A COMPARISON OF TWO TARGETS OF SERUM BILIRUBIN CONCENTRATION FOR PHOTOTHERAPY DISCONTINUATION IN NEONATAL JAUNDICE

Dissertation submitted to

The Tamil Nadu Dr. M.G.R Medical University, Chennai

In fulfilment of the requirements for the award of the degree of

Doctor of Medicine in Paediatrics

Under the guidance of

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COIMBATORE

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

CHENNAI, TAMILNADU

MAY 2019

CERTIFICATE

This is to certify that the thesis entitled **"A COMPARISON OF TWO TARGETS OF SERUM BILIRUBIN CONCENTRATION FOR PHOTOTHERAPY DISCONTINUATION IN NEONATAL JAUNDICE"** is the bonafide original research work of **Dr.VEDA SENTHIL VELAN. G,** has been done under the guidance of **Dr.K.NEELAKANDAN,** Professor and Head, Department of Paediatrics PSG IMS&R, Coimbatore in fulfilment of the regulations laid down by The Tamilnadu Dr.M.G.R Medical University for the award of MD degree in Paediatrics.

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DECLARATION

I, hereby declare that this dissertation entitled **"A COMPARISON OF TWO TARGETS OF SERUM BILIRUBIN CONCENTRATION FOR PHOTOTHERAPY DISCONTINUATION IN NEONATAL JAUNDICE"** was prepared by me under the guidance and supervision of **Dr. K.NEELAKANDAN,** Professor and Head, Department of Paediatrics, PSG IMS&R, Coimbatore.

This dissertation is submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai in fulfilment of the university regulations for the award of MD degree in Paediatrics. This dissertation has not been submitted elsewhere for the award of any other Degree or Diploma.

Dr. VEDA SENTHIL VELAN. G

CERTIFICATE

This is to certify that this dissertation work titled **"A COMPARISON OF TWO TARGETS OF SERUM BILIRUBIN CONCENTRATION FOR PHOTOTHERAPY DISCONTINUATION IN NEONATAL JAUNDICE "** of the candidate **Dr.VEDA SENTHIL VELAN. G,** with registration Number **201717501** for the award of **DOCTOR OF MEDICINE** in the branch of **PAEDIATRICS**. I personally verified the urkund.com website for plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 1% of plagiarism in the dissertation.

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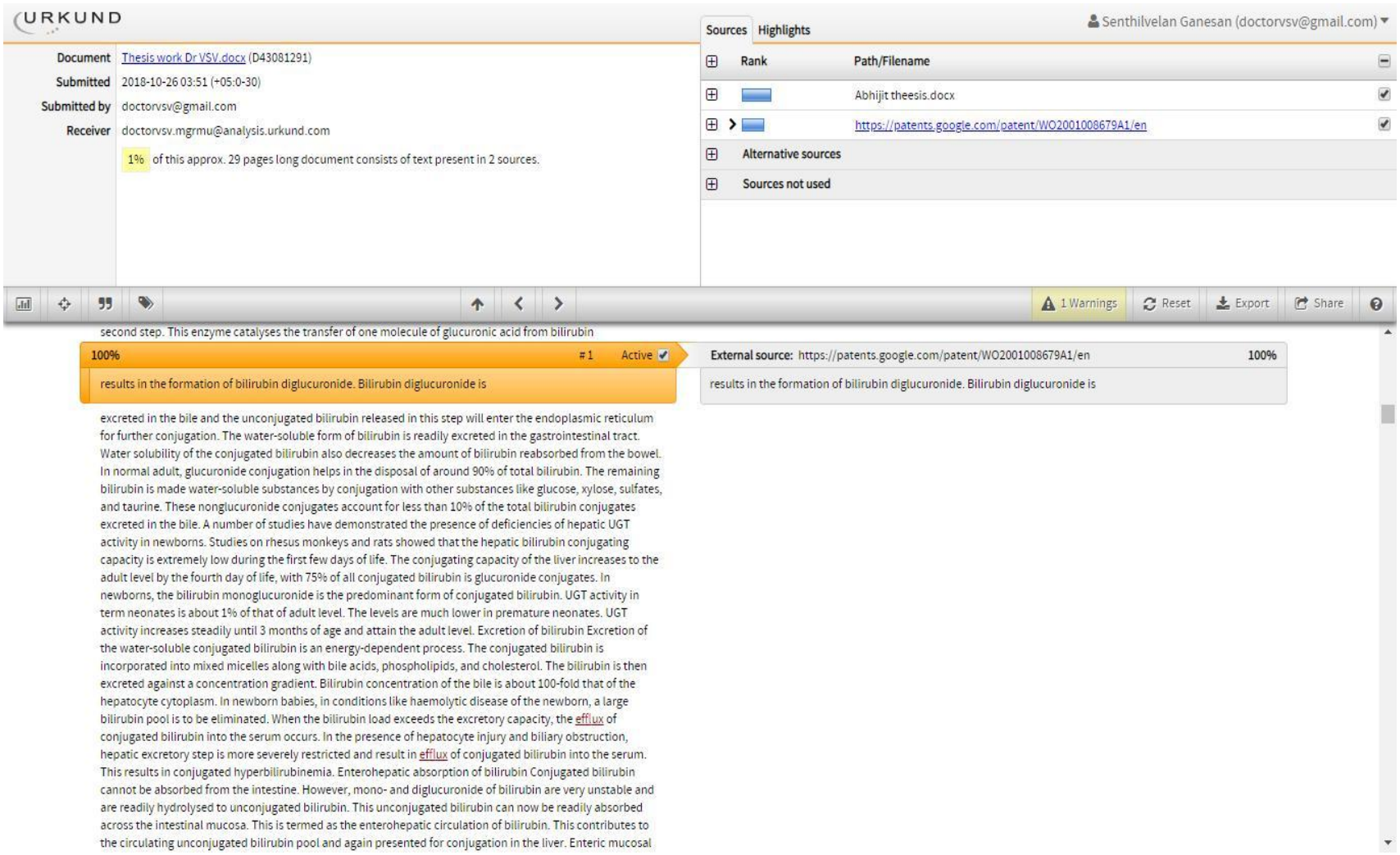
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CONTENTS

INTRODUCTION

Neonatal hyperbilirubinemia is one of the common morbidity in the newborn babies. Most of the babies develop hyperbilirubinemia in early neonatal period. Approximately 60% of healthy term infants and 80% of premature infants develop clinically visible jaundice in the first week of life.In the majority of cases, jaundice is mild and transient. It occurs due to immaturity of the liver's excretory pathway for bilirubin, when the bilirubin production is more in initial days of life. Hence, most of the babies do not require treatment for neonatal jaundice. Some babies may show significant rise in serum bilirubin and require treatment to avoid serious brain injury. This occurs in the early neonatal days which may prolong the duration of hospital stay following the delivery of the baby.

High serum bilirubin may cause acute bilirubin encephalopathy, a most dreaded complication of neonatal jaundice(1).Acute bilirubin encephalopathy (ABE) may evolve into kernicterus (chronic bilirubin encephalopathy), which is characterized by movement disorders like dystonia and/or choreoathetosis, hearing loss and oculomotor palsy.

Total serum bilirubin is the measure of albumin-bound bilirubin in the serum. The small circulating fraction of bilirubin, not bound to albumin or other serum proteins is called unbound or “free” bilirubin. Free bilirubin is the one which crosses the blood brain barrier and act as a vehicle for the bilirubin induced neurological insult.Bilirubin-induced neurotoxicity depends on the interaction between the level and duration of “free” bilirubin exposure of the brain. The laboratory measurement of circulating free bilirubin

is not unavailable. Hence we must rely on the total serum bilirubin and the bilirubin/albumin (B/A) ratio to assess the risk for acute bilirubin encephalopathy and to decide on starting treatment.

The key measures to prevent bilirubin encephalopathy in term and late-preterm neonates includes hyperbilirubinemia risk assessment, appropriate and timely birth-hospitalization follow-up, and timely and effective treatment of marked hyperbilirubinemia with phototherapy and/or exchange transfusion.

Phototherapy and exchange transfusion are the main modalities of treatment for neonatal hyperbilirubinemia. Current AAP phototherapy(2), and exchange transfusion treatment thresholds for infants greater than or equal to 35 weeks' gestation are shown in Figs. respectively. Phototherapy remains the most widely used modality of treatment for neonatal jaundice. Phototherapy is effective in reducing the serum bilirubin level in most of the newborn babies. Some babies with severe hemolysis, may show increasing serum bilirubin while on phototherapy and end up requiring exchange transfusion to prevent bilirubin encephalopathy.

In clinical guidelines by American Academy of Pediatrics for diagnosis and treatment of jaundice(2), charts are available to decide when a newborn baby should be treated with phototherapy and exchange transfusion. Depends on the gestational age of the newborn and the associated risk factors, charts were referred and treatment options were decided. The guideline does not recommend when the phototherapy can be stopped. For infants readmitted for phototherapy after discharge from birth hospitalization, it was

recommended to stop phototherapy when total serum bilirubin drops below 13-14mg/dl. This recommendation cannot be applied to younger neonates, for whom phototherapy may need to started at total serum bilirubin level<13 mg/dl.

Rebound hyperbilirubinemia can occur afterstopping phototherapy. It is due to continued underlying alteration in bilirubin metabolism which results in resurgence of serum bilirubin level. The rise in serum bilirubin level may sometimes necessitates readmission for treatment with either phototherapy or exchange transfusion to prevent neurological damage by the bilirubin.Hence it is necessary to find out the level at which phototherapy can be stopped without increasing the chance of rebound hyperbilirubinemia.

The United Kingdom's National Institute for Health and Care Excellence guidelines(3) recommends stopping phototherapy at serum bilirubin level of >3mg/dl below the treatment threshold.

In a pilot study conducted by Barak et a(4)l, they compared the outcome of two group of jaundiced but otherwise healthy newborn randomized to one of the two targets of bilirubin concentration for discontinuation of phototherapy. They found no significant difference in the occurrence of rebound when phototherapy was discontinued at a TSB of ≥1 mg/dl versus ≥3mg/dl below the AAP phototherapy threshold[5 out of 25 versus 5 out of 27 respectively, p=0.58], but the trial was a pilot study included only 52 neonates. They recommend further study with larger sample size.

We proposed to conduct a study with larger sample size to find the serum bilirubin level at which the phototherapy can be stopped.

RESEARCH QUESTION:

In newborns of ≥35weeks gestational age with neonatal hyperbilirubinemia treated as per AAP guidelines, does discontinuing phototherapy at serum bilirubin level 1.0-2.9mg/dl and ≥3mg/dl below the treatment threshold cause difference in the occurrence of significant rebound hyperbilirubinemia?

AIM AND OBJECTIVES

AIM:

To compare the occurrence of significant rebound hyperbilirubinemia between two group of jaundiced new born for whom phototherapy was stopped at serum bilirubin level 1.0-2.9 mg/dl and ≥3 mg/dl below the treatment threshold as per AAP guidelines.

OBJECTIVES:

Primary objective is to find out the number of babies who develop significant rebound hyperbilirubinemia following discontinuation of phototherapy at SBR level of 1.0-2.9 mg/dl and ≥3mg/dl below the treatment cut off in AAP chart.

Secondary objectives are i) to compare the total duration of phototherapy between two groups and ii) to compare the durationof hospital stay between two group.

REVIEW OF LITERATURE

Neonatal Hyperbilirubinemia

Neonatal hyperbilirubinemia reflects the developmental changes in production, metabolism, and excretion of bilirubin. It is characterized by (1) an increased bilirubin load on immature hepatocytes and (2) decreased hepatic clearance of bilirubin. The increased hepatic bilirubin load is due to overproductionof bilirubin which in turn occurs due to large red cell mass, reduced red cell life span, and in some newborns, hemolytic conditions may accelerate red cell turnover. Decreased bilirubin clearance in newborns results from reduced hepatic bilirubin uptake and conjugation. In addition, an increased reabsorption of bilirubin from the intestines, enterohepatic circulation reduces the bilirubin excretion and increases the bilirubin load on the immature liver.

In newborns, bilirubin has the propensity for deposition in skin and mucus membranes producing yellowish discoloration. It may also deposits in the brain and producing acute and chronic bilirubin encephalopathy. A thorough knowledge of the bilirubin metabolism is essential to understand the management principles and the potential complications.

Bilirubin Metabolism

Bilirubin is produced as an end product of two stage heme catabolism in the reticuloendothelial system. Heme is the oxygen carrying component present in the hemoglobin. Destruction of the red blood cells results in the release of heme from

haemoglobin. In the first step, heme is converted to biliverdinIXa and this rate limiting step is catalysed by heme oxygenase-1.This result in the release of free iron and carbon monoxide in equimolor amounts. Iron is reutilized in the hemoglobin synthesis and the carbon monoxide is excreted through lungs. Biliverdin is blue green, water soluble and nontoxic product of heme.Biliverdin is readily excreted by the liver and kidneys. In mammals, biliverdinreductase converts the biliverdin to bilirubin IXa. Bilirubin IXa is the only toxic isomer of bilirubin. Bilirubin is virtually water insoluble at physiological pH and hence it can cross all biological membranes including blood brain barrier. 1 gram of hemoglobin, on degradation produces 34mg of bilirubin. Bilirubin must be conjugated by hepatic enzyme, uridinediphosphoglucuronateglucuronosyltransferase before getting excreted in bile.

The carbon monoxide(CO) produced as the result of heme degradation binds to carboxy haemoglobin and excreted by lung. Quantitative estimation of the carbon monoxide excretion offers reasonable assessment of the heme degradation and bilirubin production in infants without any lung disease.4

Bilirubin Production

Bilirubin is derived from the heme, which is released from the destruction of RBCs. Carbon monoxide excretion demonstrated that the bilirubin production is increased two to three times than the adult in day one of life. Bilirubin production is estimated to be 8 to 10mg/kg of body weight per day. This increased bilirubin production rapidly decreases over next two days. Factors which explain this increased production of

Bilirubin in early post natal days include 1)reduced life span of RBCs, 70 to 90 days compared to 120 days in adult, 2) very large pool of hematopoietic tissue, which stops functioning after birth, 3) increased turnover of cytochromes and 4) increased bilirubin absorption from the intestines, enterohepatic circulation.

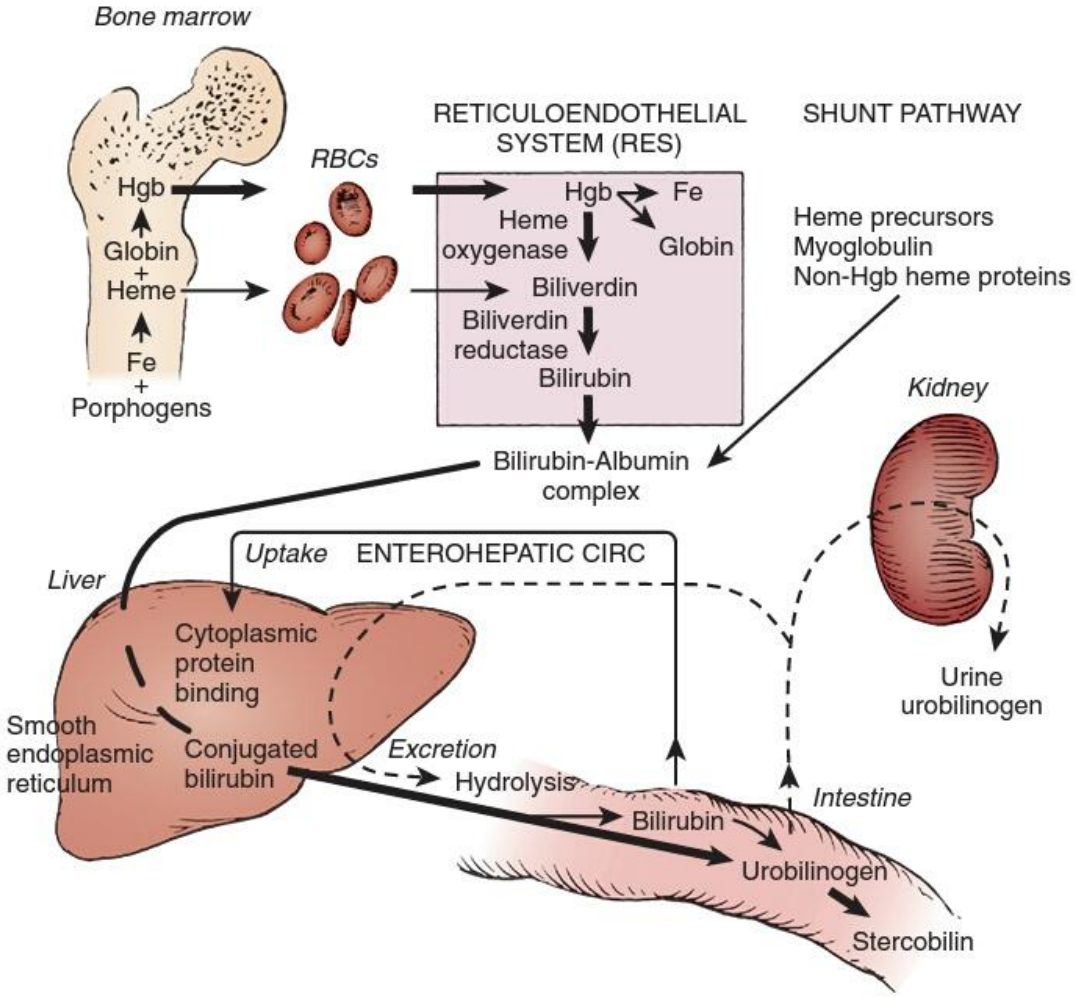


Figure 1: Bilirubin synthesis, transport and excretion

Bilirubin Transport

Unconjugated bilirubin is insoluble in water at pH 7.4. In plasma it is readily bound to albumin. On average, about 7 to 8 mg/dl of unconjugated bilirubin bound to each gram of albumin. Newborns have reduced plasma binding capacity than adults. Reduced binding can be because of reduced serum albumin concentration reduced binding capacities. The unbound bilirubin fraction is believed to be more sensitive predictor of bilirubin induced neurological dysfunction. But currently, there is no reliable method to measure the unbound bilirubin fraction.

