, poor feeding.

E) BREASTFEEDING JAUNDICE ¹²

Incidence is 12% to 13% in breast fed infants

IT is common in breast fed infants than formula fed infants. It occurs due to decreased intake of breast milk hence decreased gut motility and increased enterohepatic circulation.

F) BREASTMILK JAUNDICE ⁽¹²⁾

Incidence in term infants is 2% to 4%. It is of late onset and peaks by 14 days of life, occurs due to 3-alpha,20 pregnandiol compound in breastmilk which interferes with bilirubin metabolism. The bilirubin levels will be elevated if breastfeeding is continued and levels will fall by 4 to 12 weeks of age.

IV) IMPAIRED BILIRUBIN EXCRETION

Anatomical abnormalities or functional abnormalities can cause impaired bilirubin excretion causes are as follows

A) ANATOMICAL ABNORMALITIES

BILIARY TRACT OBSTRUCTION

Causes include biliary atresia, bile duct abnormalities, gall stones, choledochal cyst.

BILIARY ATRESIA

It is the most common cause of obstructive jaundice in infants, it may be extra hepatic or intrahepatic.. Intrahepatic type is mostly associated with syndromes namely Alagille and Agenes syndrome.

a) Extrahepatic biliary atresia

Extrahepatic may be present as alone or it may be associated with trisomy 13 or 18 or polysplenia

More common than intrahepatic biliary atresia. Stools are cheesy white colored. In histopathology of liver there will be periportal fibrosis and proliferation of bile duct. Scintigraphy of hepatobiliary system and PCLB along with visualisation at the point of operative cholangiography provide definitive information. Kasai operation should be done before 2 months of age.

b) Intrahepatic biliary atresia

Intrahepatic type is mostly associated with syndromes namely Alagille, Agenes syndrome. Liver histopathology shows inflammatory changes with hypoplasia of bile canaliculi.

Other causes are non syndromic paucity of intrahepatic bile duct, bile duct stenosis, or rupture of bile duct, lymph node enlargement, hemangiomas, pancreatic cysts and cystic fibrosis.

B) INFECTIOUS CAUSES:

Viral hepatitis B&C, giant cell neonatal hepatitis, Epstein barr virus, Adenovirus, Coxsackie virus, Rubella, Echovirus, CMV

C) BACTERIAL CAUSES :

Syphilis, Staphylococcus, Tuberculosis, Listeria, E.coli, Streptococcus.

D) PARASITIC CAUSES:

Toxoplasma

E) DRUGS

Vitamin k in large doses, kanamycin cause jaundice by blocking Y acceptor Protein. novobiocin, moxalactam, gentamycin, chloramphenicol competes with glucuronyl transferase, salicylates blocks bilirubin binding sites of bilirubin. oxytocin usage in mother causes hyperbilirubinemia.

F) METABOLIC CAUSES:

Dubin Johnson syndrome, Rotor syndrome, Galactosemia, Tyrosinemia, Alpha 1 Antitrypsin deficiency, Cystic fibrosis, Hemochromatosis, Zellweger syndrome, storage disorders, Fructosemia, Bylers disease

G) OTHER CAUSES :

Prolonged parenteral nutrition, erythroblastosis fetalis, infants supported on ECMO.

H) INSPISSATED BILE SYNDROME

It is commonly seen in babies suffering from RH(hemolytic disease). It is due to transient difference between the maturity of excretory and conjugatory

functions of hepatocytes. The syndrome improves gradually once the Rh hemolytic disease is treated⁽⁷⁵⁾

NEONATAL HEPATITIS

The important cause accounting for 40% is idiopathic neonatal hepatitis. Infections such as viral, spirochetal, parasitic infections also contribute to neonatal hepatitis. Bile stained stools are present. Enlargement of liver and spleen is present. Viral infections such as Echovirus, Coxsackie B and Herpes simplex will present as fulminant hepatic failure. Giant cells will be present in histopathological examination. Hepatitis B virus acquired by the neonate may also cause neonatal hepatitis.

PERSISTENT NEONATAL JAUNDICE:

Physiological jaundice disappears at three weeks of age but it may persist beyond three weeks of age due to indirect or direct hyperbilirubinemia.

Breastmilk Jaundice, Gilbert Syndrome, Hypothyroidism, pyloric stenosis, malaria, cephalohematoma, Down's syndrome, Urinary tract infection, Crigler Najjar Syndrome are the causes of persistent prolonged indirect hyperbilirubinemia.

Neonatal hepatitis, inspissated bile syndrome, sepsis, malformation, metabolic disorder, total parenteral nutrition are the causes of prolonged direct hyperbilirubinemia

CLINICAL PRESENTATION:

HISTORY : any family history of jaundice, anemia, splenectomy, liver disease. Siblings with jaundice or anemia, maternal illness during pregnancy, maternal drug intake, mode of delivery should be asked.

Frequency of stooling, adequate intake of milk, vomiting.

PHYSICAL EXAMINATION:

Jaundice progresses in head to foot direction, highest bilirubin levels are typically associated with yellowish discoloration of palms and soles. It is detected by applying finger pressure to blanch the skin in order to notice the color of subcutaneous tissue and skin for serum bilirubin levels. Visual inspection is not a reliable indicator. For inspection of sclera and eyes baby should be slightly moved front and back with support there by stimulating the vestibular apparatus eyes will open. The cephalocaudal progression of jaundice is apparently related with respect to the skin thickness. It is necessary to examine all neonates twice a day in good day light to detect hyperbilirubinemia.

IUGR babies are more prone to develop jaundice. Microcephaly associated with intrauterine infections. Any cephalhematoma, bruising, or other enclosed hemorrhages, any pallor, petechiae, hepatosplenomegaly, omphalitis, chorioretinitis, evidence of hypothyroidism.

CLINICAL EXAMINATION OF NEONATAL JAUNDICE



INVESTIGATIONS:

Screening of total serum bilirubin, blood type, Rh typing, and antibody screening of the mother.

Blood type, Rh typing, direct coombs test, peripheral smear for RBC morphology, hematocrit, direct bilirubin levels.

If evidence in support of hemolysis, G6PD screening.

Transcutaneous bilirubinometer

PRINCIPLE-Computerised spectrophotometry.

The circulating bilirubin in infants peaks at 3 – 4 days of age, at that time almost all babies are discharged. Hence portable transcutaneous bilirubin monitors can be used to assess the neonatal jaundice^{(14) (19)} Transcutaneous bilirubin can be measured using Bilicheck^{(15), (18)} it is reported that the value may change depending on the site of sampling, degree of prematurity and skin colour.

It cannot be used to assess the severity of jaundice in neonates undergoing phototherapy^{(16), (17)}. Transcutaneous bilirubinometer can be used as a screening tool in assessing neonatal jaundice (12)

TRANSCUTANEOUS BILIRUBINOMETER



HIGH PERFORMANCE LIQUID CHROMATOGRAPHY is the gold standard choice of measurement of total serum bilirubin, but this method is used only in research laboratories

CARBON MONOXIDE MEASUREMENT.

etCO measurement carbon monoxide is produced in equi molar concentration to bilirubin production and its measurement in breath can be done (12)

Ictrometer-used by inexperienced health workers by matching color codes with the skin color.

BILIMETER

Micro centrifuged sample of blood is taken in a capillary tube which gives instant digital value.

ADDITIONAL INVESTIGATIONS

Evaluation for sepsis, congenital infections, screening for metabolic disorders, thyroid function.

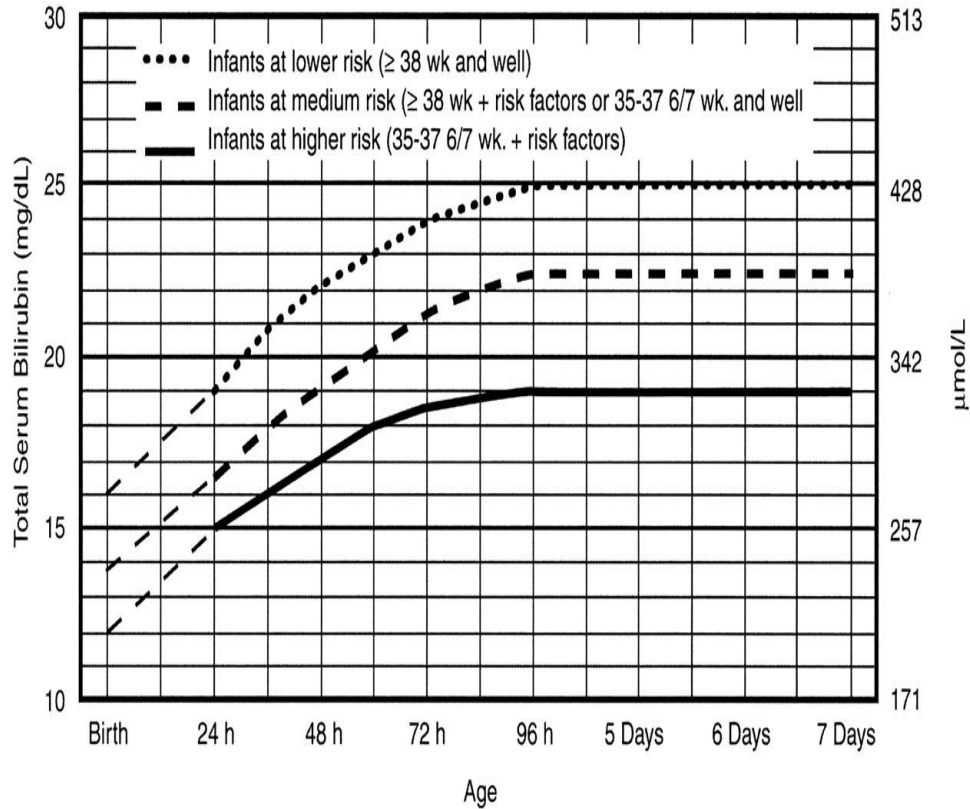
RED FLAG SIGNS IN JAUNDICE

- Jaundice appearing before 24 hours of life
- Rising serum bilirubin levels more than 0.2mg/dl/hr
- Serum bilirubin levels requiring phototherapy

- Associated with vomiting, lethargy, poor feeding, apnea, tachypnea, temperature instability, persistence of jaundice more than 8 days in term infant and 14 days in preterm infant.
- Previous sibling with jaundice, significant bruising, east asian ethnicity
- Lower gestational age, isoimmune or other hemolytic disorders.

Nomogram: The most commonly used nomogram in assessment of neonatal hyperbilirubinemia is Bhutani's nomogram. Age of the baby in hours is represented in X axis and the total serum bilirubin in Y axis. Neonates were divided into high risk, medium risk and low risk.