Bilirubin exists in four different forms in circulation. It includes, 1) unconjugated bilirubin reversibly bound to albumin, 2) free bilirubin, unconjugated bilirubin not bound to albumin, 3) conjugated bilirubin released from liver into circulation, to be excreted by renal or biliary system, 4) conjugated bilirubin covalently bound to albumin. Unconjugated bilirubin may increase in newborn with excessive hemolysis or reduced bilirubin glucuronidation. Conjugated bilirubin will increase in cholestatic conditions. δBilirubin can be increased in newborns with prolonged conjugated hyperbilirubinemia due to liver disorders.

Hepatic Uptake

Bilirubin dissociates from albumin before entering the hepatocytes. Bilirubin uptake by the liver is partly by carrier mediated diffusion and partly by organic anion transporter proteins. In the hepatocyte cytoplasm unconjugated bilirubin bound to

ligandin. Ligandin are the major intracellular transport proteins, they binds to bilirubin and keeps the toxic unbound fraction of bilirubin low. Z protein , a hepatocyte carrier protein, binds to bilirubin with a lower affinity. The equilibrium between the rate of bilirubin released into the circulation and its elimination determines the total serum bilirubin concentration at any specific time.

The reduced capacity of hepatic uptake of unconjugated bilirubin has been thought to be an important factor for physiological jaundice. In newborns, the reduced bilirubin uptake is not considered as important as the immature bilirubin conjugation in the development of unconjugated hyperbilirubinemia during first three to four days of life. Bilirubin uptake deficiency may contribute to hyperbilirubinemia in the second week of life when the bilirubin conjugation increases and reaches adult level.

Bilirubin Conjugation

As unconjugated bilirubin is water insoluble, it must be converted into a more polar, water soluble substance before being excreted into the bile. The conjugation is a two step process in which bilirubin is conjugated with two molecules of glucuronic acid. In the hepatocytes, bilirubin is transported to the smooth endoplasmic reticulum and gets conjugated. Conjugation of bilirubin is catalysed by the enzyme uridine diphosphate-glucuronosyl transferase (UDPGT-1). The UDPGT-1 enzyme first catalyzes the transfer of one glucuronic acid molecule to form bilirubin monoglucuronide. A reduction of the enzyme activity to less than 1 % may result in unconjugated hyperbilirubinemia.

Bilirubin monoglucuronide is water soluble and it can be excreted into bile as a diglucuronide. The next step is the conjugation of a second glucuronide molecule to a monoglucuronide. This step is also catalysed by the same UGT1A1 enzyme, which is present in the endoplasmic reticulum. UDP-glucuronide glucuronosyl transferase (transglucuronidase) is another enzyme which may also play a role in the second step. This enzyme catalyses the transfer of one molecule of glucuronic acid from bilirubin monoglucuronide to bilirubin monoglucuronide. This results in the formation of bilirubin diglucuronide. Bilirubin diglucuronide is excreted in the bile and the unconjugated bilirubin released in this step will enter the endoplasmic reticulum for further conjugation.

The water-soluble form of bilirubin is readily excreted in the gastrointestinal tract. Water solubility of the conjugated bilirubin also decreases the amount of bilirubin reabsorbed from the bowel. In normal adult, glucuronide conjugation helps in the disposal of around 90% of total bilirubin. The remaining bilirubin is made water-soluble substances by conjugation with other substances like glucose, xylose, sulfates, and taurine. These nonglucuronide conjugates account for less than 10% of the total bilirubin conjugates excreted in the bile.A number of studies have demonstrated the presence of deficiencies of hepatic UGT activity in newborns. Studies on rhesus monkeys and rats showed that the hepatic bilirubin conjugating capacity isextremely low during the first few days of life. The conjugating capacity of the liver increases to the adult level by the fourthday of life, with 75% of all conjugated bilirubin is glucuronide conjugates. In

newborns, the bilirubin monoglucuronideis the predominant form of conjugated bilirubin.UGT activity in term neonates is about 1% of that of adult level. The levels are much lower in premature neonates.UGT activity increases steadily until 3 months of age and attain the adult level.

Excretion Of Bilirubin

Excretion of the water-soluble conjugated bilirubin is an energy-dependent process. The conjugated bilirubin is incorporated into mixed micelles along with bile acids, phospholipids, and cholesterol. The bilirubin is then excreted against a concentration gradient.Bilirubin concentration of the bile is about 100-fold that of the hepatocyte cytoplasm. In newborn babies, in conditions like haemolytic disease of the newborn, a large bilirubin pool is to be eliminated. When the bilirubin load exceeds the excretory capacity, the efflux of conjugated bilirubin into the serum occurs. In the presence of hepatocyte injury and biliary obstruction, hepatic excretory step is more severely restricted and result in efflux of conjugated bilirubin into the serum. This results in conjugated hyperbilirubinemia.

Enterohepatic Absorption Of Bilirubin

Conjugated bilirubin cannot be absorbed from the intestine. However, mono- and diglucuronide of bilirubin are very unstable and are readily hydrolysed to unconjugated bilirubin. This unconjugated bilirubin can now be readily absorbed across the intestinal mucosa. This is termed as the enterohepatic circulation of bilirubin. This contributes to

the circulating unconjugated bilirubin pool and again presented for conjugation in the liver. Enteric mucosal enzyme β-glucuronidase, is present in both term and premature neonates in high concentrations. Studies indicate that about 25 percent of bilirubin excreted into the intestines were reabsorbed after getting converted into unconjugated bilirubin. 10 percent of bilirubin excreted in the bile is unchanged and excreted in stool. Remaining bilirubin is converted into urobilinoids and excreted in the stool. The unconjugated bilirubin present in the intestines of the neonates are high when compared to adults, this results in the increased enterohepatic circulation. This excess unconjugated bilirubin is the result of increased bilirubin production and the increased bilirubin content of the meconium. Also neonates does not have the intestinal bacterial flora to convert the bilirubin to urobilinogen, this results in the increased bilirubin available in the intestine to get absorbed. β glucuronidase activity of the intestinal mucosal cells also high in the neonates and causes increased hydrolysis of the conjugated bilirubin.

Physiologic Bilirubinemia

The normal increase in serum bilirubin occurs in neonates that should not be called as hyperbilirubinemia. The correct term would be physiologic bilirubinemia. Fig. shows the natural increase in serum total bilirubin during the first week of life. The peak of the bilirubin level occurs at about day 5 of life.

During the last weeks of gestation, the destruction of RBCs, which are formed during the earlier gestation, results in a 150% increase in the production of bilirubin per unit of body weight. The UGT activity of human fetus is extremely low, around 0.1% of adult

activity, before 30 weeks of gestation. The UGT activity gradually increases to reach about 1% at term. This reduced UGT activity along with the increased production of bilirubin, increased enterohepatic circulation and reduced hepatic uptake results in the physiologic bilirubinemia in neonates. In fetus the hyperbilirubinemia will not occur as the unconjugated bilirubin which is produced will be cleared by the placenta. Even in severe hemolytic condition like isoimmunisation the jaundice is usually mild and only anemia is very apparent. After birth, when the baby is separated from the placenta, bilirubin starts to increase. The increase in the serum bilirubin is excessive in case of hemolytic diseases. However the placenta is impermeable to conjugated bilirubin, hence if jaundice is noted soon of the birth conjugated bilirubinemia should be suspected. Also in fetus, conjugation occurs in liver and excreted into intestines. In meconium, β glucuronidase activity is found which is responsible for the conversion of conjugated bilirubin to unconjugated bilirubin and get reabsorbed into the circulation. The process may be protective from severe hyperbilirubinemia due to hemolysis during intrauterine life.

In severe hemolytic disease of the fetus, the bilirubin concentration of the amniotic fluid increases. The bilirubin may increase after direct transfer from the placenta or the cord blood vessels. Amniotic fluid bilirubin concentration is considered as a marker of the fetal anemia.

In term neonates, the total bilirubin increases gradually and attains the peak concentration at 72 to 120 hours. There was a significant racial difference in the duration

of the peak bilirubin concentration. White population usually will have an earlier peak than the Asian population. Prevalence of breastfeeding also significantly affect the peak bilirubin concentration with breastfeeding babies will have a higher peak than the formula feeding counterparts. Clinical examination will reveal icterus when the total serum bilirubin exceeds 5 to 6mg/dl. As the serum bilirubin level increases, the clinical icterus progresses in a cephalo-caudal direction. Hence at low total serum bilirubin, icterus is appreciable over the head and the sclera. When the bilirubin level increases the icterus gradually progress to abdomen and extremities. Clinical examination is very much subjective and depends on the experience of the observer. Nowadays, noninvasive transcutaneous bilirubinometer is available to measure the skin color objectively. The reliability of the transcutaneous bilirubin measurement is better than the visual examination.

In preterm neonates, the physiologic jaundice is more severe than the term counterparts. These babies will have a peak bilirubin concentration at about fifth day of life. This delayed peak is probably due to the delayed maturation of UGT activity in preterm neonates. Although the maturation of the hepatic UGT activity is delayed in preterm babies, the maturation is faster when compared to the in utero maturation.

Pathologic Unconjugated Hyperbilirubinemia

Increased serum concentration of the unconjugated bilirubin is of concern because of the risk of bilirubin encephalopathy. Although some reports are available to suggest that the conjugated hyperbilirubinemia also associated with the increased risk of bilirubin

encephalopathy. The mechanism by which, the conjugated bilirubin resulting in encephalopathy is not clear. Most of the studies which are available on the kernicterus relate the total bilirubin concentration to the cause of kernicterus. Also in these studies the concentration of conjugated bilirubin comprises a small fraction.

The total bilirubin concentration at any point time is determined by the balance between multiple factors. The factors influencing the total serum bilirubin level includes production, conjugation and excretion of the bilirubin. Significant changes also occur in this complex system during the first week of life. It includes increased heme catabolism and the increasing hepatic bilirubin conjugating capacity, as it gradually matures. The net result of this physiological process is that the concentration of total bilirubin gradually increases till day 5 and then decreases. Some of the pathological condition gets superimposed on this physiological process and results in the exaggerated or prolonged neonatal hyperbilirubinemia. These conditions may affect any step of bilirubin metabolism like bilirubin production, conjugation or excretion.

Causes OfUnconjugated Hyperbilirubinemia

Disorders Of Bilirubin Production

The most common causes of unconjugated hyperbilirubinemia in neonatal period include isoimmune haemolytic disease and G6PD deficiency.

Neonates with hyperbilirubinemia due to acute hemolysis appear to have increased risk of bilirubin encephalopathy than the neonates without hemolysis. Watchko et al(5),in

their report stated that the hyperbilirubinemia without hemolysis is less dangerous than those with hemolysis in causing kernicterus. In another study authors found that the males with hyperbilirubinemia for more than five days and a positive Coombs test had significantly lower IQ scores than the mean for the population. Kuzniewicz et al(6), found that in children with a positive Coombs test, a total serum bilirubin level more than 25mg/ dl was significantly associated with low IQ scores. Another study(7) reported that the threshold total bilirubin to identify babies with encephalopathy was lower when associated with hemolysis. A neonate with Rh isoimmunisation and a serum bilirubin concentration of 20-24mg/dl have an increased risk of bilirubin encephalopathy than a healthy neonate without hemolysis at a same bilirubin concentration.

Table 1: Hemolytic causes of Unconjugated Hyperbilirubinemia

Isoimmunization • Rh incompatibility • ABO incompatibility • Other blood group incompatibilities
Erythrocyte Biochemical Defects • Glucose-6-phosphate dehydrogenase deficiency • Pyruvate kinase deficiency • Hexokinase deficiency
Structural Abnormalities Of Erythrocytes • Hereditary spherocytosis

• Hereditary Elliptocytosis • Infantile pyknocytosis
Infection • Bacterial • Viral
Blood Sequestration • Cephalhematoma • Subdural hematoma • Hemangioma

American Academy of Paediatrics recommends starting phototherapy or exchange transfusion at a lower total serum bilirubin level in a neonate with haemolytic disease when compared with a healthy neonate (11). This does not mean that healthy neonates are immune to bilirubin encephalopathy. A study be Maisels et al(8) reported the occurrence of kernicterus in neonates without hemolysis.

Hemolytic disorders of newborn are broadly divided into immune and nonimmune hemolysis.

Isoimmunization

The hallmark of isoimmune haemolytic disorder is the positive Coombs test. This indicate that the maternal antibody get crossed the placenta and detectable in the fetus.

Rh Isoimmune Haemolytic Disease

In the past, it was the most common cause of severe hyperbilirubinemia and bilirubin encephalopathy. After the increased usage of Anti D immunoglobulin and improved monitoring of fetus, the occurrence of severe haemolytic disease with Rh incompatibility is low. Recent studies showed that the blood group of the fetus can be identified in the antenatal period itself by PCR from fetal cell obtained from maternal blood samples(9) or amniocentesis(10). The degree of anaemia in fetus and the need for antenatal transfusion can be determined by measuring the middle cerebral artery peak systolic velocity.

Rh blood group antigen are highly antigenic and cause severe isoimmunisation, that lead to fetal hydrops.Even 0.1ml of fetomaternal hemorrhage can produce marked sensitization by D antigen. Rh disease can cause intrauterine hemolysis and it continues in the neonatal period. If left untreated severe anemia and hydrops can occur. After birth, severe hyperbilirubinemia and kernicterus can occur.

The isoimmunisation starts when the Rh negative mother get exposed to D antigen during trans placental fetomaternal transfusion of fetal RBC's. After exposure to D Antigen, maternalimmune system produce anti –D immunoglobulin G. These IgG antibodies crosses the placenta and attacks the fetal RBC's.Antigen antibody reaction occurs and leads to hemolysis and anemia. This immune response is more severe in successive pregnancies.Anemia in fetus leads to

appearance of immature RBCs in circulation. Hydrops is characterized by generalized edema, pleural & pericardial effusion. This effusion may be due to combined factors like hypoproteinemia, tissue hypoxia and capillary leak. Anemia will further complicate the hydrops by producing congestive cardiac failure and venous congestion. Increased COHb levels in the fetal blood obtained by cordocentesis can confirm the presence of inutero RBC destruction. In utero hemolysis can manifests as fetal anemia.Even with severe hemolysis, the serum total bilirubin concentration is usually below 5mg/dl, as it was cleared by the placenta. Jaundice may start to appear after delivery. In the initial stage, the unconjugated bilirubin contribute to the total bilirubin, later when the bilirubin load is high the hepatic system can be saturated and the conjugated bilirubin starts appearing in the serum. This leads to the increasing conjugated fraction of bilirubin over time in Rh isoimmunisation. Other reasons that may contribute to conjugate bilirubin rise are the rapid maturity of the hepatic conjugating function when compared to the excretory function.

ABO Incompatibility

After the use of immune prophylaxis, the incidence of Rh isoimmunisation has decreased and ABO incompatibility is common nowadays.It is the most common cause of hemolytic disease of newborn. Immune hemolysis due to ABO incompatibility is usually mild and rarely cause severe hemolysis with hyperbilirubinemia.In recent studies from various countries on the bilirubin

encephalopathy, infants with ABO incompatibility comprises of 19 to 55% (11)(12)(13)(14).