BHUTANI NOMOGRAM

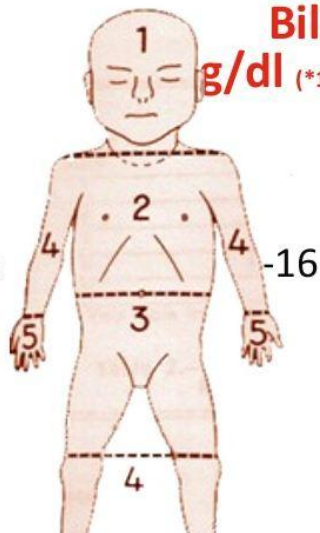


- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥ 5 mg/dL ($85 \mu\text{mol/L}$) above these lines.
- Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Clinical assessment of jaundice (Kramer's staging)

Area of body

- Face
- Upper trunk
- Lower trunk & thighs
- Arms and lower legs
- Palms & soles



Bilirubin levels g/dl (*17=umol)

Zone-1: 4-6

Zone-2: 6-8

Zone-3: 8-12

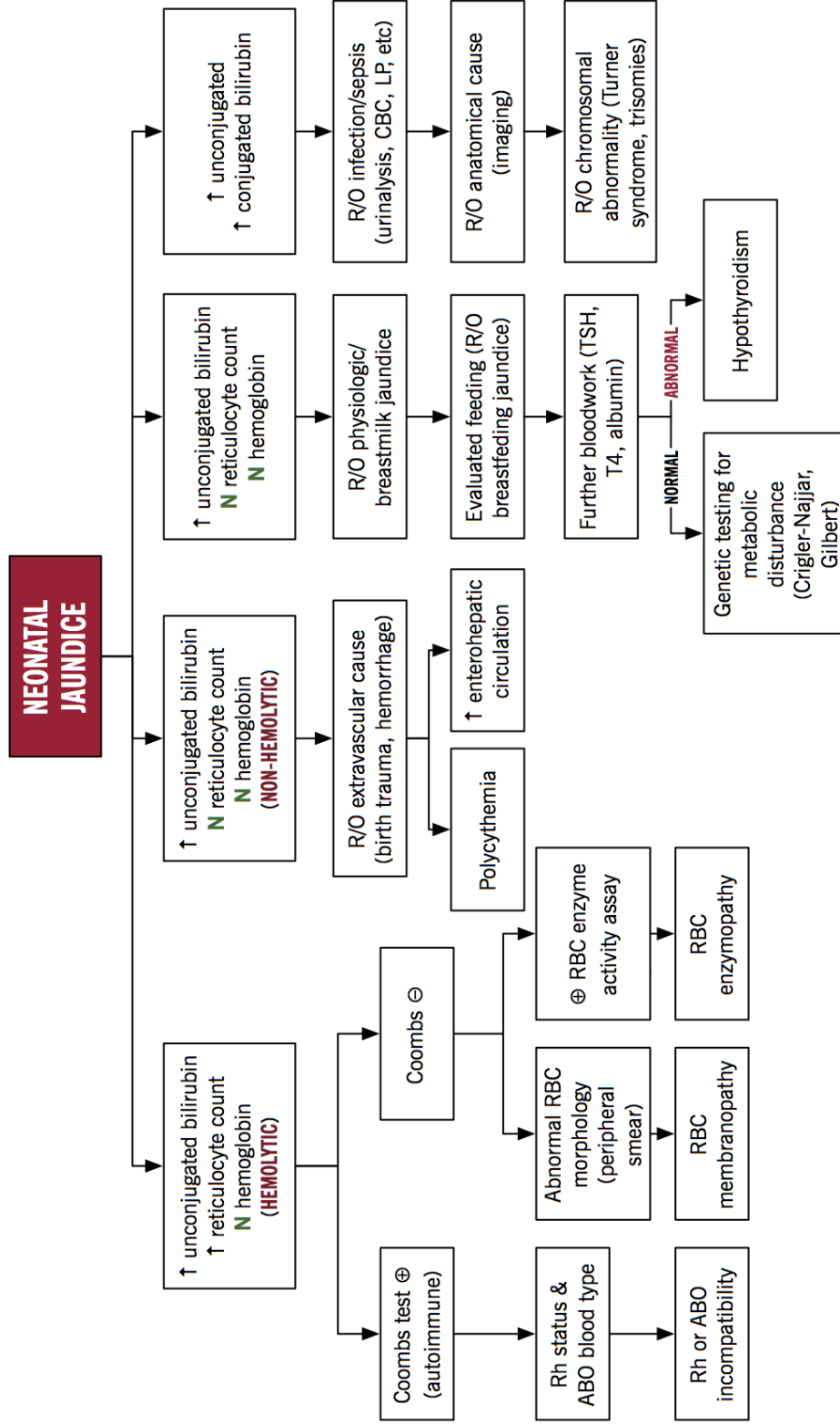
Zone-4 :12-14

Zone-5 :>15

TREATMENT:

NEONATAL HYPERBILIRUBINEMIA | Approach to neonatal jaundice

Amanda Yaworski



Phototherapy, exchange transfusion, intravenous immune globulin, drugs and albumin therapy.

➤ **PHOTOTHERAPY:**

Bilirubin is absorbed in the wavelength of 400-500 nm and blue lamps with a output at 425-475 nm are efficient for phototherapy ^{(21), (26)}

1. MECHANISM OF PHOTOTHERAPY:

a) Photoisomerisation

Unconjugated bilirubin (4z, 15z,) is converted to (4z,15e) which is less toxic and easily excreted^{(35) (40)} Photoisomers make up 20% of biliurbin after 12 hours of initiation of phototherapy The amount of irradiance used is 6microwatt/cm²/nm.

b) Structural isomerisastion

It is due to the intramolecular cyclisation leading to lumirubin conversion. Once lumirubin is formed, it cannot be reabsorbed which makes up 2-6% of bilirubin concentration during phototherapy⁽²⁷⁾⁽³⁴⁾

Irradiance : 6-12microwatt/cm²/nm. This is the most important pathway for lowering serum bilirubin.

c) Photo-Oxidation

It converts bilirubin to polar products which is excreted in urine^(22,32)

It is the least effective mechanism of phototherapy.

2. FACTORS FAVORING PHOTOTHERAPY :

Irradiance, spectrum of light, distance from the infant, area under exposure^(25, 37)

A. Irradiance : conventional phototherapy 8-12microwatt/cm²/nm

B. Intensive phototherapy : 30microwatt/cm²/nm

C. Spectrum Of Light : 430-490 nm

D. Distance From The Infant

-Conventional phototherapy: 20cm

-Intensive phototherapy : 10 cm

E. Area Under Exposure : Eyes should be covered with biliband, frequent positional change every 2 hours, hydration.(27) (39)

Using high intensity gallium nitride light emitting diodes –intensive phototherapy can be given.

3.TYPES OF PHOTOTHERAPY :

A. SINGLE SURFACE PHOTOTHERAPY(SSPT):

The infant is exposed to light source from either above or below in single surface phototherapy.

B. DOUBLE SURFACE PHOTOTHERAPY:

It is more effective than SSPT. The infant is exposed to light source from both above and below. Fibre optic bilibankets provide additional effectiveness and through halogen bulbs phototherapy is provided from above. In our country Compact Florescent Tubes are most commonly used.

Light banks: Alternating blue and fluorescent lights. In case of severe hyper bilirubinemia, neo blue phototherapy lights are used. Bulbs should be changed every three months.

C.SPOT PHOTOTHERAPY :

It is used for infants under radiant warmers^(28,37)

D.FIBREOPTIC BLANKETS :

It is used for both single and double surface phototherapy.

4. MONITORING OF CHILD UNDER PHOTOTHERAPY :

In case of incubator usage distance from baby to light should be 5-8 cm, and temperature is monitored in servo mode.

Fluid : 10-20% extra fluid should be given, baby should be weighed twice a day.^(24,32)

Home Phototherapy : It is effective and cheaper. Implemented with fibreoptic blankets, candidates for home phototherapy are breastfed infants. AAP recommends home phototherapy only for newborns within phototherapy optional range.^(30, 32)

5. INDICATIONS FOR PHOTO THERAPY

Infants weight between 1 to 1.5kg- Total serum bilirubin levels 7 to 9mg/dl

Infants weight between 1.5 to 2kg- Total serum bilirubin levels 10 to 12mg/dl

Infants weight between 2 to 2.5kg- Total serum bilirubin levels 13 to 15 mg/dl

PROPHYLACTIC PHOTO THERAPY

ELBW infants, severely bruised infants, hemolytic disease of newborn.

CONTRAINDICATIONS FOR PHOTOTHERAPY

In case of direct hyperbilirubinemia caused by obstructive jaundice or liver disease phototherapy is contraindicated. Bronze baby syndrome occurs due to bronze pigment which is toxic.

SIDE EFFECTS OF PHOTO THERAPY

- a. Insensible water loss it may be up to 40 percent for term infants and 80 to 180 percent for preterm infants.
- b. Redistribution of blood flow as it increases blood flow in left pulmonary artery and cerebral arteries.
- c. Diarrhoea –increased bilesalts and unconjugated bilirubin
- d. Hypocalcemia-because of secretion of melatonin from pineal gland.
- e. Tanning of skin,retinal damage,mutations, DNA strand breaks, tryptophan is reduced in aminoacid solutions exposed to phototherapy.
- f. Reduced maternal infant interactions

ROLE OF SUNLIGHT IN NEONATAL HYPERBILIRUBINEMIA⁽⁷⁵⁾

The phototherapy wavelength should be in the range of 400nm-500nm.

Sunlight is not effective because UVA and UVB are absorbed in the atmosphere. Sunlight exposure can cause skin damage⁽⁷⁵⁾ thus sunlight for the treatment of neonatal hyperbilirubinemia is neither safe nor effective.

➤ EXCHANGE TRANSFUSION⁽⁴²⁾

INDICATIONS FOR EXCHANGE TRANSFUSION

- a. To remove antibody and sensitized RBCS.
- b. To correct anemia in hydrops fetalis⁽⁴⁷⁾
- c. Phototherapy unable to prevent rise in bilirubin levels

IN HEMOLYTIC DISEASE

- a. Cord bilirubin level >4.5mg/dl and cord hemoglobin level <11g%.
- b. Rise in bilirubin level >1mg/dl/hr inspite of phototherapy⁵⁸
- c. Bilirubin level >20mg/dl
- d. Progression of anemia⁽⁵³⁾

MECHANISM OF EXCHANGE TRANSFUSION

This method removes partially hemolysed and antibody coated RBCS and replace with donor RBCS lacking the sensitizing antigen. bilirubin is also

removed from the plasma. The remaining extravascular bilirubin bind with albumin in the exchanged blood and excreted. ⁽⁵⁰⁾

PROCEDURE:

Fresh blood to be used <7 days old, in case of Rh hemolysis and ABO incompatibility O negative or Rh compatible blood with mother and infant crossmatched against mother and infant blood group. In case of nonimmune hemolysis blood is typed and crossmatched against plasma and red cells of infant.

BLOOD VOLUME REQUIRED:

Double the blood volume of infant (normal blood volume 80ml/kg) ⁽⁵⁷⁾

Infant is placed under servo controlled radiant warmer, vitals should be monitored with intravenous cannula insitu. The blood should be warmed to 37 degree. Under strict aseptic precautions umbilical cord is softened with saline soaked gauze to locate the vein and to insert the catheter. Most of the exchanges are done by push pull technique. Blood should be removed in small aliquots of 5 to 10 ml for <2kg and more than 20 ml for >2kg. The recommended time is 1hr. After the exchange transfusion phototherapy is continued and bilirubin is checked for every 4 hrs. ⁽⁵⁵⁾

COMPLICATIONS OF EXCHANGE TRANSFUSION

HYPOGLYCEMIA-Glucose concentration of CPD blood is around 250 to 300mg% hence stimulate insulin secretion and cause hypoglycemia.