ABO heterospecificityis the situation when the blood group of the baby is either A (or) B and mother with blood group 'O' this combination can occur in about 12% of the pregnancies. These women with blood group O can have raised titersof anti A (or) Anti B antibodies that they may naturally occurred even before their first pregnancy.In person with O blood group the anti A and Anti B antibodies.

These babies with isoimmunisation have a risk of developing severe hyperbilirubinemia after birth. In babies with blood group A or B and mother had blood group B, around 30 percent of babies will have a positive Coombs test. End tidal carbon monoxide, a measure of heme catabolism showed an increased excretion of carbon monoxide in babies with isoimmunisation. It is also important to note that not all babies with positive Coombs test develop severe hyperbilirubinemia requiring phototherapy. Although the disease is mild in most babies, some babies will develop severe hyperbilirubinemia requiring intensive treatment with IVIG or exchange transfusion. Also babies with negative Coombs test can develop severe hyperbilirubinemia. Absence of disease in the Coombs positive babies can be explained by the presence of reduced A and B antigenic sites on RBCs in neonatal period. Antibodies may also bind to the antigenic sites present in the other tissues causing less severe haemolytic disease. Hence, the positive coombs test alone cannot be considered for defining a baby as having haemolytic disease. Criteria which can support to define hemolysis in a baby with ABO

incompatibility include Indirect hyperbilirubinemia on day 1, baby with a or B blood group and mother having O group, spherocytosis on the smear, elevated reticulocyte count and increased end tidal CO. All babies born to mother with O blood group should be carefully followed and investigated when required.

Other antigens which are present in the RBCs and cause hemolysis in newborn include anti-c, anti- Kell and anti- E anti. Alloimmunization due to these antibodies can cause severe hemolysis during intra uterine period. Anti Kell isoimmunisation can produce fetal anaemia due to suppression of erythropoiesis in addition to hemolysis.

Nonimmune Hemolysis

The cause for nonimmune hemolysis in newborn includes erythrocyte enzymatic defects like G6PD deficiency and Pyruvate kinase deficiency, erythrocyte structural defects like HereditarySpherocytosis and Hereditary Elliptocytosis. Other condition which can result in hemolysis includes infection and sequestration of blood within the body cavities.

Disorders of Bilirubin Conjugation

It includes Crigler-Najjar syndrome type 1and 2, which is characterised by complete absence or reduced activity of the hepatic UGT activity. Type 1 is more severe and develops by around day 3 and progress during the first month of life. Type 2 is a less severe and often benign disease.

Pyloric stenosis can be associated with reduced UGT activity and result in unconjugated hyperbilirubinemia. Usually post-surgery when the obstruction is relieved the serum bilirubin level decrease gradually and reach the normal level in less than 3 days.

Hypothyroidism is also associated with unconjugated hyperbilirubinemia due to reduced UGT activity and reduced hepatic uptake of bilirubin. This leads to prolonged hyperbilirubinemia. Hence thyroid function test is suggested for infants with hyperbilirubinemia.

Disorders of Enterohepatic Circulation

It includes two types of jaundice associated with breastfeeding, one is breastfeeding failure jaundice and the other breast milk jaundice.

Breast failure jaundice occurs in the exclusively breastfed babies in the first weeks of life. Mothers who find difficulty in establishing good breastfeeding techniques were at risk of ineffective breastfeeding. This results in the poor oral intake by the baby and leads to stasis of the intestinal contents. This result in the increased enterohepatic circulation of bilirubin and more bilirubin will be handled by the immature liver. This series of events result finally in exaggerated unconjugated hyperbilirubinemia. Breastfeeding failure jaundice can be prevented by ensuring frequent breastfeeding and proper lactation counselling.

Breast milk jaundice occurs later part of first week and may continue till third week of life. Usually the peak serum bilirubin ranges from 5 to 10 mg/dl at two weeks of life. This peak is followed by a gradual decrease in the serum bilirubin level over months. Some babies may get severely affected and have a maximum serum bilirubin level of 20 to 30 mg/dl. In contrast to babies with breastfeeding failure babies these babies feed well and grow well. Studies shown that the presence of non-esterified long chain fatty acids in the milk as a cause for breast milk jaundice. Usually these neonates were well appearing and no treatment is needed unless the serum bilirubin rises to a dangerous level. In those circumstances, interruption of breastfeeding and supplemented with formula feeding, for about 1 to 3 days well result in fall of serum bilirubin level to 50% of the previous level. Before interrupting breastfeeding other causes of hyperbilirubinemia like hemolysis, hypothyroidism, should be excluded.

Sequelae of Unconjugated Hyperbilirubinemia

In children with kernicterus, intellect may be spared sometimes, but the physical handicaps may be severe to lead an independent life. Also, some children with kernicterus might not had features of any bilirubin encephalopathy during their newborn period. A recent study on 25 cases of kernicterus found that 60 percent of children could not walk, 52 percent only able to feed themselves and 36 percent had severe intellectual disability. Mortality rate of kernicterus is 50 percent in term neonates. In preterm babies, the signs of encephalopathy may not be evident.

Factors which influence the bilirubin encephalopathy include increased bilirubin production, altered bilirubin binding capacity of albumin and altered permeability of blood brain barrier. It is believed that when the bilirubin binding capacity of albumin exceeds the limit and unbound fraction of bilirubin increases in serum, bilirubin encephalopathy occurs. The bilirubin binding capacity of albumin decreased in condition like sepsis and hypoxemia. Also the free fatty acids increases in sepsis and hypoxemia, this displaces the bilirubin from albumin and free bilirubin level increases in the serum resulting in bilirubin encephalopathy. Disruption of blood brain barrier in condition like meningitis and hypoxemia can result increased permeability to bilirubin and neuronal damage. After entering brain bilirubin interferes with the functions of neuronal cell and can also cause damage to DNA.

It is well know that unconjugated bilirubin can penetrate the brain cell and result in neuronal damage. This is the reason why unconjugated hyperbilirubinemia is carefully managed in infants. Although it was thought that kernicterus have been extinct from the developed countries, studies shows that the condition still continues to occur. Acute bilirubin encephalopathy and its sequelae, kernicterus are a preventable condition. It cannot be said that single total bilirubin concentration as a safe or a dangerous one. The total serum bilirubin concentration widely used to determine the need for treatment is a poor predicator of neuro developmental outcome . In a study by Gamaleldin et al(7), they found that there was little correlation between the admission total bilirubin and occurrence of acute biliary encephalopathy.

As per another study (15), bilirubin neurotoxicity is unlikely in a healthy term infants without any hemolytic condition with a total bilirubin concentration of less than 25mg/ dl. In presence of risk factor like hemolysis, prematurity or sepsis, bilirubin encephalopathy can occur at a lower total bilirubin level.

In a term infant with active hemolysis, total bilirubin concentration should not exceed 18-20 mg /dl. Hyperbilirubinemia should be considered as potentially dangerous condition as it can cause a spectrum of neurological dysfunction ranging from mild and transient encephalopathy to a serve permanently disabling neurological impairment, kernicterus. It is also important to note that the bilirubin metabolism is a dynamic process and any one serum bilirubin value is not sufficient to assess the risk of neurological damage in a neonate. Other factors like gestational age and general health should also be considered in evaluation of neonate with hyperbilirubinemia.

The incidence of kernicterus differ between countries and range from 0.4 to 2 per lakh children in the developed countries. In developing countries and in areas with less developed health services, the incidence of kernicterus is still higher. As the occurrence of kernicterus is rare, the incidence of extreme hyperbilirubinemia (total serum bilirubin >25mg/ dl) can be taken as a surrogate for determining the incidence of kernicterus. Even with good surveillance for

hyperbilirubinemia during the hospital stay and following discharge, a zero rate of extreme hyperbilirubinemia is difficult to achieve.

The readmission rate for hyperbilirubinemia ranges from 0.17% to 3.2% .The common cause for readmission for hyperbilirubinemia were prematurity, inadequate breastfeeding and early discharge . Even with close surveillance in a well organized health system (16), extreme hyperbilirubinemia occurred in 0.14% of newborn and 0.01% had total bilirubin concentration more than 30mg/dl. As per another study(17) 0.12% of newborn with 35 weeks or more gestational age, had bilirubin concentration above the AAP cut-off for exchange transfusion.

Acute Bilirubin Encephalopathy

It is characterized by poor feeding, lethargy, hypotonia and high pitched cry in a neonate with severe hyperbilirubinemia. Hyperextension of extensor muscle may follow later. This early bilirubin induced encephalopathy may be transient and is not necessary that an infant with acute bilirubin encephalopathy later show features of kernicterus. This is suggested by the reversal of symptoms like lethargy following an exchange transfusion in a baby with features of acute bilirubin encephalopathy. Brain stem auditory evoked response may show changes characteristic of acute bilirubin encephalopathy. Prolonged latencies in peak IV- V and interface I-V suggestive of brainstem conductive dysfunction. These changes usually reverse following the decline in the total bilirubin concentration. Long term follow up of children with abnormal BAER findings during their neonatal period is not

available, hence the significance of abnormal BAER is still questionable. Abnormal BAER suggest that the injury occurs in the 8th cranial nerve and the function of cochlea will be normal. Hence in neonate suspected of having bilirubin induced auditory damage, BAER should be performed MRI findings in acute bilirubin encephalopathy includes focal changes in medial lobe of hippocampus and globus pallidus.

Kernicterus

If Acute Bilirubin Encephalopathy (ABE) was not recognized and treated properly it can progress to permanent neurological impairment. Kernicterus was the term used in the past to described the pathological change of bilirubin toxicity in the brain. The areas commonly involved are the basal ganglia, hippocampus, sub thalamic nucleus and cerebellum. Cerebral cortex is relatively spared . Autopsy of infant affected with kernicterus showed lesion in intestinal mucosa, renal tubular cells and pancreatic cells. Several phases have been described to denote the progression from ABE to chronic athetoid cerebral palsy. Phase I is characterized by the presence of poor suck. hypotonia and reduced sensorium. Phase 2 is marked by fever, hypertonia, retrocolis to frank opisthotonus posturing. Phase 3 is characterized by high pitched cry, poor feeding, visual and hearing disturbances and athetosis. Some neonates may have seizures during phase 3. The usual duration for the progression of the disease is 24 hours. Long term survivors usually will show classical sign of kernicterus . It

includes tetrad of choreo - athetoid cerebral palsy, upward gaze palsy, sensorineural hearing defect and dental dysplasia during childhood.

The intellectual functions of the child will be spared mostly. Mental retardation though seen is not a common morbidity. These children although have normal intelligence commonly suffer from severe physical handicaps. Children who never had features of bilirubin encephalopathy in neonatal period can show features of bilirubin induced neurological damage in later age. The theory postulated for this phenomenon is that children might suffer from subclinical encephalopathy at neonatal period and manifest at later age. They mostly have features of motor dysfunction or abnormal cognitive function.

A recent report from California illustrates the clinical picture of the children who never had encephalopathy pictures at neonatal period. 60% of them fail to walk at a mean age of around 8 years. Severe mental retardation was found in 36% of those children and 32% had no features of intellectual disability. Epilepsy and visual or auditory impairment were also commonly seen in those children.

Preterm neonates will not show typical clinical picture of bilirubin encephalopathy, and they usually appear sick. In preterm neonates bilirubin can enter the brain at lower levels of serum bilirubin level than in term neonates. Also the bilirubin staining of central nervoussystem structures may not indicate kernicterus in preterm infants. They may be due to differences in blood brain barrier (BBB) permeability to

bilirubin and bilirubin metabolism than occurs in the brain structures. Mortality rate in kernicterus is about 50% of term infants and in preterm infants it may be even higher.

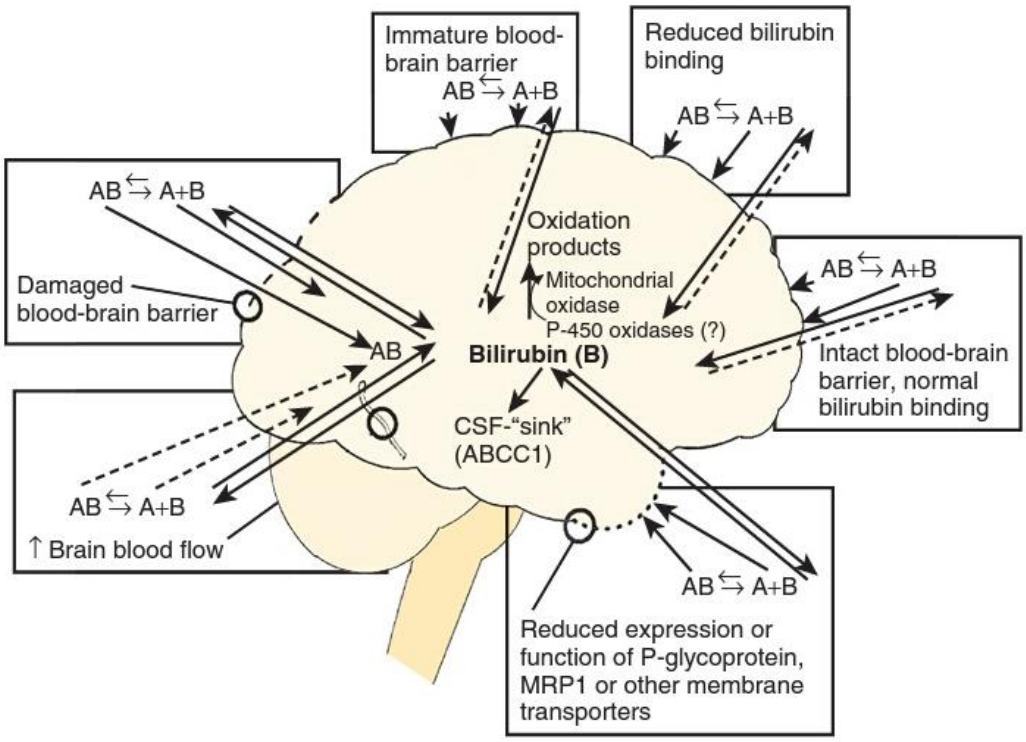


Figure 2: Mechanisms of bilirubin induced neurotoxicity

Bilirubin enters the brain through various mechanisms. It includes (1) bilirubin production that exceeds the buffering capacity of the blood, (2) changes in the bilirubin-binding capacity of albumin, (3) increased permeability of BBB to bilirubin and (4) some unknown factors.

Unconjugated bilirubin is highly lipid soluble and it primarily binds with albumin in plasma. It can also bind to other substances like β-globulin when the albumin-binding capacity is saturated.

It was believed that bilirubin toxicity occurs in circumstances where the albumin-binding capacity of bilirubin is saturated. This results in increased unbound or “free” bilirubin concentration in blood.

Each human albumin molecule can bind with at least two molecules of bilirubin.

At a molar ratio of 1, one gram of human albumin binds with 8.2 mg of bilirubin. When the albumin concentration is 3 g/dL, the bilirubin binding capacity is about 50mg/dl.

The bilirubin-binding capacity of albumin will be decreased in any sick neonates. Also, the serum albumin concentration is often low in sick neonates when compared to the healthy neonates. Hence these sick term and premature neonate are at increased risk for neurological damage at lower serum bilirubin levels. The change in the bilirubin binding capacity of albumin in acidosis was not well studied.

Free fatty acids, which are increased in neonates with sepsis and hypoxemia, are capable of displacing bilirubin. Drugs like indomethacin, and salicylates can displace bilirubin. Ampicillin, when injected rapidly can displace the bilirubin from albumin.

Disruption of blood-brain barrier will results in the passage of substances that were normally prevented from entering the brain. Hypertonicity of intravascular fluid, meningitis, and hypoxia are the conditions in which the permeability of bilirubin into brain is increased. It was found that unconjugated fraction of bilirubin is a substrate for phosphorylated glycoprotein and this substance present in the blood-brain barrier play a

major role in preventing the free passage of substances into the brain. P-GP is an ATP dependent plasma membrane transport protein. It transport various substances across the biologic membranes. Other factors are also identified to play a major role in regulating bilirubin entry into the brain.

Kernicterus has been reported in adults with Crigler-Najjar syndrome type I, when serum bilirubin concentrations increased to more than 45 to 55 mg/dL. In neonates the kernicterus can occur in a serum bilirubin level less than seen with the adults. This suggests that the blood brain barrier may mature over age.

Bilirubin may be produced within the brain in addition to reticuloendothelial system. The brain contain two isoforms of heme oxygenase, HO-1 and HO-2, they convert heme to biliverdin. In normal circumstances, HO-1 shows little activity in the brain, but in response to stress this enzyme get up regulated. Majority of HO activity in the brain is due to the result of constitutive enzyme HO-2. Both of these enzymes, HO-1 and HO-2 are distributed in only selected areas of the brain, many of them play roles in motor and auditory function.