HYPOCALCEMIA AND HYPOMAGNESEMIA-citrate in CPD blood binds ionic calcium and magnesium⁽⁵⁴⁾

HYPERKALEMIA- potassium levels higher in store pRBCs.

ACID BASE IMBALANCE- Citrate in blood metabolized to alkali. In case of sick infants acidosis occurs.

BLEEDING-Thrombocytopenia, deficient clotting factors.

INFECTION-Hepatitis, Cytomegalovirus, HIV, Malaria, Bacteremia

HEMOLYSIS- due to overheating of blood.

GRAFT VERSUS HOST DISEASE- maculopapular rash, eosinophilia, lymphopenia. This can be prevented using irradiated blood.

➤ **INTRAVENOUS IMMUNOGLOBULIN**

High dose immunoglobulin can be given (0.5 to 1g/kg/dose) repeat in 12hrs, possibly acts by reducing hemolysis in both Rh incompatibility and ABO incompatibility

RHO(D)IMMUNE GLOBULIN can be given to mothers at 28 weeks and again within 72 hrs of delivery who were Rh negative and spouse Rh positive.⁽⁷⁵⁾

DRUGS

METALLOPROTOPHYRINS

A) Tin-mesoporphyrin

Tin is a competitive inhibitor of heme oxygenase. The rate limiting enzyme in bilirubin production is hemeoxygenase. Side effects include skin rashes, hepatic and renal toxicity.

B) Zinc it acts by decreasing enterohepatic circulation.

C) Oral agar can be used as they act by reducing enterohepatic circulation

D) Orotic acid acts by promoting bilirubin conjugation. Its utility is limited due to high cost.

E) Phenobarbitone can be used as it acts by inducing microsomal enzyme, increasing bilirubin conjugation, increasing bile flow and excretion. It is used in the treatment of Crigler najjar syndrome type 2.

F) Cholestyramine can be used in the treatment of neonatal hyperbilirubinemia

Which enhances the excretion of bilirubin and bilesalts hence by decreasing enterohepatic circulation. Side effects are constipation and hyperchloremic acidosis.⁽⁷⁵⁾

➤ Albumin infusion

5% salt free albumin can facilitate effective removal of bilirubin. It can be used before exchange transfusion, but the utility is limited due to high cost and rare risk of transmission of viral infections⁽⁷⁵⁾

COMPLICATIONS OF NEONATAL HYPERBILIRUBINEMIA

KERNICTERUS - BILIRUBIN ENCEPHALOPATHY is a neurologic syndrome due to the deposition of indirect bilirubin in the cranial nerve nuclei and basal ganglia and it also refers to yellowish staining of the brain by unconjugated bilirubin together with neuronal injury. Incidence is 30% in infants with bilirubin levels >25mg/dl and untreated hemolytic disease.⁽⁵³⁾⁽⁶⁴⁾

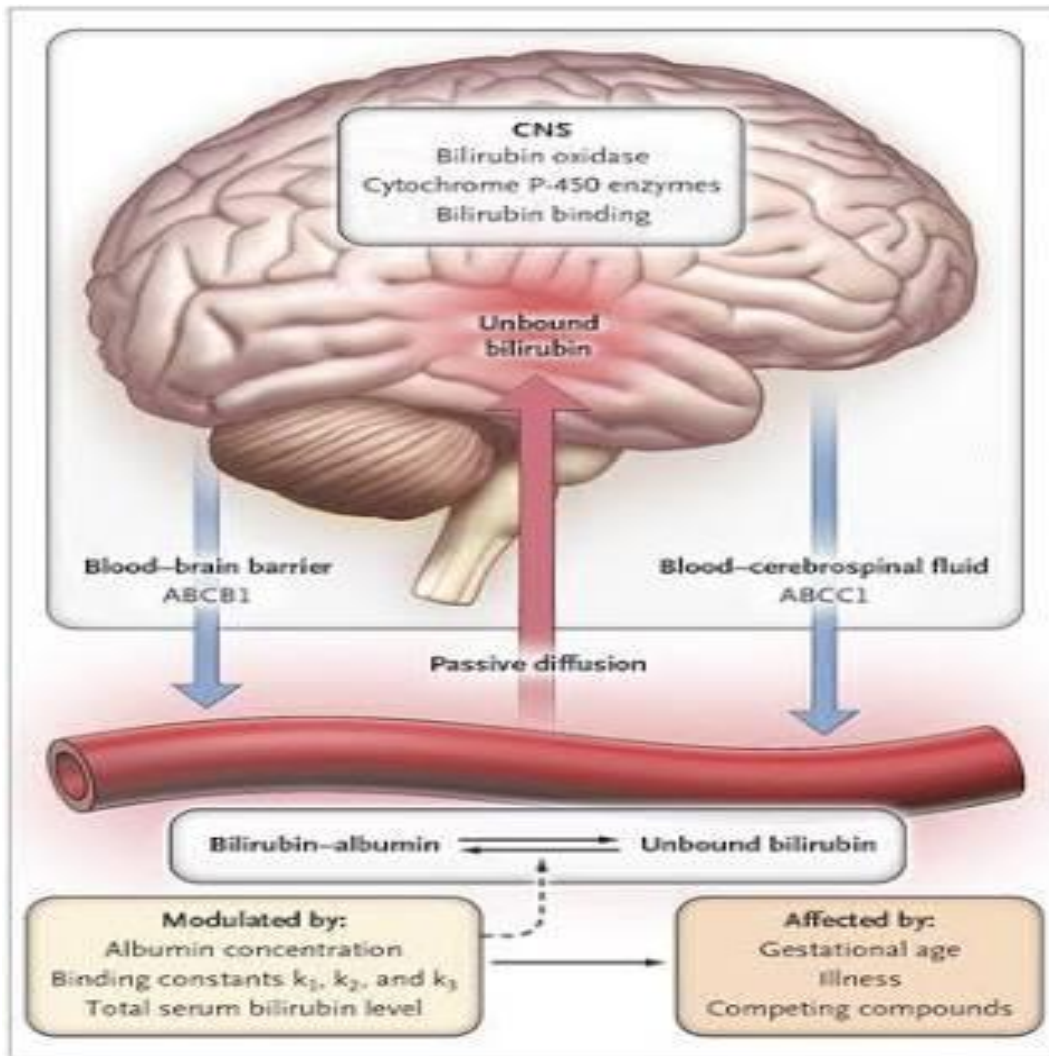
PATHOPHYSIOLOGY

It is multifactorial.

- a. unconjugated bilirubin levels >20mg/dl⁽¹²⁾
- b. albumin levels - one gram of albumin will bind 8.5 mg of bilirubin, binding decreased in sick and premature infants.⁽⁶¹⁾

- c. blood brain barrier integrity is disrupted in hyperosmolarity, asphyxia, hypercarbia, premature infants ⁽¹⁰⁾
- d. neuronal susceptibility-basal ganglia, cranial nerve nuclei mainly 8th cranial nerve nuclei, cerebellar nuclei, hippocampus and anterior horn cells. ⁽⁶³⁾
- e) sepsis, hypoglycemia, large doses of VitK
- f) trauma, cephalhematoma, dehydration
- g) Hepatitis.

MECHANISM OF KERNICTERUS



CLINICAL FEATURES

Early phase: hypotonia, lethargy and high pitched cry

Intermediate phase: hypertonia of extensor muscles (opisthotonus), irritability, fever and seizures .Most of the infants die in this phase.⁽¹⁰⁾

Advanced phase : hypotonia, shrill cry, apnea, seizures, coma and death.⁽⁶⁰⁾

60)

Other signs includes setting sun sign, fever, abnormal moro response only extension of arms will be there no flexion component followed by rolling of eyeballs.

CHRONIC BILIRUBIN ENCEPHALOPATHY

Infants surviving acute phase leads to choreoathetosis, sensorineural deafness, dental defects and impaired cognitive functions, delayed motor skills, upward gaze palsy.⁽⁵⁸⁾

BIOCHEMICAL DETERMINANTS OF BILIRUBIN ENCEPHALOPATHY

- 1) Bilirubin level more than 25mg/dl.
- 2) Bilirubin protein ratio 3.5 or more.
- 3) HBABA dye binding capability < 50%.
- 4) Salicylate saturation index of 8.
- 5) Sephadex G25 measures both free and bound bilirubin to albumin, if the level of both free and bound bilirubin is less than 0.1mg/dl then the sephadex column is not yellow stained.
- 6) Binding of bilirubin to RBC > 4mg/dl.
- 7) Peroxidase method involves measuring free bilirubin > 20nmol/L

Kernicterus and hearing:

In BERA there is significant suppression of all waves there will be increased latency in I,III,IV,V waves.

PROGNOSIS

Among affected infants, 80% have spastic quadriplegia, deafness, choreoathetosis, mental retardation and more than 75% of infants die.⁽⁵⁷⁾

PREVENTION

- a. universal screening of hyperbilirubinemia in 24 to 48 hrs after birth.
- b. follow up if the infant is discharged earlier than 48hrs.
- c. identify the risk factors.
- d. bilirubin levels should be analysed by measuring serum bilirubin levels not clinically.
- e. delay in initiating treatment
- f. failure of giving adequate importance to history such as lethargy and poor feeding.^{(54) (59)}
- g) adequate breast feeding⁽⁷⁵⁾
- h) treatment of comorbidities such as sepsis, hypothermia, hypoglycemia, avoiding large doses of VitK⁷⁵

➤ **Differential diagnosis**

- a) sepsis

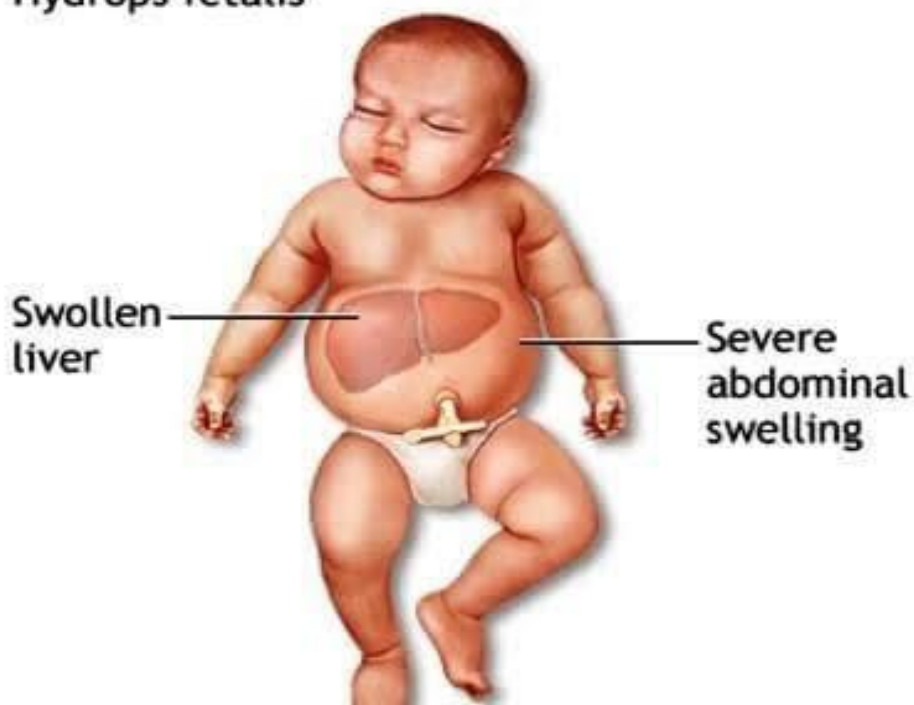
- b) cerebral palsy
- c) birth asphyxia
- d) bacterial meningitis
- e) head trauma

HYDROPS FETALIS

Abnormal and increased collection of fluid in more than two fetal compartments (placenta, pleura, skin, pericardium, peritoneum).^{(67) (66)}

Hydrops fetalis incidence is in the decreasing trend nowadays due to the early recognition and treatment.

Hydrops fetalis



CAUSES

- **HEMATOLOGIC CAUSES**

D antigen contribute for >90% of cases and the remaining cases are due to E or C antigen. Infusion of Rh positive blood to Rh negative woman through blood transfusion, abortion, delivery, mother will be sensitized and start producing IgM antibodies initially and later IgG antibodies which can cross the placenta and cause hemolytic manifestations. Other causes are homozygous thalassemia, twin to twin transfusion, leukemias and G6PD deficiency. ⁽⁶⁸⁾

- **CARDIOVASCULAR CAUSES:**

Heart block, arrhythmias, hypoplastic left heart disease, myocarditis, endocardial fibroelastosis, cardiac masses, premature closure of foramen ovale.

- **RENAL CAUSES:**

Hydronephrosis, renal vein thrombosis, renal hypoplasia, urinary tract obstruction.

- **INFECTIOUS CAUSES**

Syphilis, Rubella, CMV, Adenovirus, Hepatitis, Herpesvirus, Adenovirus, Leptospirosis, Parvovirus, Chagas disease.

- **PULMONARY CAUSES**

Congenital diaphragmatic hernia, cystic adenomatoid malformations, chylothorax.

- **PLACENTA OR CORD ABNORMALITIES**
- **GASTROINTESTINAL CAUSES**

Meconium peritonitis, atresia of intestine. ⁽⁶⁷⁾

- **CHROMOSOMAL ABNORMALITIES**

CLINICAL FEATURES

The severity of the disease range from pallor to severe anemia, massive hepatosplenomegaly, heart failure, respiratory distress, jaundice, bilirubin encephalopathy, hypoglycemia, petechiae , DIVC. (64)

INVESTIGATIONS

Blood grouping and typing of mother and infant, coombs test, redcell antibody titres, RBC indices, hemoglobin electrophoresis, ESR, Betke stain to identify fetal red cells, fetal echo, ultrasonogram, lupus tests, fetal blood sampling for karyotype, CBC, hemoglobin, electrophoresis, cultures, PCR, DNA studies, albumin, Xrays, LFT, amniocentesis for viral infections, metabolic studies. (62)

MANAGEMENT OF FETUS

When the hematocrit is less than 30% umbilical vein transfusion is done .Packed RBCS cross matched against mother serum are given by slow push method . Leukoreduction and irradiation should be done to prevent graft versus host disease. Survival rate is 89% complications include preterm delivery, fetal distress, perinatal death. (12)

MANAGEMENT OF NEWBORN

Fresh low titre O blood group leukoreduced and irradiated should be available. If signs of hemolysis are present then immediate resuscitation, supportive therapy should be started such as small transfusion of RBC's, volume expansion for hypotension, acidosis correction with sodium bicarbonate

and ventilation support for respiratory failure. Most severe cases require exchange transfusion.

INTRAVENOUS IMMUNOGLOBULIN

Reduces the necessity for duration of phototherapy, exchange transfusion and length of hospital stay

PREVENTION

ANTI D (300 microgram) administration at 28 weeks of gestation and within 72 hrs of delivery in Rh negative mothers sensitized with RH positive infants.⁽⁵³⁾

REVIEW OF LITERATURE

Alaeidin et al study ⁽⁷³⁾ was carried out on 94 healthy newborns(47 FT and 47 PT) from the obstetrics department and NICU of Ismailia General Hospital. Babies were chosen according to specific inclusion and exclusion criteria.

The study group was followed up clinically and by laboratory investigations. Total serum bilirubin in umbilical cord was measured at birth, and followed up using transcutaneous bilirubinometry during the first week of life to find out babies developing significant hyperbilirubinemia and in need for treatment.

The gender distribution of the study showed that baby boy was insignificantly higher than the baby girl . The mean gestational age was 38.70 ± 1.38 weeks in full term compared to 35.62 ± 0.64 in preterm. The mean birth weight was 3.302 ± 0.207 Kg in full term compared to 2.936 ± 0.207 Kg.

Regarding the needed treatment among study population, it was found that 40.4% of preterm and 29.8% of full term needed phototherapy and no one of both groups needed exchange transfusion.

Total and direct cord bilirubin was slightly higher among full term compared to preterm. However these differences were not significant.

The cut off points for total cord bilirubin in preterm and full term was 2.05 and 2.15 mg/dl respectively.

The strongest predictor of receiving phototherapy was total cord bilirubin compared to gestational age, ABO, incompatibility, Rh incompatibility and sex.

The study concluded that during first week of life , cord blood bilirubin is indicative of severity of jaundice in healthy full term and late preterm without complications. Indication for phototherapy in full term and preterm was cord blood bilirubin levels ≥ 2.05 mg/dl and 2.15 respectively and also the presence of mother/baby blood group incompatibility .

Gurudeepsingh et al⁽⁷²⁾ study

The study group consisted of neonates delivered in MMIMSR -100 full-terms Appropriate for gestational age .

Incidence of hyperbilirubinemia was 14% with Mean umbilical cord blood bilirubin was 1.63 ± 0.73 . Neonatal hyperbilirubinemia and mode of delivery ($p > 0.005$) was not statistically significant. neonatal hyperbilirubinemia and sex of the baby and maternal age ($p > 0.05$) was not statistically significant.

There is no association between mother's blood group and the increased risk of hyperbilirubinemia in neonates.

Association between neonatal hyperbilirubinemia and increasing umbilical cord blood bilirubin ($p = 0.001$) was statistically significant. Using umbilical cord blood bilirubin level of 1.9 mg/dL hyperbilirubinemia showed sensitivity of 92.8%, specificity of 83.7% , negative predictive value of 98.6% and positive predictive value of 48.1%. the study showed that umbilical cord blood bilirubin is an indirect indicator of serum bilirubin to indicate the

development of neonatal hyperbilirubinemia and decide need for intervention in healthy term neonates.

Amar Thakshande et al study⁽⁷¹⁾ was conducted in 200 healthy term neonates born in KHS hospital sewage. The study showed the incidence of pathological hyperbilirubinemia was 28 (6%) and there were no significant differences between the cases who did and the cases who did not develop significant hyperbilirubinemia with respect to these factors (such as Rh incompatibility, delivery route , birth weight) and is associated with the risk of hyperbilirubinemia . But there exist a differences between the neonates affected with significant hyperbilirubinemia and unaffected neonates with respect to sex, history of siblings with hyperbilirubinemia , cord bilirubin level.

These results are in good agreement with other studies but differ from others especially regarding sex. In this study, the cord bilirubin level of >2 mg/dL has the highest sensitivity (71.5%), and this critical bilirubin level had a very high (98.1%) negative predictive value and fairly low (45.4%) positive predictive value . The study showed that cord bilirubin values predicts the risk of hyperbilirubinemia and minimize the hospital stay.

Nagwa et al conducted a correlational study between umbilical cord serum bilirubin (UCB) & subsequent development of hyperbilirubinemia. The risk of developing severe hyperbilirubinemia is seen in Newborns presenting cord blood bilirubin levels $> 4\text{mg}/100\text{ml}$ were followed up and reassessed. The mean serum bilirubin levels was $>16\text{mg}/\text{dl}$ at 72 hours of postnatal age with a peak level of $17 \pm 4.3\text{mg}/\text{dl}$ at 68 ± 17.5 hours of postnatal age. There is a strong

association between the cord blood bilirubin and the newborn's bilirubin level at different postnatal ages. In the study, the cutoff point for the cord blood bilirubin was 2.0mg/dl. With this cutoff point, whenever values that were greater than or equal to 2mg/dl, indicates the probability of more than 50% for the need of phototherapy .

Rosenfeld et al analyzed a group of 108 full-term newborn and concluded that babies with an umbilical cord blood bilirubin level of $< 2\text{mg/dl}$ had a 4% chance of developing significant jaundice, in comparison with a 25% risk of developing jaundice presented by the ones with levels $> 2\text{mg}/100\text{ml}$ and need for phototherapy.

Knudsen et al, carried out a study to demonstrate that newborns with clinical jaundice have higher levels of umbilical cord blood bilirubin and those with cord blood bilirubin $>2\text{mg/dl}$ required phototherapy later. This proved that it is possible to define newborn risk group for developing neonatal severe hyperbilirubinemia by measuring umbilical cord bilirubin.

Alpay et al, observed that serum bilirubin $>6\text{mg/dl}$ on the first day of life had 90% sensitivity of predicting a subsequent TSB $>17\text{mg/dl}$ between 2nd and 5th day of life. At this critical serum bilirubin value, the negative predictive value was 97.9%. No cases with TSB of 2mg/dl had the highest sensitivity (89.5%), and this critical bilirubin level had a very high (98.7%) negative predictive value and fairly low (38.6%) positive predictive value.

Eswara et al prospectively determined the critical cord serum bilirubin level to predict significant hyperbilirubinemia in healthy term newborns. In their study a total 51 of 288 (18.09%) were found to have significant hyperbilirubinemia and the umbilical cord bilirubin level cut off point was 2 mg/dl with good sensitivity (94.12), specificity (90.9%), negative predictive value (98.59%) and positive predictive value (69.57%) .

Knudsen et al⁽⁷⁷⁾ reported umbilical cord serum bilirubin concentration as a predictor of subsequent jaundice was studied in 291 newborns. It was possible to define subgroups of infants with significantly higher or lower risks of developing jaundice. If cord bilirubin was below 1.17 mg/dl, 2.9% became jaundiced as opposed to 85% if cord bilirubin was above 2.3 mg/dl. Furthermore, 57% of jaundiced infants with cord bilirubin > 2.3 mg/dl required phototherapy, but if cord bilirubin was < 2.3 mg/dl it is only 9%. Cord blood bilirubin level >2.5 mg/dl is a high risk indicator for predicting neonatal hyperbilirubinemia.

Bernaldo et al reported that the indirect cord blood bilirubin levels indicates the severity of jaundice in full-term newborns without complications, up to third day of life. Levels that ≥ 2 mg/100 ml indicates 53% probability of developing hyperbilirubinemia requiring phototherapy.

Zakianahar⁽⁷³⁾ et al study showed that Cord blood bilirubin level of ≥ 2 gm/dl has a sensitivity of 70% and specificity of 89% in predicting the risk of neonatal hyperbilirubinemia.

Ramprasanth et al study was conducted to assess the usefulness of the cord blood bilirubin estimation as a predictor of subsequent neonatal hyperbilirubinemia in a healthy term infants who require phototherapy.

A prospective cohort study 100 term newborn was conducted at tertiary care centre.