Biliverdin reductase that is present in the brain, catalysing the conversion of biliverdin to bilirubin. The bilirubin which is formed is rapidly cleared in normal circumstances by bilirubin oxidase; Studies suggests that this fraction of bilirubin pool can cause kernicterus. These enzymes are developmentally regulated and their functions were influenced by many of the disease states previously mentioned. The bilirubin is produced and metabolized in brain and so it must be transported out of the brain.

Conditions causing disturbances in the bilirubin transport mechanism may cause damage to the developing brain.

Once bilirubin has entered into the CNS, it can cause neuronal damage by variety of mechanisms. The mechanism which were studied include (1) passage through the cell membranes into the lipids of cellular organelles such as mitochondria, then it can interfere with some important steps in energy metabolism; (2) bilirubin can binding to specific cellular membrane, or cytoplasmic proteins, and then it inhibit their function; and (3) bilirubin cause damage by directly interfering with the function of DNA. The bilirubin induced neurotoxicity is under research and much of the mechanisms were yet to be identified.

As already discussed, HO catalyzes the reaction that convert heme into biliverdin. This result in releasing equimolor quantity of CO. Carbon monoxide can function as a neurotransmitter inside the CNS and it has been to play a critical role in memory. However, CO can also behave as a neurotoxin and results in deleterious effects, which may sometimes results in neuronal necrosis. The deposition of bilirubin in the brain in patients with kernicterus may not be the primary insult as previously thought, but can be a marker of neuronal damage produced by some other mechanisms. Bilirubin has a very good antioxidant property and at normal levels, provides protection from oxidative injury.

Independent of the mechanism of bilirubin neurotoxicity, clinical decisions regarding the management of hyperbilirubinemia and the institution of therapy are based on the total serum bilirubin concentration.

Diagnosis of Unconjugated Hyperbilirubinemia

About two out of three babies born will show clinical jaundice, but the number of babies who develop severe jaundice will be less. The duty of paediatrician is to find babies who are at risk of severe jaundice.

The AAP guidelines provide recommendation for the evaluation of jaundice in newborn(2).

Total Serum Bilirubin measurement:

Once a baby is noted to have jaundice clinically, total serum bilirubin should be done. The measurement of direct fraction of bilirubin was not shown to be useful in earlier stages but it must be measured in babies with prolonged jaundice and in babies when direct hyperbilirubinemia is suspected. In most of the babies repeat serum bilirubin measurement is necessary to know the trajectory and also to ensure that the threshold level to start the treatment was not reached. Sometimes daily serum bilirubin measurement is necessary until the declining trend in the serum bilirubin is documented. In is necessary to judge a neonate clinically and suggest whether the bilirubin monitoring can be done as outpatient or hospitalization is needed. Hence babies should be categorizes as low risk or high risk depends on the chance of developing severe jaundice.

Babies with onset of jaundice less than 24 hours, with hepatosplenomegaly or with evidence of hemolysis are considered to have higher risk of developing severe hyperbilirubinemia.

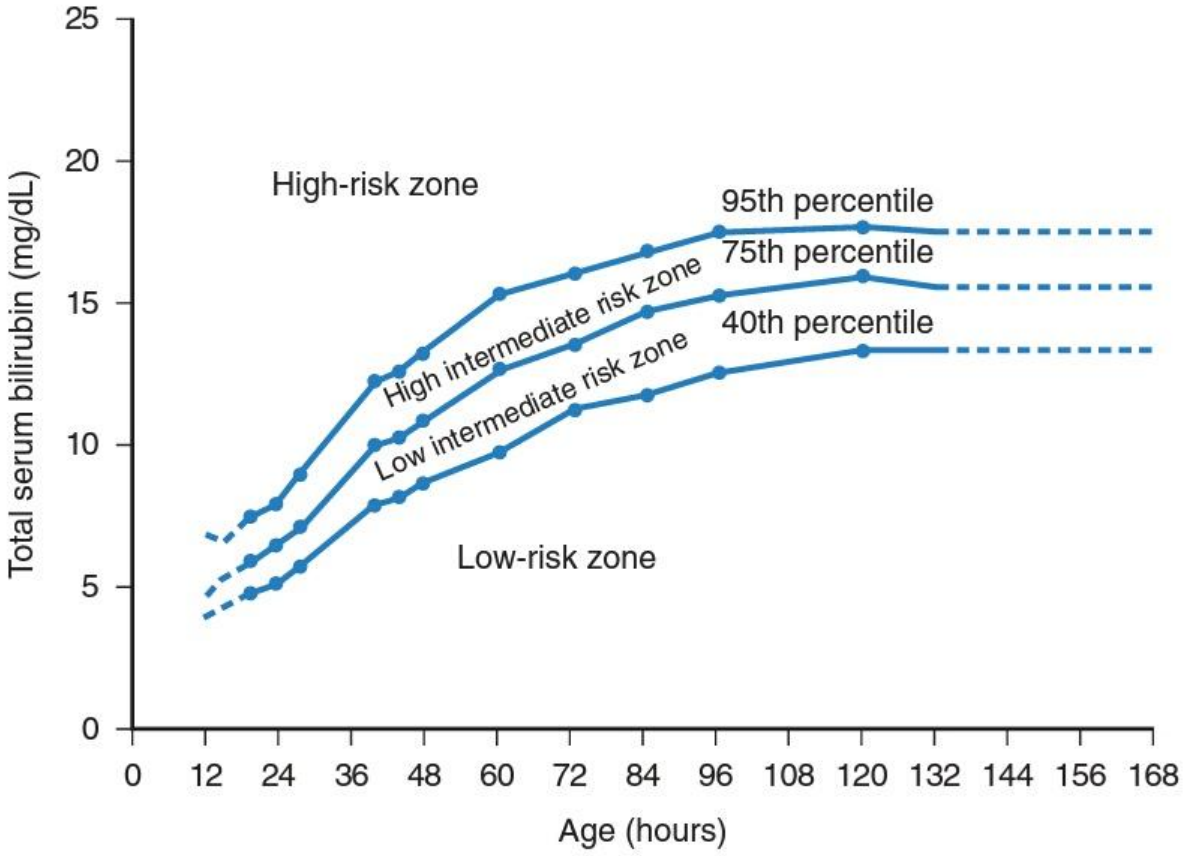


Figure 3: Bhutani's normogram for predicting risk for severe hyperbilirubinemia

Bhutani et al, published an hour specific bilirubin normogram of predischarge total bilirubin concentration to predict the risk of developing severe hyperbilirubinemia. The risk of severe jaundice in a baby with a pre discharge serum bilirubin at high risk zone (95th percentile) is 57%. The risk is 13% for high intermediate risk zone (75th to 95th percentile), 2.1% for a baby with serum bilirubin in low intermediate risk zone (40th to

75th centile). Infant with pre discharge bilirubin fall on low risk zone (<40th percentile)has no risk of severe jaundice. Although the risk of severe jaundice is almost nil if the pre discharge serum bilirubin falls on low risk zone, AAP recommends that all neonates should be followed up within few days after discharge. Repeat serum bilirubin should be plotted on the normogram to know the trajectory. If the serum bilirubin level crosses from a lower risk zone to a higher risk zone, it should be considered significant and further close follow up is needed.

Methods of bilirubin estimation also should be taken into consideration. High Performance Liquid Chromatography (HPLC) is the most accurate method for estimation of serum bilirubin. Other methods may under estimate the serum bilirubin level to varying degrees.

In a neonate with hyperbilirubinemiafurther evaluation should be done in situations like (1) cord blood bilirubin level >4mg/dl, (2) rate of bilirubin rise is more than 0.5mg/dl/hour over a period of 4-8 hours, (3) rate of rise more than 5md/dl/ day, (4) serum bilirubin level increased to more than 15mg/dl in a term neonate, (5) more than 10 mg/dl in a preterm neonate, or (6) when the jaundice persists for more than 14 days.

Second line investigations in a neonate with hyperbilirubinemia should be based on the history and physical examination. History should include the pattern of feeding and a detailed family history to get a clue for familial cause of hyperbilirubinemia. Physical examination should include a careful examination of neurological status and organomegaly for haemolytic cause.

Initial laboratory investigation should include maternal blood grouping and typing, direct Coombs test, haemoglobin, blood smear for RBC morphology and reticulocyte count. In babies with ABO incompatibility direct Coombs test should be repeated at least once because at initial stages it can be negative even with evidence of hemolysis.

End tidal Carbon Monoxide (ETCO) will be elevated in haemolytic conditions, but it is not readily available. G6PD assay can be ordered in selected babies with unexplained jaundice with evidence of hemolysis. Other investigations like enzyme studies and genetic testing can be reserved for selected babies with chronic hyperbilirubinemia. In babies with conjugated hyperbilirubinemia, liver function test should be included in investigation package.

Factors which should be considered while assessing a neonate for risk of developing bilirubin encephalopathy should include total serum bilirubin, gestational age and evidence of hemolysis(2)**.** AAP guidelines recommends provide recommendations for initiating treatment for neonates with >35 weeks of gestational age.

The determination of unbound serum bilirubin concentration can be a more definitive marker to assess the risk of encephalopathy in a child. Studies(18)(19), shown that the unbound bilirubin concentration better correlate with the bilirubin encephalopathy than the total serum bilirubin.

Transcutaneous Bilirubinometry

This method provides a more objective measure of skin colour from which serum bilirubin can be estimated. The device uses reflectance photometry to assess the skin colour. Studies have shown that in serum bilirubin level <15mg/dl, the transcutaneous bilirubinometry will provide values within a range of 2 to 3 mg/dl. This can be taken as a screening method for predischarge bilirubin measurement, but not for initiating treatment. Also in serum bilirubin level >15mg/dl, this method is not adequately studied.

End Tidal Carbon Monoxide

Heme is broken down into equimolor concentrations of bilirubin and carbon monoxide (CO). Hence the concentration of CO in the end tidal breath can be used to identify the rate of heme degradation. This ETCOcan be used to identifythe rate of heme degradation. This ETCO can accurately measure the heme catabolism. Hence, ETCO can be used to identify a neonate with increased bilirubin production.

Bilirubin to Albumin Molar Ratio (BAMR)

The unconjugated bilirubin level can be indirectly measured by the bilirubin to albumin ratio. The bilirubin binding capacity of the albumin can vary significantly in sick newborns. BAMR can be used as a determinant to decide on the need for exchange transfusion in a baby. Also, AAP guideline (2), mentioned that serum albumin <3.0 g/dl is a risk factor for bilirubin encephalopathy.

Treatment of Unconjugated hyperbilirubinemia

Phototherapy remains as the mainstay of treatment for neonatal hyperbilirubinemia. It is well known for decades that phototherapy can reduce the total serum bilirubin and also prevent the rise of serum bilirubin in haemolytic conditions. Other treatments which are available includes exchange transfusion, IVIG and phenobarbitone.

Phototherapy

Phototherapy is most commonly used treatment modality for neonatal hyperbilirubinemia. It decreases the serum bilirubin level and also it prevents the rise of serum bilirubin. It is effective irrespective of the cause of unconjugated hyperbilirubinemia. As there was no long term side effects reported so far, it is considered as safe for short term treatment. It also reduces the number of exchange transfusions in severe hyperbilirubinemia. Also neonates who were treated with phototherapy in addition to exchange transfusion reported to have less severe neurological sequelae.

Phototherapy can reduce the serum bilirubin be three independent mechanism. Photoisomerization is the most important mechanism of the three. The Z form of unconjugated bilirubin IXα is converted into E form. This E isomer is more soluble and can be excreted in bile without conjugation. Structural isomerization converts bilirubin into lumirubin and this also can be excreted without conjugation. The third mechanism is

the photooxidation, the productof photooxidation results in the production of monopyroles, dipyroles and biliverdin. These can be excreted in bile without further conjugation.

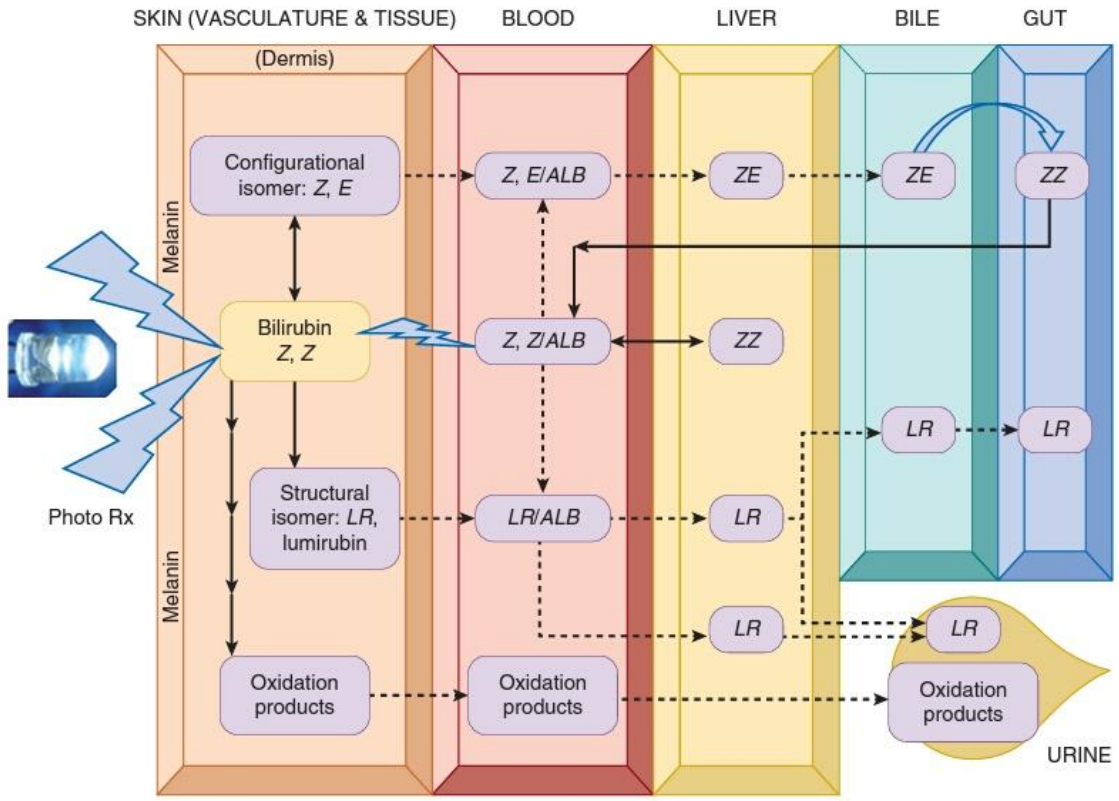


Figure 4: Mechanisms of Action of Phototherapy

Different devices are used worldwide for delivering phototherapy and most of them are not standardised. Physicians should have knowledge about the factors influencing the efficacy of phototherapy. It includes the light source used, irradiance of the phototherapy unit and the body surface area exposed to phototherapy. The wave length of the light used is the most important variable determining the efficacy of phototherapy. The ideal wave length should be in between 460 and 490 nm. Studies(3)

have shown that phototherapy with green light is also equally effective in treatment of neonatal jaundice. The green light phototherapy was not widely accepted.

Irradiance is the second important variable which determines the efficacy of phototherapy. Minimum irradiance needed to provide phototherapy is 6-12 $\mu W/cm^2/nm$. Normally phototherapy therapy unit will be placed at 40 cm distance from the neonates. If effective phototherapy is needed the distance can be adjusted to 15- 20 cm. For intensive phototherapy, the irradiance can be increased to >30 $\mu W/cm^2/nm$.

Increasing the body surface area exposed is another way of increasing the efficacy of phototherapy. The lamps should be placed behind the Plexiglas. These Plexiglas will protect the infant from Ultra violet radiation that can be emitted from tha light source used. Minimal clothing should be allowed to increase the surface area exposed to phototherapy.

AAP guidelines (2) recommend using intensive phototherapy when the serum bilirubin increases and approaching the threshold for exchange transfusion. Intensive phototherapy is defined as >30 $\mu W/cm^2/nm$ irradiance delivered to maximum surface area of the neonate.

Blue light emitting diodes (LED) are the new methods introduced recently. They are effective in providing high intensity phototherapy without the disadvantage of heat production. These lamps also have longer life and need not be changed frequently.

Intermittent phototherapy is a newer concept, bur studies with on- off cycle of 6 – 12 hours did not shown to be effective in delivering phototherapy. The time period taken for the bilirubin to restore in skin for Photoisomerization occurs in less than 3 hours, hence intermittent phototherapy with on- off cycles less than 1 hour was found to be equally effective as continuous phototherapy. This intermittent phototherapy provides adequate time for mother infant bonding and breast feeding.

Home phototherapy is another method that was recently studied. The advantages of home phototherapy include reduced cost, increased maternal bonding and parental satisfaction. The effectiveness of the home phototherapy was not extensively studied and was not recommended in neonates with higher serum bilirubin concentration or when the total serum bilirubin is approaching exchange transfusion threshold.

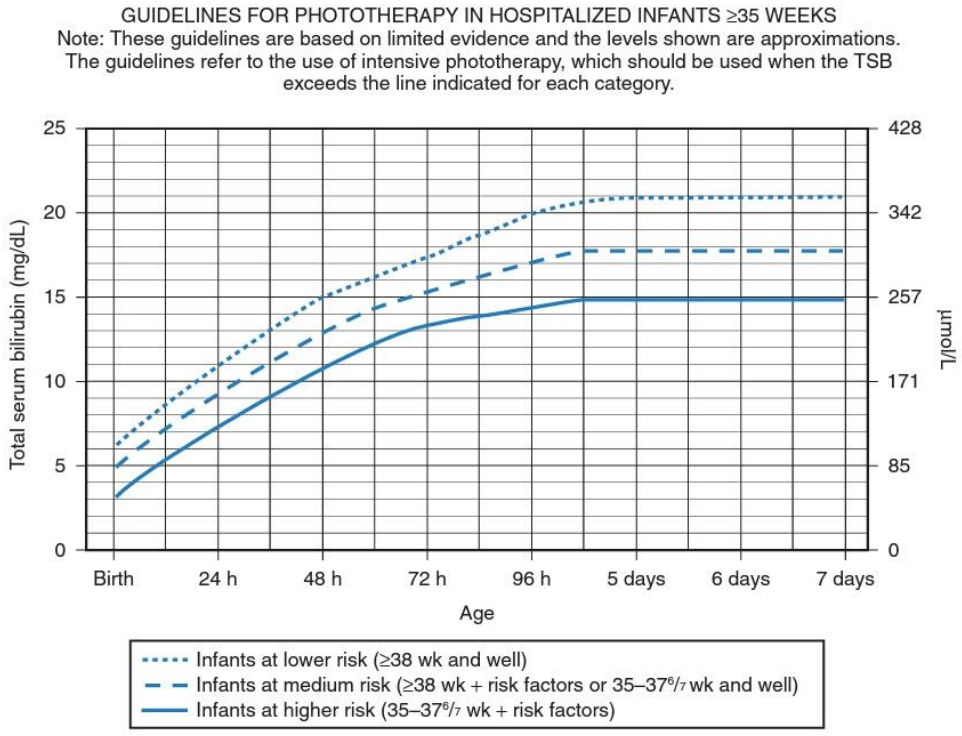


Figure 5: AAP guidelines for phototherapy in infants with ≥ 35 weeks gestation

AAP guidelines(2), provide recommendation on serum bilirubin for initiation of phototherapy. The factors taken into consideration while referring the guidelines were the gestational age, the risk factors and the postnatal age. AAP guidelines did not provide recommendation for neonates with <35 weeks of gestational age. NICE guidelines provided graphs for use in treatment of premature neonates with phototherapy and exchange transfusion.

Lazar et al(20), in his study on 58 numbers with non hemolytic neonatal hyperbilirubinemia (28 term and 30 preterm infants) he tried to find out the serum bilirubin level at which phototherapy could be stopped. In that study, phototherapy was started in healthy term infants when total serum bilirubin reached 17mg/dl and 14mg/ dl in preterm infants. In their study phototherapy was discontinued arbitrarily at total serum bilirubin of 13± 0.7mg/ dl in full term infant and 10.7± 12mg/dl in preterm infants . They found that there was no significant rise in serum bilirubin in both term and preterm infants. Based on his study, they suggested to stop phototherapy when the total serum bilirubin is 14mg/ dl (or) less in full term and 12mg/ dl or less in preterm infants with 32- 36 weeks of gestation.They also suggested that repeat bilirubin measurement was not necessary after stopping physiotherapy .

Tan et al(21), recommended two consecutive bilirubin value< 11mg/dl for stopping phototherapy. He also suggested daily monitoring of serum bilirubin for minimum two day to determine maximum rebound

Del Vechioet al(22), in 1991 reviewed their experience with 48 neonates over a period of 18 months. He found that only one infant required re- initiation of phototherapy out of 48 healthy neonates. The mean serum bilirubin at discontinuation of phototherapy was 15.1mg/ dl and the average serum bilirubin at rebound when checked at 6-8hrs after stopping was 14.9mg/dl.

He supported the view of Yetmanet al(23), and Lasar et al(20), that the rebound bilirubin measurement was not needed after stopping phototherapy in healthy infants.Babies with hemolytic condition (or) preterm infants were not included in his study. Rebound bilirubin measurement was checked at 6-8 hrs after stopping the phototherapy in this study.

In another retrospective study by Maiselset al(24), aimed to determine the number of infants who received repeat phototherapy, they included 303 term and near term infants. In the study infants were divided into two groups based on whether phototherapy was started during birth hospitalization or re admitted for phototherapy in babies discharged previously. In the study, the decision to initiate and to discontinue phototherapy, and measurement of rebound bilirubin were made by treating physicians.

In group I, 13 of 158 babies (8.2%) received second course of phototherapy and in group II, 1 of 144 infants (0.7%) received phototherapy. They noted that increase in total serum bilirubin following discontinuation of phototherapy was significantly lower in group 2.The age at which the phototherapy was started were

high in group 2 (4.6±1.8 days) . Hence this fall of the peak of natural course of neonatal jaundice. This could be the reason for the less rebound serum bilirubin in group 2 . They suggested for infants during birth hospitalization and with hemolytic disease, a rebound bilirubin level should be checked after 24 hours of discharge. They also suggested that rebound bilirubin measurement was not necessary in infants readmitted for phototherapy as the rebound increase is less likely. The limitation of the study was that,it was a retrospective study and there is no standard protocol to stop phototherapy in the babies. It wasdone as per the discretion of the treating physician.

Al Saediet al, in 2002(25), published a retrospective study, which aimed to determine whether serum bilirubin rebound occurs within 24 hours after discontinuation of phototherapy in term infants . In 301 infants with mean gestational age of 39.4±14 days and birth weight 3200±600gms, the serum bilirubin at discontinuation of phototherapy was 179±47 micromole/L and the rebound serum bilirubin level was 177 ±47 micromole/L . In the study.the follow up bilirubin was measured at 8.3±5.3 hours . The limitation of this study include the study design, a retrospective study and the discontinuation of phototherapy was done as per the treating physician's discretion . The follow up serum bilirubin measured at an earlier age,with mean age of 8.3 hours showed no significant increase the bilirubin level.

Kaplan et al(26), published their study in September 2005, they did a prospective clinical survey aimed to determine the incidence of post phototherapy plasma total bilirubin rebound. They did the study on 226 term and near term neonates treated with phototherapy. He defined the significant rebound hyperbilirubinemia when the total bilirubin >250µmol/L. In the study , they tested the plasma total bilirubin at 24 hours after discontinuation of phototherapy (12 -36 hours). Of the 226 neonates, 30 developed significant rebound of plasmabilirubin and twenty two of them were treated with repeat phototherapy.Multiple logistic regression analysis showed that the positive direct Coombs test and gestational age <37 weeks were the significant risk factor for the cause for rebound hyperbilirubinemia.Number of neonate who developed rebound bilirubin was more when the phototherapy was started at age <72 hours than it was started>72 hrs. The strength of the study was the prospective design and they had a predefined cut off of >256 micromole/L of total plasma bilirubin as the significant rebound bilirubinemia.They mentioned that their routine indication for discontinuation of phototherapy was 205µmol/L (12mg/ dl) and they defined the significant rise as 25% increase from their discontinuation cut off . They measured the plasma bilirubin at 24 hours (between 12 and 36 hrs) after stopping phototherapy. They also did a subgroup analysis based whether the phototherapy was started during birth hospitalization or during re admission.In the second group, none of the babies showed significant rebound hyperbilirubinemia . In their study, out of the 30 neonate who developed significant bilirubin rebound, 22 were reinitiated with

phototherapy.They found out that therisk factor for reinitiation of phototherapy included direct Coombs test positivity, gestational age <37week and G6PD deficiency. The decision to start repeat phototherapy was at the discrete of the attending neonatologist in the study. They didn't have protocol to start phototherapy in rebound jaundice.From their study,they suggested the neonate with the risk factor such as Coombs positive isoimmunisation, neonates with <37 weeks gestation and neonate treated <72 hrs are at high risk of rebound bilirubinemia . They suggested to follow these babies for rebound jaundice.

Erdeve et al,(27), evaluated rebound bilirubin level measured within 12hrs after discontinuation of phototherapy . They included a total of 375 neonates, 305 term and 70 preterm neonates. In their study the mean total bilirubin level at starting phototherapy was 15.41±0.38 mg/dl and at stopping phototherapy was 10.86 ± 0.14mg/dl. The rebound bilirubin measured at 12hrs after stopping phototherapy showed a mean level of 10.84 ±0.14. He reported that the rebound in serum bilirubin was low and almost half (49.1%) of neonate had reduction in serum bilirubin after stopping phototherapy when checked for rebound hyperbilirubinemia.

Their study reported that 5.1% of neonates (19/375) needed repeat phototherapy.Out of 19 neonates, 16 were term and 3 were preterm . In their study they used the charts which were recommended by AAP for the institution of phototherapy .

Bansal et al(28), in their study aimed to determine the incidence of post phototherapy bilirubin rebound, they included 245 neonates. The study included both term and preterm neonate and they followed the AAP guidelines for starting phototherapy for neonates with >35 weeks gestational age. They stopped phototherapy in neonates with hemolytic jaundice when two consecutive total serumbilirubin levels were less than 14mg/dl and in non- hemolytic conditionsthey stopped phototherapy when the serum bilirubin falls less than 14mg/dl for neonates with<35 weeks of gestational age. They used hours specific cut-off for starting and stopping phototherapy. They stopped phototherapy when totalserum bilirubin falls 2mg/dl below the level at which phototherapy was started. They measured the rebound bilirubin at 24±6hrs after stopping phototherapy. They defined significant bilirubin rebound as when the post phototherapy bilirubin rises to a level needing reinitiation of phototherapy. In these study of 245 neonates, post phototherapy bilirubinwas measured for 232 neonates.They found that 17 neonates (7.3%) developed significant rebound jaundice and the bilirubin rise was 2-3mg/dl after stopping phototherapy in babies with significant bilirubin rebound. From the study, they concluded that the risk factors for significant bilirubin rebound were gestational age < 35 weeks, birth weight <2000gms and onset of jaundice < 60 hours of age.It was also stated that after excluding these mentioned risk factors, the incidence of significant rebound was only 2.3% (2/86). They included both term and preterm neonate in their study.

In their study they stopped phototherapy at 14mg/dl for the neonates with GA >35 weeks with the presence of risk factor like hemolysis. In neonates, with onset of jaundice <60 hrs of age with risk factors, the cut off of 14mg/dl could be high to stop phototherapy. This could be the reason why in their study, they experienced a higher rebound in these neonates.

Berkwitt et al(29), in his retrospective study aimed to evaluated the clinical utility of inpatient rebound bilirubin level.Out of 226 neonates, rebound bilirubin levels were measured at 61 ±2.4 hours in 130 neonates and rebound bilirubin level were not measured in 96 neonates. Theoutcome measured were the length of hospital stay and readmission for phototherapy. They found that there was no significant difference in readmission rate between the two groups. They also conclude that need for phototherapy were significantly low when the phototherapy was continued till the serum bilirubin reaches to <14mg/dl .

A randomized trial by Niknafs et al(30), aimed to compare the significant bilirubin rebound after phototherapy in two groups of neonates with two levels of bilirubin for discontinuation of phototherapy . In the first group phototherapy was discontinued when the serum bilirubin reaches 11mg/dl or the 40th percentile of Bhutani's normogram. In the second group, phototherapy was stopped when the total serum bilirubin level drops to 13mg/dl or the 75th percentile as per Bhutani's normogram.Serum bilirubin was measured after 24 hrs of stopping phototherapy. They defined the significant rebound when the bilirubin increase more than 2mg/dl

or it reaches the 95th percentile. Their study included 115 neonate, of which 13 neonates developed significant rebound after stopping phototherapy, 9 neonates in the first group and 4 neonates in the second group. But the difference was not statistically significant. They concluded that discontinuation of phototherapy at a lower serum bilirubin would not result in the rebound rise in bilirubin . Also in their study, they reported that 6 out of 13 neonates with risk factors developed significant rebound after 24 hours of stopping phototherapy. Hence they suggested a longer period of follow up after stopping phototherapy if the infants had risk factor for significant hyperbilirubinemia.

Soni et al(31), published a study from North India, the study aimed to determine the incidence and risk factors for the post phototherapy rebound hyperbilirubinemia.the study included neonates with gestational age more than 34 weeks of gestation and treated as per AAP guidelines. They measured serum bilirubin at around 24 hours and they defined significant rebound when the rise in serum bilirubin need re institution of phototherapy. They studied 501 neonates and reported the incidence of significant rebound bilirubinemia to be 12 %. They found the risk factors associated with the significant rebound include prematurity, ABO or Rh incompatibility, G6PD deficiency and the onset of jaundice less than 72 hours. Most of the findings were concurrent with that of Bansal et al study.

Chang et al(32), in 2017 published a retrospective study which aimed to develop a prediction rule to estimate the probability of rebound hyperbilirubinemia following discontinuation of phototherapy. They suggested a prediction score which consist of three variable. In includes, gestational age < 38 weeks of gestation, age at initiation of phototherapy and the serum bilirubin level at which phototherapy was discontinued. The conclude that the chance of rebound hyperbilirubinemia can be quantified with these three variable.

METHODOLOGY

Materials and methods:

Study place: Neonatal intensive care unit, PSGIMS&R

Study design: Open labelled randomized controlled trial.

Study duration: From January 2018 to October 2018

Study population: Newborn of gestational age ≥35 weeks with neonatal hyperbilirubinemia who meet the AAP criteria for phototherapy.

Inclusion criteria:

1. Babies with gestationalage ≥35 weeks,
2. Babies with birth weight >1800 grams,
3. Babies requiring phototherapy for the first time,
4. Babies with onset of jaundice ≤7 days.

Exclusion criteria:

1. Babies planned for immediate exchange transfusion at the time of admission.

Sample size: For calculation of sample size duration of phototherapy between two groups was considered from a pilot study by Barak et al with α error of 5% and power of 80%. The estimated sample size is 99 in each group. Considering 20 % dropouts from the study, final sample size of 120 babies in each group was arrived**.**

Methodology:

The study proposal was approved by Institutional Human ethics Committee and was prospectively registered in the Clinical Trial Registry of India (CTRI No: CTRI/2018/02/011740, Registered on 07/02/2018)

New born with gestational age ≥35 weeks with neonatal hyperbilirubinemia who meet the AAP criteria for phototherapy were contacted for the study. Babies with exclusion criteria were excluded from the study. After getting written informed consent, babies were recruited for the study.

Randomization was done by variable block randomisation. Randomisation details were concealed in sequentially numbered, opaque, sealed envelope. Once the baby was recruited, envelope was opened and babies were assigned into either group A or group B as mentioned in the envelope.

In group A, phototherapy was discontinued at 1.0-2.9 mg/dl below treatment threshold at which phototherapy was initiated.

In group B, phototherapy was discontinued at ≥ 3mg/dl below the treatment threshold at which phototherapy was started.

Data including birth weight, gestational age, gender, maternal blood group, history of jaundice in siblings, breast feeding, presence of scalp hematoma and excessive weight loss were collected in the case report form (CRF).

As per the unit protocol, at admission basic investigations were done. It includes Complete blood count, peripheral smear, Direct Coombs test, reticulocyte count and serum albumin. Additional investigation for septic screen and G6PD assay were done when clinically indicated.

Babies were given phototherapy and serum bilirubin was monitored every 6 hours during phototherapy. Babies with serum bilirubin level approaching exchange transfusion threshold were monitored more frequently.

Phototherapy was discontinued once serum bilirubin drops to 1.0-2.9mg/dl or ≥3.0mg/dl below treatment threshold as per the group assigned. After stopping phototherapy, serum bilirubin was checked at 6 and 24 hours for rebound hyperbilirubinemia.

If the serum bilirubin after stopping phototherapy increase to the age and risk specific cut-off as per American Academy of Paediatrics phototherapy charts, phototherapy was reinitiated. The second course of phototherapy was stopped when the total serum bilirubin level decreases to less than 13mg/dl as per our unit protocol.

We defined significant rebound hyperbilirubinemia as an increase in the serum bilirubin to a level requiring second course of phototherapy.