Cord blood bilirubin $> 2.15\text{mg/dl}$ has a sensitivity of 65% and specificity of 65% % in prediction of neonatal hyperbilirubinemia.

A study by Suchonska et al involving 187 healthy term infants showed the mean cord blood bilirubin was $1.30\text{mg}\%$ and the association between cord blood bilirubin level and subsequent risk of developing neonatal hyperbilirubinemia was statistically significant with p value <0.005 .

Jayalakshmi et al ⁽⁷⁰⁾ study involving 567 term neonates showed the association between cord blood bilirubin level and neonatal hyperbilirubinemia was studied with receiver operating characteristic analysis a cutoff value of $>1.89\text{mg}\%$ had highest sensitivity and high negative predictive value. The study was concluded saying that noninvasive cord blood bilirubin measurement can be used as a simple tool in identifying infants at risk for developing significant hyperbilirubinemia.

Knupfer⁽⁷⁸⁾ et al study showed that umbilical cord blood bilirubin is a good predictor of developing neonatal hyperbilirubinemia and showed that when cut off value of cord blood bilirubin is 3mg/dl it revealed a sensitivity of 70.3% and a negative predictive value of 65.6%.

Singal Vikram et al⁽⁸⁰⁾ study involved 500 infants and the study showed the sensitivity of developing neonatal hyperbilirubinemia was 90% when the cord blood bilirubin level was more than 1.9mg%.

Nilesh Ahire and Ravindra et al⁽⁷⁶⁾ studied 100 infants in predicting neonatal hyperbilirubinemia by sampling cord blood bilirubin levels. The study showed the sensitivity of 100% in developing hyperbilirubinemia when the cord blood bilirubin level was more than 3mg%.

Sun Wangyl, Liangjf, Dulz et al studied the cord blood bilirubin levels in predicting neonatal hyperbilirubinemia conducted in 194 infants and it was found that cord blood bilirubin levels $>2.5\text{mg/dl}$ had the sensitivity of 68.27% in predicting neonatal hyperbilirubinemia.

AIM OF THE STUDY

- To study the sensitivity of cord blood bilirubin levels in predicting neonatal hyperbilirubinemia.

OBJECTIVES

- To statistically analyze the sensitivity of cord blood bilirubin levels in predicting neonatal hyperbilirubinemia.
- To find out mean cord blood bilirubin level.

NEED OF STUDY

- To find out the term neonates who were at greater risk of developing neonatal hyperbilirubinemia.
- To plan for early discharge.
- To decrease the risk of readmission.

MATERIALS AND METHODS

STUDY POPULATION

- All term newborn babies born In Govt Kilpauk Medical college during the study period will be assessed for inclusion and exclusion criteria and will be included in the study after obtaining written informed consent.
- Study design –A hospital based prospective study
- Study period – 6 months (April 2016 - September 2016)
- Study population-180

Inclusion criteria

- Gestational age more than 37 weeks
- Absence of significant illness requiring NICU admission
- Absence of major congenital malformation.

Exclusion criteria

Newborn born to mother prone for hemolysis (OA, OB, Rh incompatibility)

- Gestational age less than 37 weeks
- Significant illness requiring NICU admission
- Mother taking drugs causing neonatal hyperbilirubinemia.
- Family history of jaundice, anemia, splenectomy, liver disease.

- Maternal illness, gestational diabetes mellitus.
- Calculation of Sample size
- Sample size was based on the study of sensitivity of cord blood bilirubin 83% authored by Amar tak shande published in current paediatrics 2005 - 2009.
- Sample size was 180 based on the following
 - Expected sensitivity of cord blood bilirubin 83%
 - Desired accuracy 7%
 - Alpha error 5%

Methodology

Approval from the Institutional scientific and Ethical committee of Government Kilpauk Medical College and Hospital Chennai was obtained. Newborns delivered in KMC who satisfy the inclusion criteria were included in the study. The parents were given counseling and informed consent was obtained from them for investigation and enrollment into the study. If at any point of time newborn was found to have parameters in the exclusion criteria then that newborn was excluded from the study.

- Under strict aseptic precautions Cord blood samples were collected from all newborns for analysis of serum bilirubin levels and blood grouping typing with the protocol inclusion criteria.

- These newborns were followed up for three days and the values of bilirubin on the third day were compared with cord blood bilirubin level.
- Under strict aseptic precautions, 2ml of cord blood was collected from the umbilical cord and sent to investigations.
- Serum bilirubin assessment
- Blood grouping and typing.
- 2ml of venous blood was collected from the baby > 72 hours for assessment of serum bilirubin.

PRINCIPLE :

VADENDER BERGH'S TEST

- Serum and cord blood bilirubin assessment was done by diazo method. 2,5-dichlorophenyldiazonium tetrafluoroborate was the diazo reagent. This reagent is used to accelerate the reaction. Pink colour is formed due to reaction between bilirubin and diazotized sulphanilic acid in the acidic medium. Limitations of the test include blood sample size, reliability and accuracy interlaboratory variations are found around 10 to 15%. variations in conjugated bilirubin measurement involves 20%.

STATISTICAL ANALYSIS

IBM. SPSS statistics software 23.0 Version was being used to analyse the data obtained. Data descriptive statistics frequency analysis was carried out to describe the collected data. Categorical variables analysed with percentage

analysis continuous variables were analysed with mean and standard deviation. The Sensitivity, Specificity, Positive predictive value and Negative predictive value were found by receiver operator curve analysis. Categorical variables association was computed with Chi-square test. In both of the above statistical tools the probability value above .05 is considered as significant level.

RESULTS AND ANALYSIS

The study was conducted in government Kilpauk medical college. The neonates who were satisfied with the inclusion criteria were included. The study was done in 180 Term neonates who were born in Govt Kilpauk medical college hospital. Study outcome as defined by total serum bilirubin of more than or equal to 15mg/dl after 72 hrs. All neonates required phototherapy and none required exchange transfusion. The incidence of neonatal hyperbilirubinemia in this study was 22.8% out of 180 term neonates.

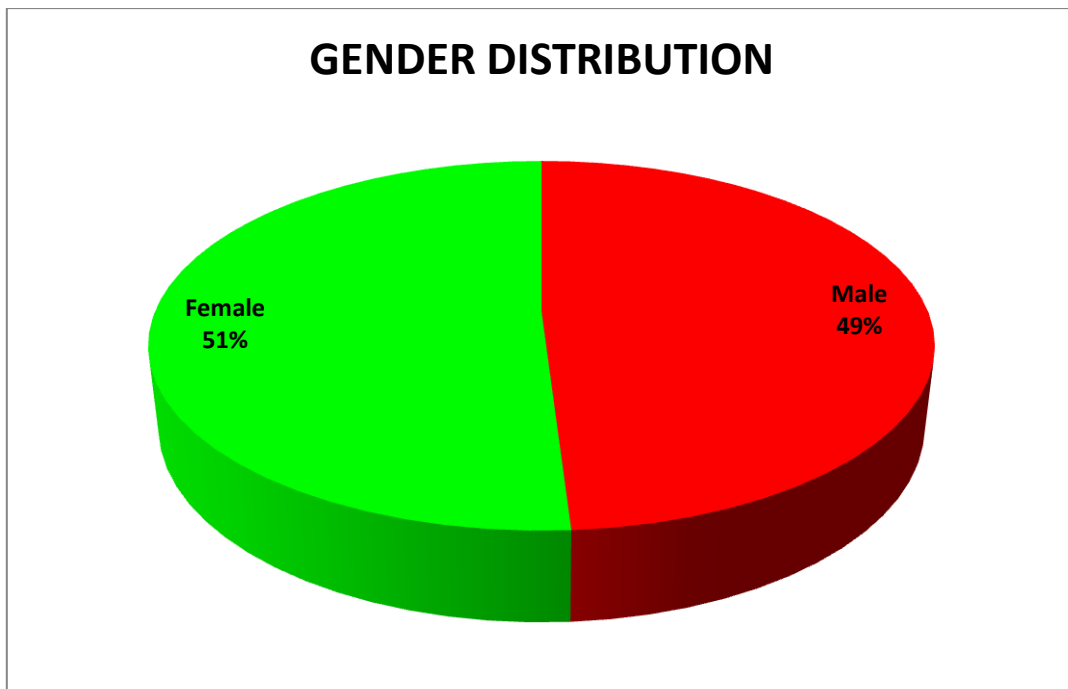


TABLE 1:

CROSS TAB: GENDER & SERUM BILIRUBIN

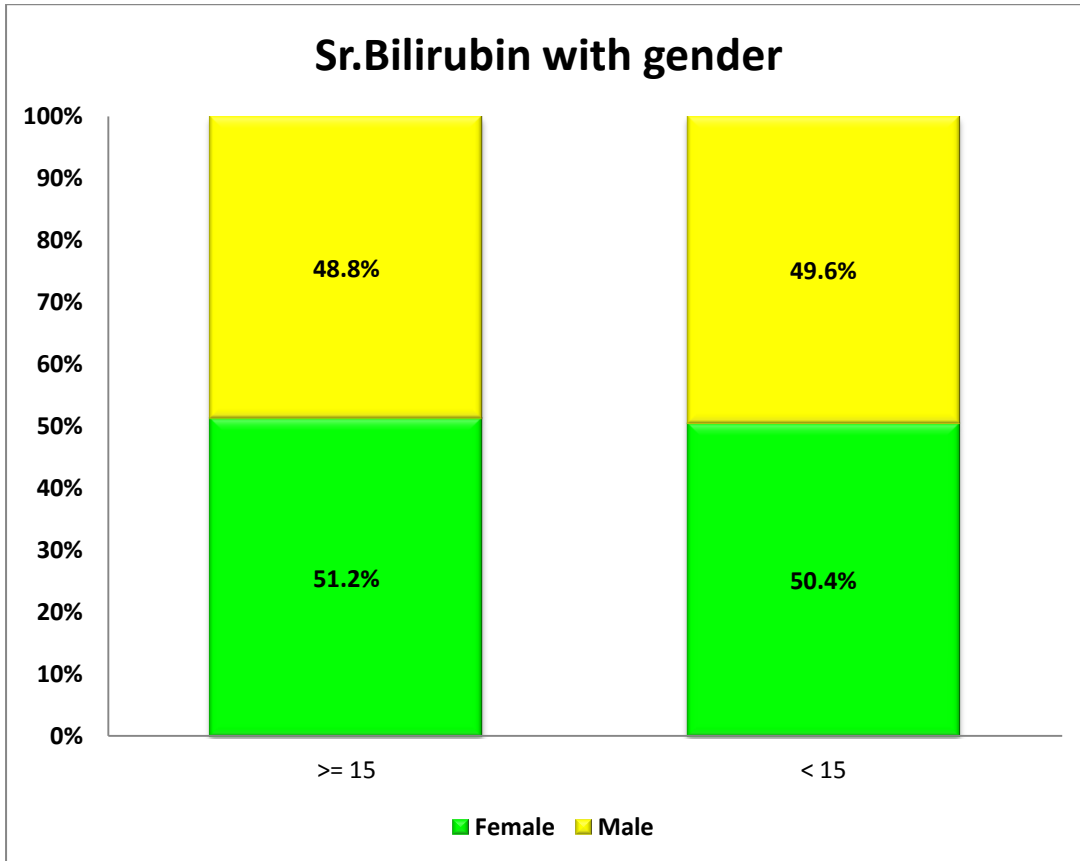
SERUM BILIRUBIN

GENDER	≥ 15	< 15
Female	51.2%	50.4%
Male	48.8%	49.6%

P - Value	** Highly Significant at $P \leq .01$
P -Value	# No Significant at $P > .05$