Statistical methods:

Number of babies who require re-initiation of phototherapy will be determined. Total duration of phototherapy including treatment after rebound hyperbilirubinemia and total duration of hospital stay will be calculated. Continuous variable will be compared using Student t test and categorical variable will be compared using chi square test. Significance is defined as a p value less than 0.05 or in case of Odds ratio determination a 95% confidence interval that did not include the digit.

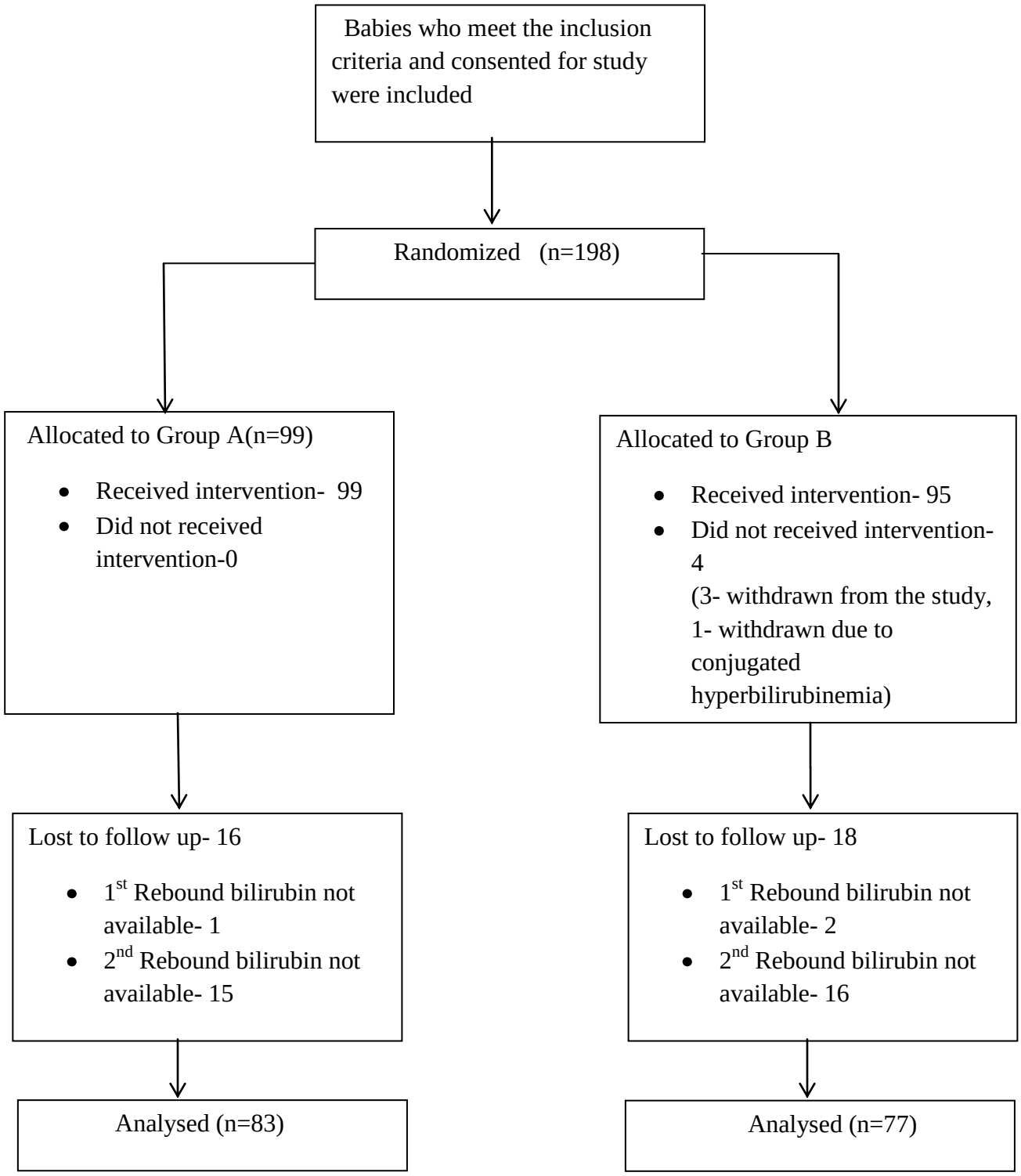
RESULTS

We have recruited a total of 198 babies and by randomisation 99 babies were assigned to group A and 99 babies were assigned into group B. All these babies were treated as per the group assigned.

In group A, 1 baby got discharged after stopping phototherapy and follow up bilirubin measurement could not be done. 15 babies were lost to follow up for second rebound bilirubin measurement. Hence the remaining 83 babies, who completed the study, were included for final analysis.

In group B, 3 babies were withdrawn from the study during treatment and 1 baby initially had unconjugated hyperbilirubinemia and recruited for the study later while treatment developed conjugated hyperbilirubinemia, hence withdrawn from the study. 2 babies got discharged after stopping phototherapy and follow up bilirubin measurement could not be done. 16 babies were lost to follow up for second rebound bilirubin measurement. Hence the remaining 77 babies, who completed the study, were included for final analysis.

22 babies from group A, for whom phototherapy was planned to stop at a serum bilirubin level 1.0 to 2.9 mg/dl below the AAP treatment threshold, had their serum bilirubin level below 3.0 mg/dl while on phototherapy.


Babies who meet the inclusion criteria and consented for study were included
Randomized (n=198)
Allocated to Group A(n=99)
Received intervention- 99
Did not received intervention-0
Allocated to Group B
Received intervention- 95
Did not received intervention- 4
(3- withdrawn from the study, 1- withdrawn due to conjugated hyperbilirubinemia)
Lost to follow up- 16
1st Rebound bilirubin not available- 1
2nd Rebound bilirubin not available- 15
Lost to follow up- 18
1st Rebound bilirubin not available- 2
2nd Rebound bilirubin not available- 16
Analysed (n=83)
Analysed (n=77)

As we followed strict protocol for phototherapy discontinuation, we did intention to treat analysis, hence we included 83 babies in group A and 77 babies in group B for analysis.

Baseline Characters:

The baseline characters were depicted in Table 2.

Table 2: Baseline characters of two groups of study population

	Group A (n= 83)	**Group B (n= 77)**	**P Value**
Birth Weight (grams)	2911.8 ± 428.9	2890.1 ± 442.7	0.754
Gestational Age (weeks)	37.8 ±1.4	37.8 ± 1.2	0.462
Male : Female ratio	1.3:1	0.6:1	0.012
Exclusively Breastfed	71 (85%)	66 (85%)	0.578
Extravasation	5 (6%)	3 (4%)	0.402
ExcessiveWeight loss	20 (24%)	28 (36%)	0.064
Hemolysis	4 (5%)	7 (9%)	0.226
DCT positivity	4 (5%)	4 (5%)	0.598
Septic screen positivity	5 (6%)	4 (5%)	0.406
AAP Category Low risk Medium risk High risk	 21 (25%) 52 (63%) 10 (12%)	 20 (26%) 48 (62%) 9 (12%)	0.994

The baseline characters of two groups of our study participants were comparable except the sex ratio.

The male: female ratio was 1.3:1 in group A and 0.6:1 in group B and the difference was statistically significant (p=0.012).

Figure shows the gender distribution between two groups. In group A, there were 47 male and 36 female babies. In group B, there were 29 male and 48 female babies.

Figure 6: Gender distribution in two groups

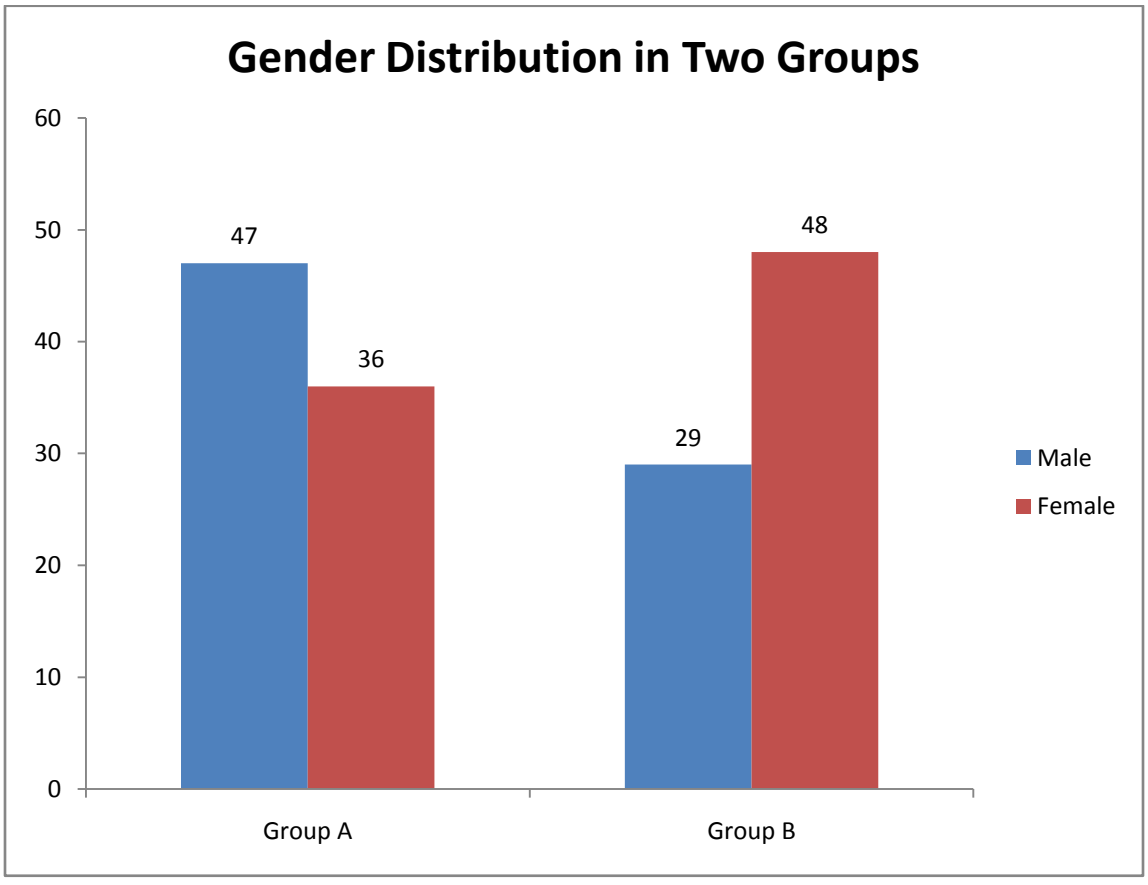
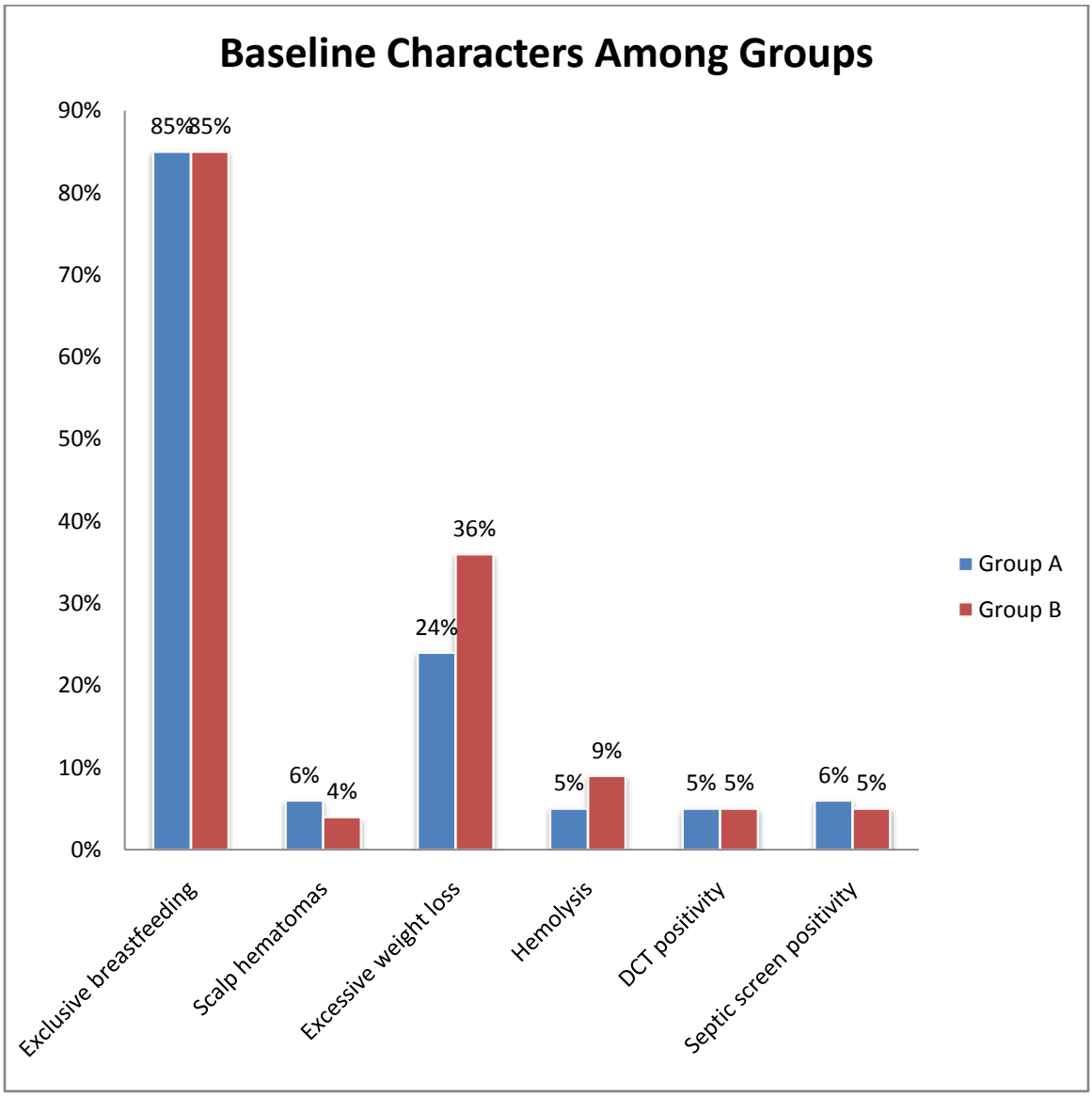


Figure 7: The baseline characters of babies in two groups.



In both the groups 85% of babies were exclusively breastfed and was not statistically significant (p= 0.578).

Scalp hematomas were present in 6% of babies in group A and 4% in group B and the difference was not statistically significant (p= 0.402).

In group A 24 % of babies found to had excessive weight loss and in group B 36% of babies had excessive weight loss and the difference was not statistically significant (p= 0.064).

Evidence of hemolysis be peripheral smear and reticulocyte was positive in 5% of babies in group A and 9% of babies in group B and the difference was not statistically significant (p= 0.226).

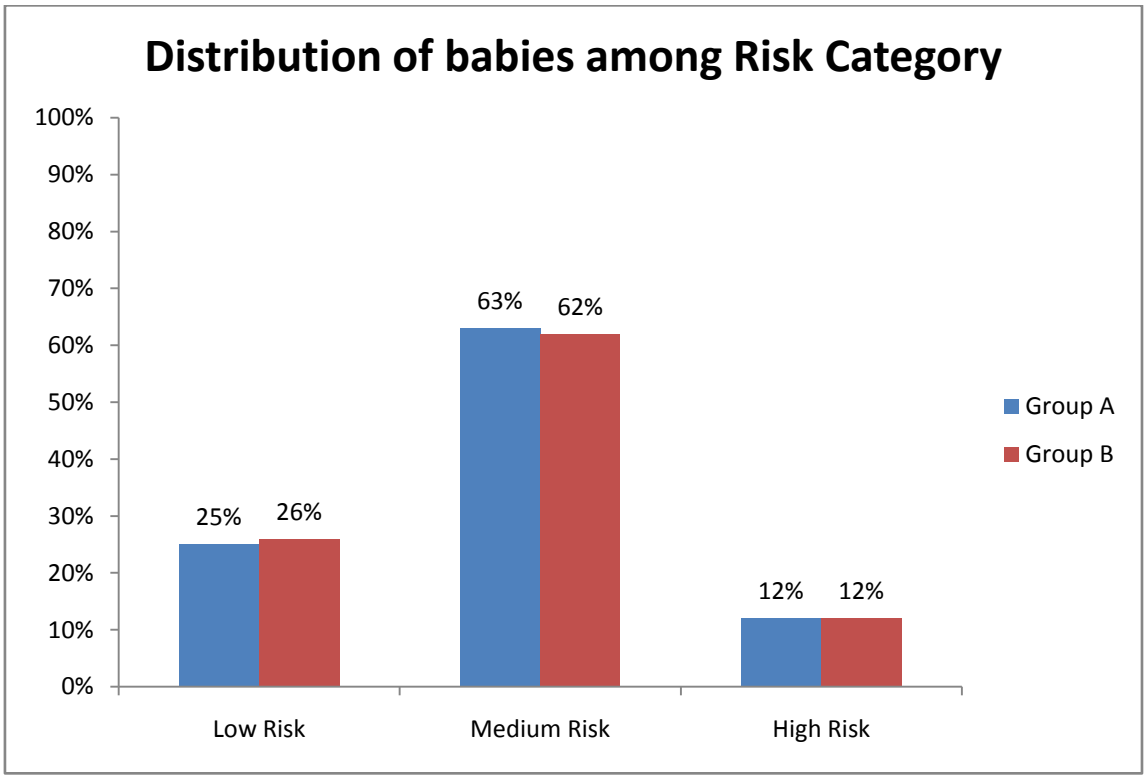
Direct Coombs test was found to be positive in 5% of babies in both the groups and the difference was not statistically significant (p= 0.598).

Septic screen was found to be positive in 6% of babies in group A and 5% of babies in group B and the difference was not statistically significant (p= 0.406).

Distribution of babies among AAP risk category

In group A we got 25% of babies with low risk, 63% with medium risk and 12% with high risk. In group B, 26% were belong to low risk, 63% were medium risk and 12% were high risk category. The distribution of babies on the basis of different AAP risk category was not statistically different between the two groups (p= 0.994)

Figure 8: Distribution of babies among AAP risk category in two groups.



Outcomes:

Table 3: The outcomes of two groups of the study

	Group A (N= 83)	**Group B (N=77)**	**P Value**
Age at initiation of phototherapy,(hours)	73.5 ± 12.6	78.4 ± 20.3	0.067
Age at stopping phototherapy, (hours)	88.5 ± 11.8	98.0 ± 20.7	0.000
Time of 1st rebound sample, (hours)	6.3 ± 0.6	6.3 ± 0.9	0.935
Time of 2nd rebound sample, (hours)	22.4 ± 9.1	22.3 ± 6.8	0.970
Duration of phototherapy, hours	14.9 ± 5.8	19.5 ±8.6	0.000
Length of hospital stay, hours	114.9 ± 25.3	116.7 ± 31.2	0.695
Newborn requiring additional phototherapy, n	2 (2.4%)	2 (2.6%)	0.661

The mean age at initiation of phototherapy was 73.5 hours (SD=12.6) in group A and 78.4 hours (SD= 20.3) in group B and the difference is not statistically significant (p= 0.067).

The mean age at stopping phototherapy was 88.5 hours (SD= 11.8) in group A and 98 hours (SD= 20.7) in group B and the difference is statistically significant (p= 0.000).

The mean time duration of first rebound bilirubin measurement after stopping phototherapy was 6.3 hours (SD=0.6) in group A and 6.3 hours (SD= 0.9) in group B and the difference is not statistically significant (p= 0.935).

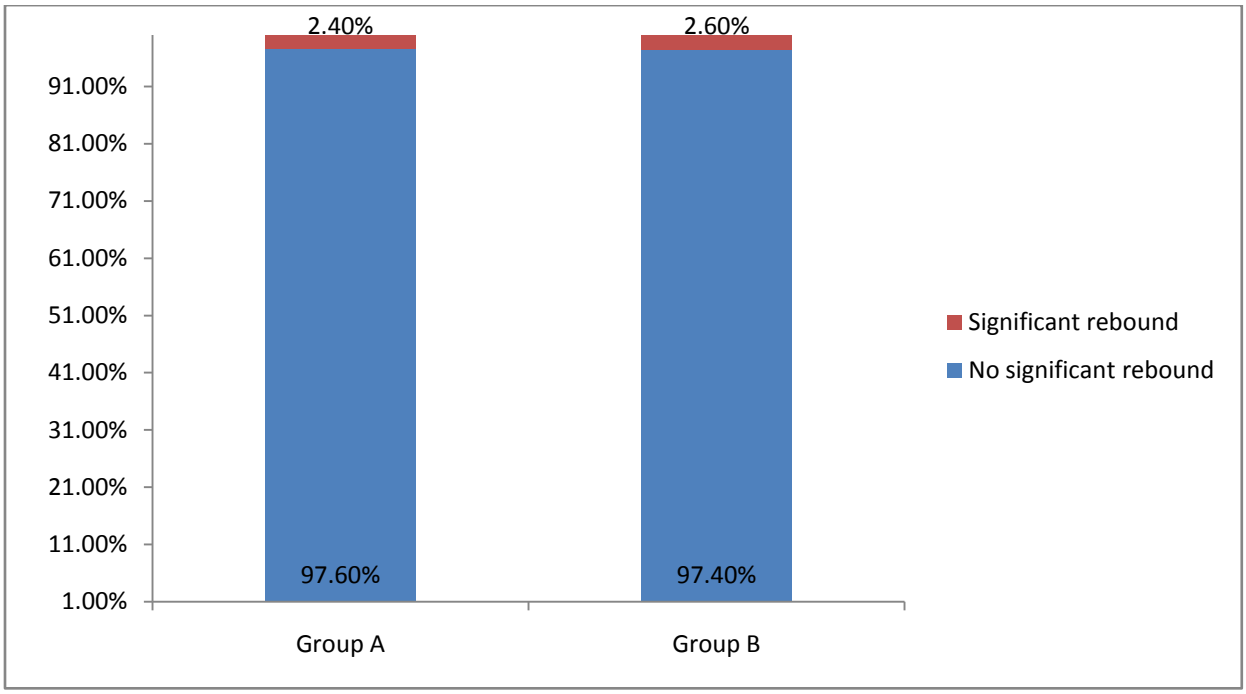
The mean time duration of second rebound bilirubin measurement after stopping phototherapy was 22.4 hours (SD=9.1) in group A and 22.3 hours (SD= 6.8) in group B and the difference is not statistically significant (p= 0.970).

The mean duration of phototherapy was 14.9 hours (SD= 5.8) in group A and 19.5 hours (SD= 8.6) in group B and the difference was statistically significant (p= 0.000)

The mean duration of hospital stay was 114.9 hours (SD= 25.3) in group A and 116.7 (SD= 31.2) hours in group B and the difference was not statistically significant (p= 0.695)

In group A 2 babies (2.4%) developed significant rebound hyperbilirubinemia and was given second course of phototherapy and in group B 2 babies (2.6%) developed significant rebound hyperbilirubinemia the difference is not statistically significant (p= 0.661).

Figure 9: The percentage distribution of babies with significant rebound jaundice in two groups



We did the sub group analysis of babies based on the risk category they belong as per the AAP guidelines.

Low Risk Category

Table 4:Outcomes of babies with low risk as per the AAP guidelines

	Group A (n=21)	**Group B (n= 20)**	**P value**
Age at initiation of phototherapy,(hours)	73.6 ± 11.8	80.3 ± 13.5	0.102
Age at stopping phototherapy, (hours)	87.2 ± 11.8	95.2 ± 12.7	0.043
Time of 1st rebound sample, (hours)	6.3 ± 0.6	6.5 ± 1.4	0.635
Time of 2nd rebound sample, (hours)	23.7 ± 10.4	21.9 ± 6.2	0.527
Duration of phototherapy, hours	13.5 ± 5.2	14.7 ± 5.0	0.448
Length of hospital stay, hours	111.7 ± 16.6	119.4 ± 23.8	0.238
Newborn requiring additional phototherapy, n	0	0	

The mean age at initiation of phototherapy was 73.6 hours (SD=11.8) in group A and 80.3 hours (SD= 13.5) in group B and the difference was not statistically significant (p= 0.067).

The mean age at stopping phototherapy was 87.2 hours (SD= 11.8) in group A and 95.2 hours (SD= 12.7) in group B and the difference was statistically significant (p= 0.043).

The mean time duration of first rebound bilirubin measurement after stopping phototherapy was 6.3 hours (SD=0.6) in group A and 6.5 hours (SD= 1.4) in group B and the difference was not statistically significant (p= 0.635).

The mean time duration of second rebound bilirubin measurement after stopping phototherapy was 23.7 hours (SD= 10.4) in group A and 21.9 hours (SD= 6.2) in group B and the difference was not statistically significant (p= 0.527).

The mean duration of phototherapy was 13.5 hours (SD= 5.2) in group A and 14.7 hours (SD= 5.0) in group B and the difference was not statistically significant (p= 0.448)

The mean duration of hospital stay was 111.7 hours (SD= 16.6) in group A and 119.4 (SD= 23.8) hours in group B and the difference was not statistically significant (p= 0.238)

None of the babies in both group developed rebound hyperbilirubinemia.

Medium risk category:

Table 5: Outcomes of babies withmedium risk as per AAP guidelines

	Group A(n=52)	**Group B(n=48)**	**P Value**
Age at initiation of phototherapy,(hours)	73.2 ± 13.7	78.8 ± 23.5	0.144
Age at stopping phototherapy, (hours)	88.1 ± 12.2	100.3 ± 24.4	0.002
Time of 1st rebound sample, (hours)	6.3 ± 0.5	6.2 ±0.6	0.504
Time of 2nd rebound sample, (hours)	21.6 ± 9.2	22.6 ± 7.4	0.564
Duration of phototherapy, hours	14.7 ± 5.7	21.4 ± 9.3	0.000
Length of hospital stay, hours	113.5 ± 27.6	116.3 ± 36.3	0.665
Newborn requiring additional phototherapy, n	1	2	0.47

The mean age at initiation of phototherapy was 73.2 hours (SD= 13.7) in group A and 78.8 hours (SD= 23.5) in group B and the difference was not statistically significant (p= 0.144).

The mean age at stopping phototherapy was 88.1 hours (SD= 12.2) in group A and 100.3 hours (SD= 24.4) in group B and the difference was statistically significant (p= 0.000)

The mean time duration of first rebound bilirubin measurement after stopping phototherapy was 6.3 hours (SD=0.5) in group A and 6.2 hours (SD= 0.6) in group B and the difference was not statistically significant (p= 0.504).

The mean time duration of second rebound bilirubin measurement after stopping phototherapy was 21.6 hours (SD= 9.2) in group A and 22.6 hours (SD= 7.4) in group B and the difference was not statistically significant (p= 0.564).

The mean duration of phototherapy was 14.7 hours (SD= 5.7) in group A and 21.4 hours (SD= 9.3) in group B and the difference was statistically significant (p= 0.000)

The mean duration of hospital stay was 113.5 hours (SD= 27.6) in group A and 116.3 (SD= 36.3) hours in group B and the difference was not statistically significant (p= 0.665).

In group A 1 babies (1.9%) developed significant rebound hyperbilirubinemia and was given second course of phototherapy and in group B 2 babies (4.1%) developed significant rebound hyperbilirubinemia the difference was not statistically significant (p= 0.47).

High Risk category

Table 6: Outcomes of babies withHigh risk as per AAP guidelines

	Group A(n=10)	**Group B(n=9)**	**P Value**
Age at initiation of phototherapy,(hours)	74.7 ± 8.3	71.9 ± 13.3	0.583
Age at stopping phototherapy, (hours)	92.8 ± 10.1	92.2 ± 10.1	0.903
Time of 1st rebound sample, (hours)	6.2 ± 0.4	6.3 ± 0.7	0.620
Time of 2nd rebound sample, (hours)	23.7 ± 5.0	21.9 ± 5.6	0.469
Duration of phototherapy, hours	18.6 ± 6.4	20.3 ± 7.8	0.603
Length of hospital stay, hours	129.1 ± 25.3	112.9 ± 10.9	0.094
Newborn requiring additional phototherapy, n	1	0	0.526

The mean age at initiation of phototherapy was 74.7 hours (SD= 8.3) in group A and 71.9 hours (SD= 13.3) in group B and the difference was not statistically significant (p= 0.583).

The mean age at stopping phototherapy was 92.8 hours (SD= 10.1) in group A and 92.2 hours (SD= 10.1) in group B and the difference was not statistically significant (p= 0.903).

The mean time duration of first rebound bilirubin measurement after stopping phototherapy was 6.2 hours (SD=0.4) in group A and 6.3 hours (SD= 0.7) in group B and the difference was not statistically significant (p= 0.620).

The mean time duration of second rebound bilirubin measurement after stopping phototherapy was 23.7 hours (SD= 5.0) in group A and 21.9 hours (SD= 5.6) in group B and the difference was not statistically significant (p= 0.469).

The mean duration of phototherapy was 18.6 hours (SD= 6.4) in group A and 20.3 hours (SD= 7.8) in group B and the difference was statistically significant (p= 0.603)

The mean duration of hospital stay was 129.1 hours (SD= 25.3) in group A and 112.9 (SD= 10.9) hours in group B and the difference was not statistically significant (p= 0.094).

In group A 1 babies (10%) developed significant rebound hyperbilirubinemia and was given second course of phototherapy and in group B none developed significant rebound hyperbilirubinemia the difference is not statistically significant (p= 0.526).

DISCUSSION

In our study, we found that the occurrence of significant rebound hyperbilirubinemia does not differ significantly between the two groups, when phototherapy was stopped at a serum bilirubin 1- 2.9 mg/dl and ≥3mg/dl below the level at which phototherapy was initiated.

Authors of different studies used various cut-off of serum bilirubin level to stop phototherapy. Tan(21), in his article, he suggested to stop phototherapy at a serum bilirubin level of 11mg/dl. Lazar et al (20) in his study used a higher serum bilirubin level than suggested by Tan, to stop phototherapy. In their study they stopped phototherapy at mean serum bilirubin level of 13±0.7 mg/dl in term babies. For preterm babies they stopped phototherapy at a mean serum bilirubin level of 10.7 ± 1.2 mg/dl. They did not include babies with haemolytic conditions in their study.

Barak et al, (4), in their pilot study compared the outcomes of two groups of neonatal hyperbilirubinemia when phototherapy was stopped at two targets below the AAP treatment threshold(2). They reported that the need for second course of phototherapy was not significantly different when phototherapy was stopped at 1mg/dl and 3 mg/dl below the AAP treatment threshold respectively. We from our study results agree the views of Barak et al.

The base line characters of our study participants were comparable in all the aspects except the sex ratio. In group A the male: female ratio was 1.3:1 and in group B it was 0.6:1. We could not achieve the final sample size of 240, that could be a possibility of the difference in sex ratio between two groups. Also we did not consider that sex of the baby would have an effect on the occurrence of significant rebound jaundice and affect the results of the study.

We found that the duration of the phototherapy is significantly less when the phototherapy is discontinued when serum bilirubin falls 1 mg/dl below AAP cut-off. The mean duration of phototherapy was about 15 hours in 1mg/dl group and about 20 hours in 3mg/dl group. This can reduce the cost for the treatment if phototherapy was stopped at a higher level without increasing the risk of rebound jaundice.

Although our study showed that the duration of phototherapy is significantly less when phototherapy was stopped at a higher level, the mean duration of hospital stay was not significantly less. The mean duration of hospital stay differs by only 2 hours between the groups. This may be due the discharging policy of the unit. Most of our hospital discharges occur by afternoon of a day. Hence even if the baby gets ready for discharge after phototherapy by late night or morning, discharges usually occur along with mother by afternoon. Another observation which supports this fact is that the age at discontinuation of phototherapy, which is significantly less in the 1mg/dl. The mean age at discontinuation of phototherapy was 88 hours when it was stopped at 1mg/dl below cut-off and 98 hours when phototherapy was stopped at 3mg/dl below cut- off.

Out of four babies who had significant rebound hyperbilirubinemia, two babies were term with gestational age more than 38 weeks with features of hemolysis. Two babies were late preterm, of which one had additional risk of hemolysis. Age at initiation of phototherapy of all the four babies was less than 72 hours. These finding corresponds with that of previous studies which reported the risk factors of rebound jaundice. Kaplan et al in his study reported that rebound jaundice was more in babies with neonates <37 weeks and in babies with onset of jaundice <72 hours.

We did the sub group analysis depends on the risk category according to the AAP guidelines. It showed that in low risk babies, no baby had experienced a significant rebound hyperbilirubinemia requiring repeat course of phototherapy in both the groups studied. Previous studies also reported that the chance for rebound jaundice was less in the absence of risk factors. Our study also supports the reports of Kaplan et al reported that the risk of significant rebound was higher in babies with gestational age <37 weeks and with hemolytic disease. Hence for low risk babies without any risk factors the chance of rebound jaundice is less and phototherapy can be stopped at a higher bilirubin level safely.

In babies with medium risk category, 1 baby from group A and 2 babies from group B had rebound hyperbilirubinemia requiring repeat course of phototherapy. But this difference is not statistically significant. The duration of phototherapy is significantly less in group A as observed in overall analysis.