CHART-2 :

GENDER Vs SERUM BILIRUBIN



Chi-Square Tests					
	Value	df	Asymp. Sig. (2- sided)	Exact Sig. (2- sided)	Exact Sig. (1- sided)
Pearson Chi-Square	.009 ^a	1	.923		
Continuity Correction ^b	0.000	1	1.000		
Likelihood Ratio	.009	1	.923		
Fisher's Exact Test				1.000	.532
No. of Valid Cases	180				

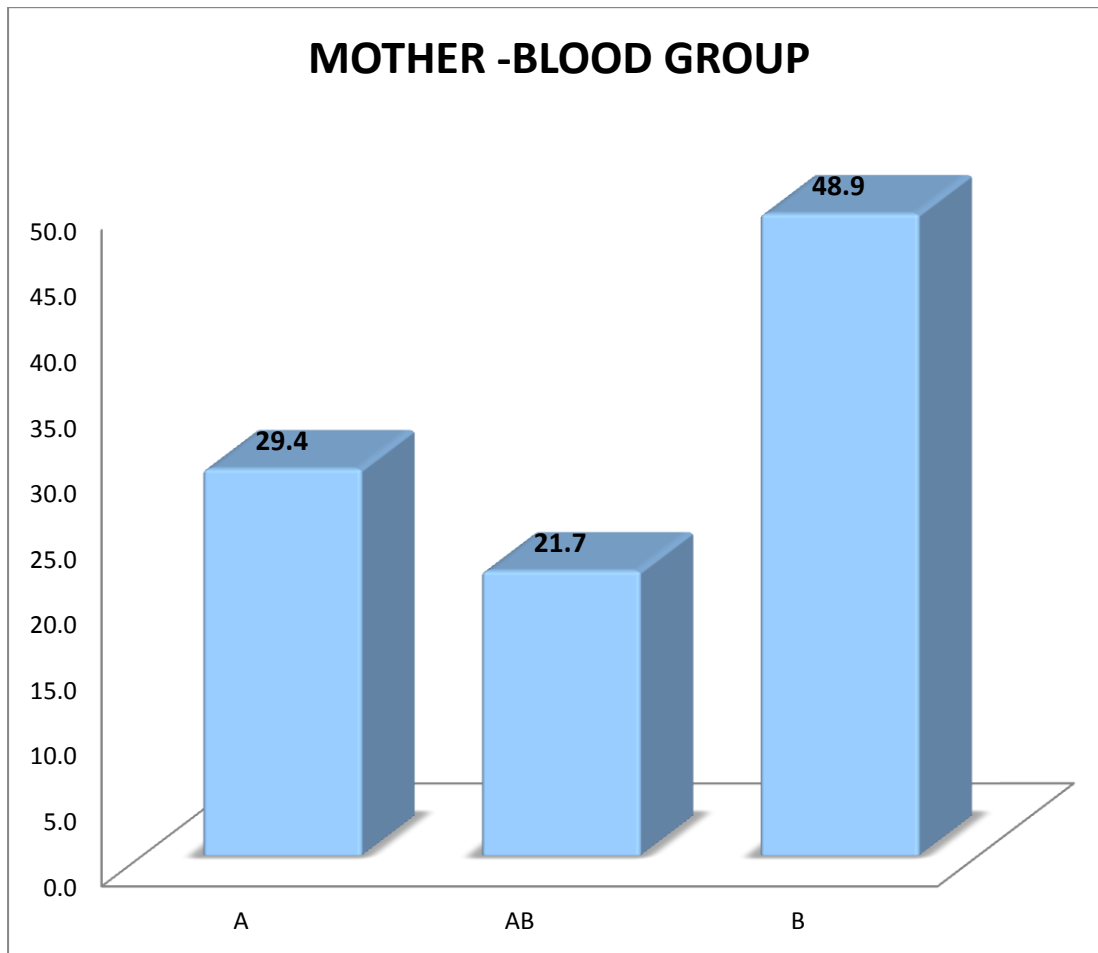
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 20.27.

b. Computed only for a 2x2 table

In the present study, sex of the baby and neonatal hyperbilirubinemia was not statistically significant.

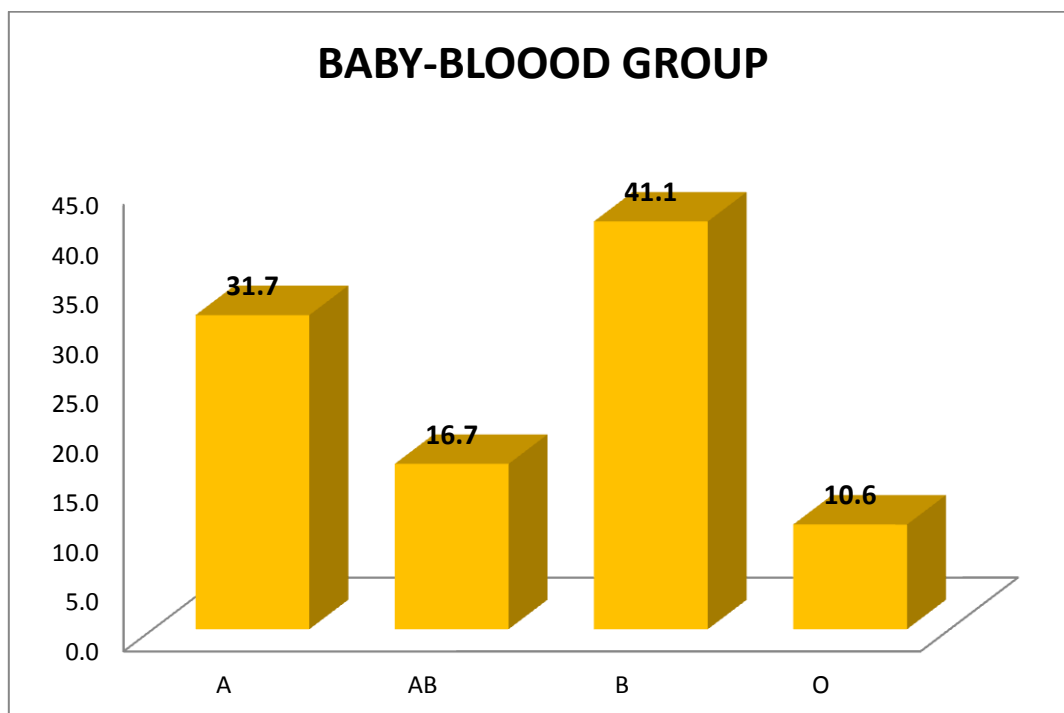
CHART-3

MOTHER BLOOD GROUP



In this study around 88 mothers had B blood group, 39 mothers had AB blood group and 53 mothers had A blood group.

mother -blood group					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	A	53	29.4	29.4	29.4
	AB	39	21.7	21.7	51.1
	B	88	48.9	48.9	100.0
	Total	180	100.0	100.0	



baby-blood group					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	A	57	31.7	31.7	31.7
	AB	30	16.7	16.7	48.3
	B	74	41.1	41.1	89.4
	O	19	10.6	10.6	100.0
	Total	180	100.0	100.0	

In this study 74 neonates had B blood group,57 neonates had A blood group,30 neonates had AB blood group,19 neonates had O blood group.

MODE OF DELIVERY

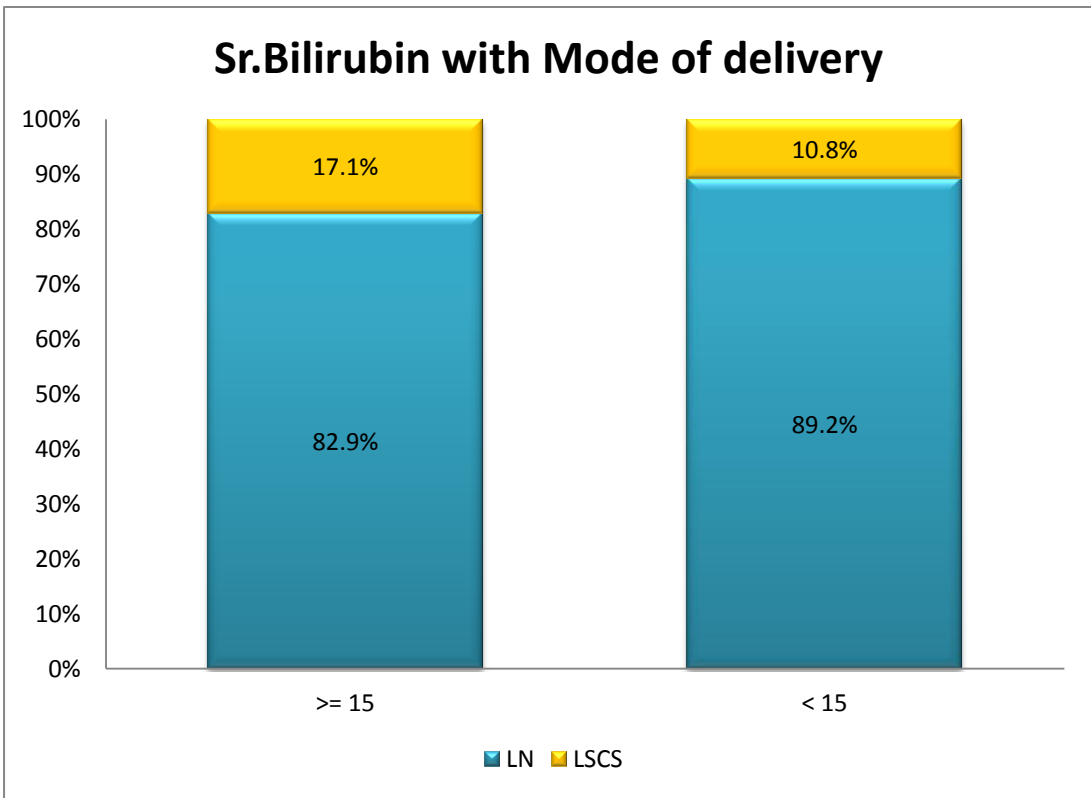
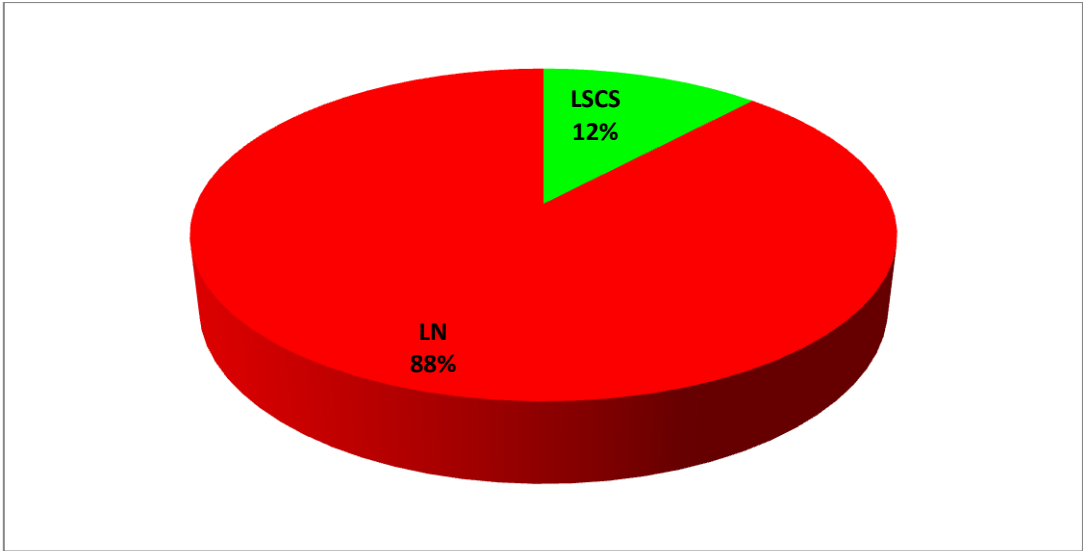


TABLE 3

MODE OF DELIVERY Vs SERUM BILIRUBIN

Crosstab						
			Sr.bilirubin Range		Total	
			>= 15	< 15		
Mode of delivery	LN	Count	34	124	158	
		% within Sr. bilirubin Range	82.9%	89.2%	87.8%	
	LSCS	Count	7	15	22	
		% within Sr. bilirubin Range	17.1%	10.8%	12.2%	
	Total		Count	41	139	180
			% within Sr. bilirubin Range	100.0%	100.0%	100.0%

Chi-Square Tests					
	Value	Df	Asymp. Sig.	Exact Sig. (2-	Exact Sig. (1-

			(2-sided)	sided)	sided)
Pearson Chi-Square	1.165 ^a	1	.281		
Continuity Correction ^b	.653	1	.419		
Likelihood Ratio	1.088	1	.297		
Fisher's Exact Test				.285	.206
No of Valid Cases	180				

a. 0 cells (0.0%) have expected count < 5. The minimum expected count is 5.01.

b. Computed only for a 2x2 table

In this study 34 neonates born by normal vaginal delivery developed neonatal hyperbilirubinemia and 7 babies born by LSCS developed neonatal hyperbilirubinemia.

In the present study no statistically significant association was found between mode of delivery and neonatal hyperbilirubinemia.

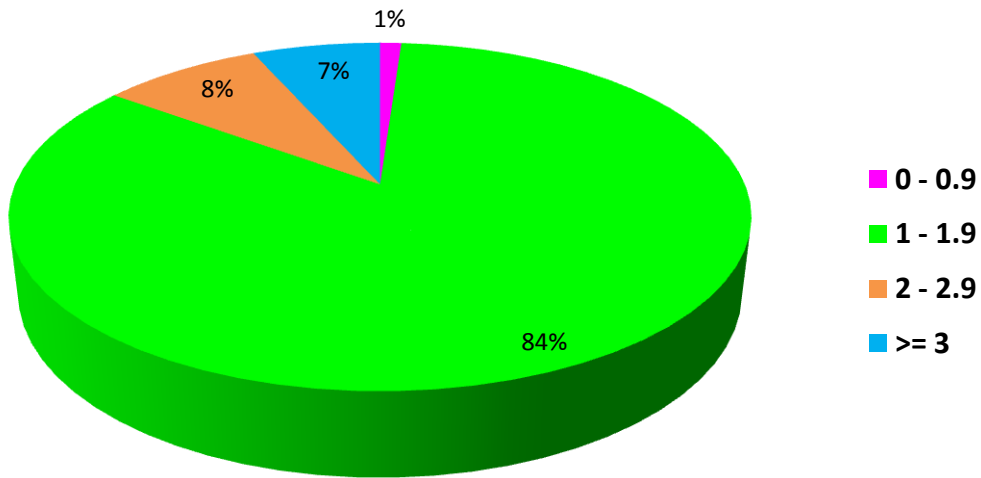
RELATIONSHIP BETWEEN CORD BLOOD BILIRUBIN LEVEL AND SERUMBILIRUBINLEVEL

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
C Bilirubin	180	.80	2.30	1.5425	.35993
Sr.Bilirubin	180	7.0	18.7	12.428	2.6137
Valid N (listwise)	180				

In this study the mean of cord blood bilirubin level is 1.5425 mg/dl with standard deviation of 0.35993.

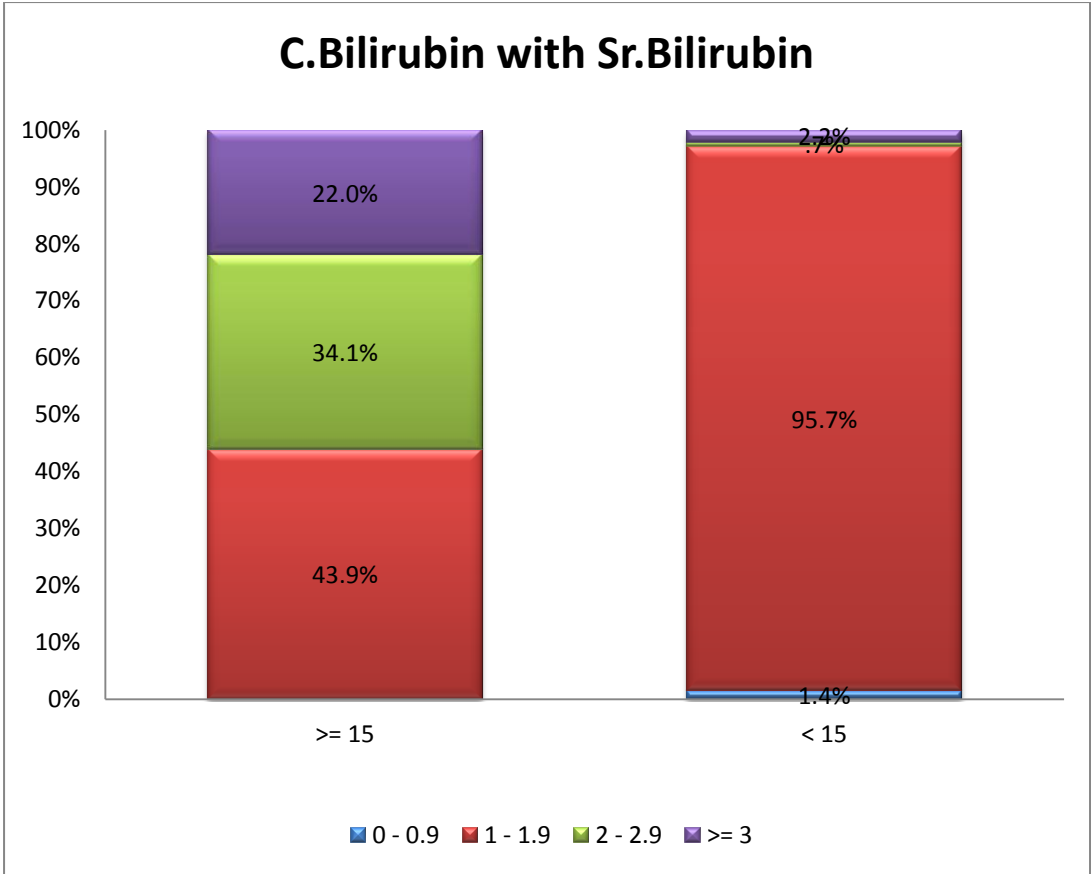
In this study the mean serum bilirubin level is 12.428 mg/dl with the standard deviation of 2.6137

Chart -4 :CORD BLOOD BILIRUBIN RANGE



CORD BLOOD BILIRUBIN RANGE	
0 - 0.9	1.1%
1 - 1.9	83.9%
2 - 2.9	8.3%
>= 3	6.7%

The cord blood bilirubin in the range of 1 to 1.9mg/dl was found in majority of neonates (84%) 8% of neonates were in the range of 2 to 2.9mg/dl and 7% of neonates had more than or equal to 3mg/dl.



CORD BILIRUBIN	Sr.Bilirubin >= 15	Sr.Bilirubin < 15
0 - 0.9		1.4%
1 - 1.9	43.9%	95.7%
2 - 2.9	34.1%	.7%
>= 3	22.0%	2.2%

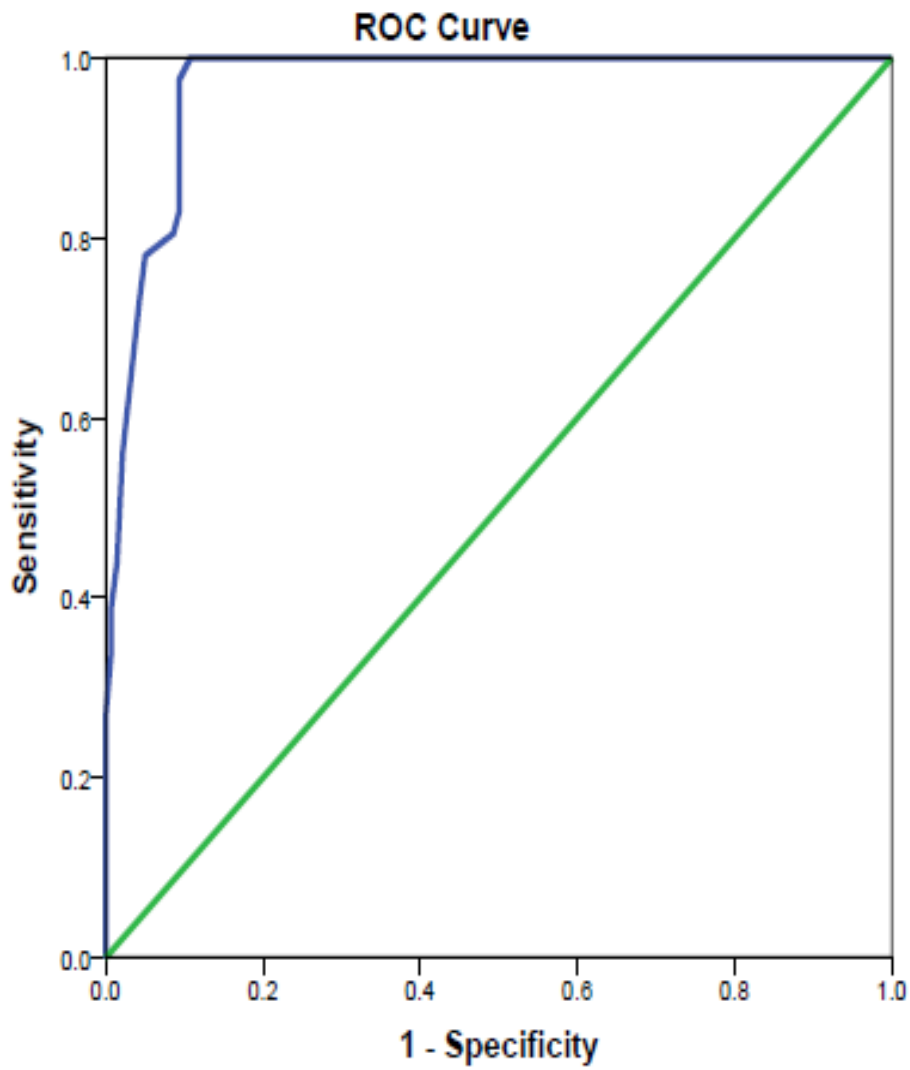
TABLE - 4:**CORD BLOOD BILIRUBIN VS SERUM BILIRUBIN**

			Sr.bilirubin Range		Total
			>= 15	< 15	
C.Bilirubin range	0 - 0.9	Count	0	2	2
		% within Sr bilirubin Range	0.0%	1.4%	1.1%
	1 - 1.9	Count	18	133	151
		% within Sr. bilirubin Range	43.9%	95.7%	83.9%
	2 - 2.9	Count	14	1	15
		% within Sr. bilirubin Range	34.1%	.7%	8.3%
	>= 3	Count	9	3	12
		% within Sr. bilirubin Range	22.0%	2.2%	6.7%
Total		Count	41	139	180
		% within Sr. bilirubin Range	100.0%	100.0%	100.0%

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	71.767 ^a	3	.000
Likelihood Ratio	61.992	3	.000
Linear-by-Linear Association	54.734	1	.000
N of Valid Cases	180		

a. 4 cells (50.0%) have expected count less than 5. The minimum expected count is .46.

ROC CURVE



Diagonal segments are produced by ties.

Area Under the Curve

Test Result Variable(s): C Bilirubin				
Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.969	.011	.000	.948	.990

The test result variable(s): C Bilirubin has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Case Processing Summary

Sr.Bilirubin Range	Valid N (list wise)
Positive ^a	41
Negative	139

Larger values of the test result variable(s) indicate for a positive actual s

a. The positive actual state is ≥ 15 .

DISCUSSION

This study was conducted in Government Kilpauk Medical College Chennai. This is a renowned tertiary care teaching centre. Our study population comprises 180 newborns born in Govt Kilpauk Medical College Hospital. Out of 180 babies 91 were female babies and 89 were male babies .In the present study no significant difference (pvalue 0.923) was found between gender of the baby and neonatal hyperbilirubinemia.. This was in accordance with study by Amartak Shande, Gurudeepsingh, Eswara et al.

Out of 180 babies 158 babies were delivered by labour naturalis and 22 babies were delivered by LSCS. In the present study no significant difference (p value 0.281) in the development of neonatal hyperbilirubinemia was identified between the cases who were born by LSCS and normal vaginal delivery. This was in accordance with study by Amartak shande, Gurudeepsingh et al. There was also no association between cord blood bilirubin and mode of delivery (pvalue0.515).About 1%of the study population had cord blood bilirubin in the range of <0.9,84% had cord blood bilirubin in the range 1 to1.9mg/dl and 8% had cordblood bilirubin in the range of 2to2.9mg/dl and 7%had cord blood bilirubin in the range of 3mg/dl and more than 3mg/dl.

The mean cord blood bilirubin in the study was 1.5425 (+0.35993to0.35993-mg/dl). The mean serum bilirubin level in the present study was12.428mg/dl(+2.6137-2.6137)

The use of the critical cord bilirubin level 1.85mg/dl will predict significant hyperbilirubinemia.

The association between cord blood bilirubin level equal to or more than 1.85mg/dl and neonatal hyperbilirubinemia was statistically significant (p.000). The relationship of cord bilirubin and serum bilirubin was studied. The probability that neonates with cord blood bilirubin level equal to or more than 1.85mg/dl would later develop hyperbilirubinemia ie, positive predictive value was 72.3%.

The negative predictive value, the probability of non hyperbilirubinemia if the cord blood bilirubin less than 1.85mg/dl was 94.7%. The sensitivity of cord blood bilirubin in predicting neonatal hyperbilirubinemia was 82.9% (if a neonate become hyperbilirubinemic ,the probability that the cord blood bilirubin was higher than or equal to 1.85mg/dl).

The specificity of cord blood bilirubin in predicting neonatal hyperbilirubinemia was 90.6%. With Receiver operating characteristic analysis, cord blood bilirubin level of equal to or more than 1.85mg/dl was determined to have high sensitivity(82.9%).

At this cord blood bilirubin level the negative predictive value was 94.7%. out of 41 babies who developed neonatal hyperbilirubinemia only 7 babies had serum bilirubin level <1.85mg/dl all others had cord blood bilirubin level more than or equal to 1.85mg/dl. Out of 139 babies who didn't develop hyperbilirubinemia only 13 babies had cord blood bilirubin level more than or equal to 1.85mg/dl.

Out of 47 babies having cord blood bilirubin level more than or equal to 1.85mg/dl 34 babies developed neonatal hyperbilirubinemia. Out of 133 neonates who had cord blood bilirubin less than 1.85mg/dl only 7 babies developed hyperbilirubinemia the present study goes well with the following studies.

Gurudeepsingh et al⁽⁷²⁾ study group consisted of neonates delivered in MMIMSR -100 full-terms Appropriate for gestational age .Incidence of hyperbilirubinemia was 14% with Mean umbilical cord blood bilirubin was 1.63 ± 0.73 . neonatal hyperbilirubinemia and mode of delivery ($p > 0.005$) was not statically significant. Neonatal hyperbilirubinemia and sex of the baby and maternal age ($p > 0.05$) was not statically significant. There is no association between mother's blood group and the increased risk of hyperbilirubinemia in neonates.

Association between neonatal hyperbilirubinemia and increasing umbilical cord blood bilirubin ($p = 0.001$) was statistically significant. Using umbilical cord blood bilirubin level of 1.9 mg/dL hyperbilirubinemia showed sensitivity of 92.8%, specificity of 83.7% , negative predictive value of 98.6% and positive predictive value of 48.1%. The study showed that umbilical cord blood bilirubin is an indirect indicator of serum bilirubin to indicate the development of neonatal hyperbilirubinemia and decide need for intervention in healthy term neonates.

Eswara et al prospectively determine the critical cord serum bilirubin level to predict significant hyperbilirubinemia in healthy term newborns. In that

study a total 51 of 288 (18.09%) were found to have significant hyperbilirubinemia. In this study, umbilical cord bilirubin level cut off point is 2 mg/dl with good sensitivity (94.12), specificity (90.9%), negative predictive value (98.59%), positive predictive value (69.57%).

Zakianahar et al study showed that Cord blood bilirubin level of ≥ 2 gm/dl has a sensitivity of 70% and specificity of 89% in predicting the risk of neonatal hyperbilirubinemia.

The present study was also in accordance with the studies conducted by Ramprasath et al, Jayalakshmi et al, Alpey et al, Knudsen et al, Nilesh ahire et al, Aleiden et al., But the study conducted by Jayashree Vasudevan was not in accordance with the above the studies⁷⁴.

LIMITATIONS OF STUDY

- Only healthy term babies were included in the study
- Preterm babies and sick babies are not included in the study.
- Babies prone for hemolysis were not included in the study.
- Diazo method of measuring serum bilirubin involves interlab variability of the results.

CONCLUSION

In the present study it was concluded that cord blood bilirubin can be used as a noninvasive screening test to predict the neonates at risk for developing significant hyperbilirubinemia.

In this study it was showed that there was a significant association between cord blood

Bilirubin level more than 1.85mg/dl and neonatal hyperbilirubinemia.No statistically significant association was found between gender,mode of delivery and neonatal hyperbilirubinemia

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INFORMED CONSENT FORM

STUDY: "A STUDY ON SENSITIVITY OF CORD BLOOD BILIRUBIN LEVELS IN PREDICTING NEONATAL HYPERBILIRUBINEMIA"

STUDY CENTRE: GOVT. KILPAUK MEDICAL COLLEGE HOSPITAL

PATIENT'S NAME:

PATIENT'S AGE:

LP NO :

Patient may check () these boxes

I confirm that I understood the purpose of the procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction

I understand that my participation in the study is purely voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

I understand that the Ethics Committeemembers, and the regulatory authorities will need not my permission to look at my health records, both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law.

I agree not to restrict the use of any data or results that arise from the study. I agree to take part in the above study and to comply with the instructions given during the study and faithfully co operate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.

I hereby consent to participate in this study.

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests.

Signature / thumb impression:

Patient's name and address: place: date:

Signature of the investigator:

Study investigator's name: place: date:

PARTICIPANTS' INFORMATION SHEET

Investigator :- Dr. C.MARY REENA

Name of the participant :-

Title: " A STUDY ON SENSITIVITY OF CORD BLOOD BILIRUBIN LEVELS IN PREDICTING NEONATAL HYPERBILIRUBINEMIA".

You are invited to take part in this research study. We have got approval from the IEC. You are asked to participate because you satisfy the eligibility criteria.

What is the purpose of this research?

The study is conducted to assess the sensitivity of cord blood bilirubin in predicting neonatal hyperbilirubinemia

BENEFITS:

This study will help to assess the babies who were more prone for developing neonatal hyperbilirubinemia and to minimize readmission and plan for early discharge.

CONFIDENTIALITY:

Patients who participated in the study and their details will be maintained confidentially and at any cost, those details will not be let out.

RIGHT TO WITHDRAW :

Patients will not be forced to complete the study. At any cost, in such circumstances the treatment will not be compromised.

Date :

Signature of the investigator: -

Place :

Signature/Thumb impression

of the participant

RIGHT TO WITHDRAW :

Patients will not be forced to complete the study. At any cost, in such circumstances the treatment will not be compromised.

Date :

Signature of the investigator: -

Place :

Signature/Thumb impression

of the participant

சுய ஒப்புதல் படிவம்

இடம் : அரசு கீழ்பாக்கம் மருத்துவக் கல்லூரி, சென்னை

எனது குழந்தைக்கு இரத்தத்தில் மஞ்சள் காமாலை ஏற்படுவதற்கான வாய்ப்புகள் உள்ளதா என்பதை தொப்புள்கொடியிலிருந்து இரத்தத்தை எடுத்து ஆய்வு செய்து கொள்வதற்கு சம்மதம்

b/o nathiya	F	A	A	1.5	12.5	LN
b/o revathi	M	A	B	1.9	17.1	LN
b/o vanmathi	F	B	B	1.95	16.4	LN
b/o vijayakumari	M	B	A	1	9.8	LN
b/o chellam	F	AB	AB	1.3	10.2	LN
b/o kodeswari	M	B	B	1.25	9.2	LN
b/o sowmiya	M	B	AB	1.5	12.5	LN
b/o subhashri	F	AB	AB	1.1	11.5	LN
b/o pushpa	F	B	B	2.2	17.5	LN
b/o rebecca	F	A	A	1.87	13	LN
b/o vasha	M	AB	AB	1.6	12.2	LN
b/o shalini	F	B	B	1.87	13.4	LN
b/o radha	F	B	B	1	9	LSCS

ABBREVIATIONS

RES	–	Reticulo Endothelial System
RBC	–	Red Blood Corpuscles
PCLB	–	Per Cutaneous Liver Biopsy
SSPT	–	Single Surface Phototherapy
CFT	–	Compact Fluorescent Tubes
HBABA	–	2-4' Hydroxy Benzene Azo Benzoic Acid
BERA	–	Brain Stem Evoked Response Audiometry
DIVC	-	Disseminated Intravascular Coagulation
PCR	–	Polymerase Chain Reaction
LSCS	-	Lower Segment Caesarean Section