In high risk category, 1 out of 10 babies from group A experienced rebound hyperbilirubinemia requiring repeat course of phototherapy. None of the 9 babies from group B had significant rebound hyperbilirubinemia. This difference is also not statistically significant. However, we got only 19 babies for analysis in this category and it constitute around 12 % of the study population. We included all the babies with neonatal jaundice hence we could not get equal distribution of cases between AAP risk category. We suggest that the high risk babies should be targeted separately and studied to ensure that stopping phototherapy at higher bilirubin level would not cause significant increase in rebound jaundice.

The strength of our study was the study design, a randomised controlled trial; hence the chances of bias were less. Although we could not get the required sample size of 99 babies in each group, we have achieved 80 percent of the required sample size. We designed the protocol to stop phototherapy in two groups at a level, either 1mg/dl or 3 mg/dl, below the AAP treatment threshold. This design is advantageous that the serum bilirubin level at which we stopped phototherapy was dynamic as that of the disease course. We got different cut off for stopping the phototherapy in each babies and it is related to their own treatment threshold.

LIMITATIONS

The limitations of this study were that we could not achieve the final sample size calculated and this study is an open labelled trial. We don't think that the lack of blinding would result in bias as we have followed a strict protocol once the baby got recruited and deviations from protocol were not allowed.

CONCLUSION

We suggest that in babies with neonatal jaundice, phototherapy can be stopped at a serum bilirubin level of 1mg/dl below the AAP treatment threshold at which phototherapy was initiated without any increased risk of rebound jaundice. We recommend that future studies should be targeted for high risk babies.

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PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

Recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
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Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

Ref. No.: PSG/IHEC/2018/Appr/FB/006

To
Dr G Veda Senthil Velan
Postgraduate
Department of Paediatrics
Guide/s: Dr K Neelankantan / Dr S Ramesh / Dr K Suvetha / Dr P Sudhakar / Dr J Suchitra
PSG IMS & R
Coimbatore

Ref: Project No.17/388

Date: January 30, 2018

Dear Dr Veda Senthil Velan,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 08.12.2017 to conduct the research study entitled "*A comparison of two targets of serum bilirubin concentration for phototherapy discontinuation in neonatal jaundice*" during the IHEC review meeting held on 05.01.2018.

The following documents were reviewed and approved:

1. Project Submission form
2. Study protocol (Version 1 dated 08.12.2017)
3. Parental consent forms (Version 2 dated 27.01.2018)
4. Data collection tool (Version 1 dated 08.12.2017)
5. Permission letter from concerned Heads of Department
6. Current CVs of Principal investigator, Co-investigators
7. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 05.01.2018 at Research Conference Room, PSG IMS & R between 2.30 pm and 5.00 pm:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mrs Y Ashraf	MPT	Physiotherapy	Female	Yes	Yes
2	Dr. K. Bhuvaneshwari	MD	Clinical Pharmacology	Female	Yes	Yes
3	Mr Gowpathy Velappan	BA., BL	Legal Advisor	Male	No	Yes

SECRETARY PSG IMS&R COIMBATORE INSTITUTIONAL HUMAN ETHICS COMMITTEE

30/01/2018

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

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4	Dr A Jayavardhana	MD	Clinician (Paediatrics)	Male	Yes	Yes
5	Mr P Karuppuchamy	M Phil in PSW	Social Scientist	Male	Yes	Yes
6	Dr G Malarvizhi	M Sc, Ph D	Nursing	Female	Yes	Yes
7	Mr. R. Nandakumar (Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
8	Dr. Parag K Shah	DNB	Clinician (Ophthalmology)	Male	No	Yes
9	Mrs P Rama	M Pharm	Non-Medical (Pharmacy)	Female	Yes	No
10	Dr. Seetha Panicker	MD	Clinician (Obstetrics & Gynaecology)	Female	Yes	Yes
11	Dr. S. Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
12	Dr G Subhashini	MD	Epidemiology	Female	Yes	Yes
13	Dr. Sudha Ramalingam (Alternate Member-Secretary, IHEC)	MD	Public Health, Epidemiology, Genetics, Ethicist	Female	Yes	Yes
14	Mrs. Swasthika Soundararaj	MBA	Lay person	Female	No	Yes
15	Dr. D. Vijaya (Member – Secretary)	M Sc, Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
    a. The exact alteration/amendment should be specified and indicated where the

30/01/2018

SECRETARY

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

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amendment occurred in the original project. (Page no. Clause no. etc.)
b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review

7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Thanking You,

Yours Sincerely,

30/01/2018

Dr D Vijaya
Member - Secretary
Institutional Human Ethics Committee

SECRETARY
PSG IMS&R
COIMBATORE-641004
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Clinical Trial Details (PDF Generation Date :- Wed, 07 Feb 2018 05:09:06 GMT)

CTRI Number	CTRI/2018/02/011740 [Registered on: 07/02/2018] - **Trial Registered Prospectively**
Last Modified On	07/02/2018
Post Graduate Thesis	Yes
Type of Trial	Interventional
Type of Study	Process of Care Changes
Study Design	Randomized, Parallel Group, Active Controlled Trial
Public Title of Study	A clinical trial to compare the effects of stopping phototherapy administered for newborn babies affected by jaundice at low and high serum bilirubin levels.
Scientific Title of Study	A comparison of two targets of serum bilirubin concentration for phototherapy discontinuation in neonatal jaundice.

Secondary IDs if Any

Secondary ID	Identifier
NIL	NIL

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
Name	Veda Senthil Velan Ganesan
Designation	Postgraduate
Affiliation	PSG Institute of Medical Sciences and Research
Address	Department of Paediatrics, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore Coimbatore TAMIL NADU 641004 India
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Details Contact Person (Scientific Query)

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Name	Ramesh S
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Source of Monetary or Material Support

Source of Monetary or Material Support
> Veda Senthil Velan Ganesan, Postgraduate, Department of Paediatrics, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore. 641004

Primary Sponsor

Primary Sponsor Details	
Name	Veda Senthil Velan Ganesan
Address	Postgraduate Department of Paediatrics, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore
Type of Sponsor	Other [Principal investigator]

Details of Secondary Sponsor

Name	Address
Ramesh S	Associate Professor, Department of Paediatrics, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore.

Countries of Recruitment

List of Countries
India

Sites of Study

Name of Principal Investigator	Name of Site	Site Address	Phone/Fax/Email
Veda Senthil Velan Ganesan	PSG Institute of Medical Sciences and Research	Neonatal Unit, Department of Paediatrics. Coimbatore TAMIL NADU	8939462670 doctorvsv@gmail.com

Details of Ethics Committee

Name of Committee	Approval Status	Date of Approval	Is Independent Ethics Committee?
Institutional Human Ethics Committee	Approved	30/01/2018	No

Regulatory Clearance Status from DCGI

Status	Date
Not Applicable	No Date Specified

Health Condition / Problems Studied

Health Type	Condition
Patients	Neonatal jaundice

Intervention / Comparator Agent

Type	Name	Details
Intervention	Group A	Phototherapy will be stopped once serum bilirubin falls 1.0 to 2.9mg/dl below treatment threshold.
Comparator Agent	Group B	Phototherapy will be stopped once serum bilirubin falls 3.0 mg/dl below treatment threshold

Inclusion Criteria

Inclusion Criteria	
Age From	1.00 Day(s)
Age To	7.00 Day(s)
Gender	Both
Details	1)Babies with gestational age ?35 weeks, 2)Babies with birth weight >1800 grams, 3)Babies requiring phototherapy for the first time, 4)Babies with onset of jaundice ?7 days.

Exclusion Criteria

Exclusion Criteria	
Details	Babies planned for immediate exchange transfusion at the time of

	admission
Method of Generating Random Sequence	Permuted block randomization, variable
Method of Concealment	Sequentially numbered, sealed, opaque envelopes
Blinding/Masking	Open Label

Primary Outcome

Outcome	Timepoints
Number of babies who require re-initiation of phototherapy.	24 hours after stopping phototherapy

Secondary Outcome

Outcome	Timepoints
Total duration of phototherapy including treatment after rebound hyperbilirubinemia and total duration of hospital stay.	Less than 7 days

Target Sample Size	**Total Sample Size=**240 **Sample Size from India=**240
Phase of Trial	N/A
Date of First Enrollment (India)	12/02/2018
Date of First Enrollment (Global)	No Date Specified
Estimated Duration of Trial	**Years=**0 **Months=**7 **Days=**0
Recruitment Status of Trial (Global)	Not Applicable
Recruitment Status of Trial (India)	Not Yet Recruiting
Publication Details	Nil
Brief Summary	This study is a randomized, open labelled, parallel group, single centre study comparing the occurance of significant rebound jaundice when phototherapy was stopped in two targets below the treatment threshold in babies with neonatal jaundice. Secondary outcomes will be compared are total duration of phototherapy and total duration of hospital stay in two groups.

CASE REPORT FORM

Name

Gender M F

OP Number

IP Number

Enrollment No

Date of admission

Date of enrolment

Date of discharge

Randomisation group A B

Date of birth

Time of birth

Gestational age

Birth weight(kg)

Mother's blood group

Baby's blood group

H/O jaundice in previous sibling Y N

Exclusive breast feeding Y N

Excessive weight loss Y N

Extravaseted blood collection Y N

Significant lethargy Y N

Temperature instability Y N

	Complete blood counts	Hb(g/dl)	Hct(%)	WBC(10^9/L)	ANC
	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Platelets (10^9/L)

Reticulocyte count | | | | %

Peripheral smear :

Direct coomb's test | Positive | Negative |

Serum Albumin (gm/dl) | | | |

G6PD | Positive | Negative |

Septic screen | Positive | Negative |

Acidosis | Y | N |

Asphyxia | Y | N |

AAP Category | | | |

SBR cut off for phototherapy | | | | |

SBR at the start of phototherapy | | | | |

Age at starting phototherapy | | | | |

Target SBR to stop phototherapy | | | | |

SBR during phototherapy | | | | | | |
| | | | | | |

Age at stopping phototherapy | | | | |

SBR after stopping phototherapy | | | | | | |
| | | | | | |

IV fluid therapy | Y | N |

IVIG therapy | Y | N |

Exchange transfusion | Y | N |

Repeat phototherapy | Y | N |

Duration of phototherapy | | | | |

Duration of hospital stay | | | | |

Outcome

SOP 03-V 3.0 / ANX 10-V 3.0

Institutional Human Ethics Committee
PSG Institute of Medical Sciences and Research, Coimbatore

Parental Consent Form

Title of Study: A comparison of two targets of serum bilirubin concentration for phototherapy discontinuation in neonatal jaundice.

Name of the Principal Investigator: Dr. G. Veda Senthil Velan
Department: Department of Pediatrics

Your child is invited to participate in a study of "Comparison of two targets of serum bilirubin concentration for phototherapy discontinuation in neonatal jaundice".

My name is Dr. G. Veda SenthilVelan, and I am a postgraduate at PSG Institute of Medical Sciences and Research, Coimbatore. This study is (state how study relates to your program of work or your supervisor's program of work). Neonatal jaundice is a common problem affecting newborn babies and phototherapy is the main modality of treatment. As per standard treatment guidelines, serum bilirubin level for starting phototherapy was available. There is no definite guideline available for serum bilirubin level at which phototherapy can be stopped in neonatal jaundice. Hence we propose to conduct this study.

I am asking for permission to include yourchild in this study because this study involves newborn with gestational age of 35 weeks with neonatal jaundice requiring phototherapy.

I expect to have 240 participants in the study.
If you allow your child to participate, we will enroll your child and randomly allocate your child in either group A or group B. As per standard treatment guidelines your child will be treated and serum bilirubin will be monitored every 6 hours. Depending on the group the baby is assigned phototherapy will be stopped once serum bilirubin drops 1.0-2.9mg/dl or more than 3.0mg/dl below the treatment threshold. After stopping phototherapy serum bilirubin will be checked at 6 hours and 24 hours to look for rebound jaundice.
Risk: Your child may develop rebound jaundice which can be due to cause and severity of the disease. Additional course of phototherapy may be needed if serum bilirubin increases beyond the cut off and the stay may be extended for one more day.
Benefits: Your child may require lesser duration of phototherapy and hence lesser duration of hospital stay.

Any information that is obtained in connection with this study and that can be identified with your /child will remain confidential and will be disclosed only with your permission. His or her responses will not be linked to his or her name or your name in any written or verbal report of this research project.

Your decision to allow your child to participate will not affect your or his or her present or future relationship with PSGIMS&R or PSG Hospitals. If you have any questions about the

study, please ask me. If you have any questions later, call me at 8939462670. If you have any questions or concerns about yourchild's participation in this study, call 8939462670.

You may keep a copy of this consent form.
You are making a decision about allowing your child to participate in this study. Your signature below indicates that you have read the information provided above and have decided to allow him or her to participate in the study. If you later decide that you wish to withdraw your permission for your child to participate in the study, simply tell me.

You may discontinue his or her participation at any time. *This will not affect in any way your future treatment in this hospital.*

Printed Name of thechild

Signature of Parent(s) or Legal Guardian with Date Signature of Investigator with Date

Institutional Human Ethics Committee phone number:0422 4345818

மனித நெறிமுறைக் குழு

பூ சா கோ மருத்துவக் கல்லூரி மற்றும் ஆராய்ச்சி நிறுவனம், கோவை

பெற்றோர் ஒப்புதல் படிவம்

ஆய்வின் தலைப்பு: "மஞ்சள் காமாலையால் பாதிக்கப்பட்ட பச்சிளம் குழந்தைகளுக்கு அளிக்கப்படும் ஒளிக்கதிர் சிகிச்சையை இடை நிறுத்துவதற்கு சீரம் பிளுரூபின் அளவின் இரண்டு இலக்குகளை ஒப்பிடும் ஆய்வு"

முதன்மை ஆராய்ச்சியாளர் பெயர்:மரு. க. வேத செந்தில் வேலன்

குழந்தைகள் மருத்துவத்துறை

இந்த ஆய்வில் உங்கள் குழந்தை பங்கேற்க அழைக்கப்படுகிறார்.

மரு. க. வேத செந்தில் வேலன் ஆகி நான் பூ சா கோ மருத்துவக் கல்லூரியின் குழந்தைகள் மருத்துவத்துறையில் மருத்துவ பட்ட மேற்படிப்பு படித்துக் கொண்டி ருக்கிறேன். பச்சிளம் குழந்தைகள் மஞ்சள் காமாலையால் அதிகம் பாதிக்கப் படுகிறார்கள். அவர்களுக்கு ஒளிக்கதிர் சிகிச்சை முக்கியமான சிகிச்சையாக விளங்குகிறது. உலக அளவில் ஏற்றுக்கொள்ளப்பட்ட சிகிச்சை வழிகாட்டுதல் படி ஒளிக்கதிர் சிகிச்சையை தொடங்குவதற்கான சீரம் பிளுரூபின் அளவு கணிக்கப்பட்டுள்ளது. ஆனால் அந்த சிகிச்சையை நிறுத்துவதற்கான சீரம் பிளுரூபின் அளவு பற்றிய சரியான வழிகாட்டுதல் இல்லை. எனவே இந்த ஆய்வு மேற்கொள்ள முடிவு செய்யப்பட்டது.

இந்த ஆய்வு 35 வாரங்கள் பூர்த்தி அடைந்து பிறக்கும் பச்சிளம் குழந்தைகளுக்கு ஏற்படும் மஞ்சள் காமாலைக்கு அளிக்கப்படும் ஒளிக்கதிர் சிகிச்சையை பற்றியது. எனவே உங்கள் குழந்தை பங்கேற்க அனுமதி அளிக்குமாறு கேட்டுக் கொள்கிறோம்.

ஆய்வில் பங்கு பெறும் குழந்தைகளின் எண்ணிக்கை 240 என எதிர்பார்க்கப்படுகிறது.

இந்த ஆய்வில் உங்கள் குழந்தை பங்கேற்க நீங்கள் அனுமதி அளித்தால் நாங்கள் உங்கள் குழந்தையை சம வாய்பிட்டு பிரிவு(அ) அல்லது பரிவு (ஆ) வில் ஒதிக்கீடு செய்வோம். பின்னர் உங்கள் குழந்தைக்கு தரமான சிகிச்சை வழிகாட்டுதல் படி ஒளிக்கதிர் சிகிச்சை அளிக்கப்பட்டு 6 மணி நேரத்திற்கு ஒரு முறை சீரம் பிளுரூபின் அளவு கண்காணிக்கப்படும். உங்கள் குழந்தை ஒதுக்கப்பட்டுள்ள பிரிவை பொறுத்து சீரம் பிளுரூபின் அளவு சிகிச்சை அளிக்க தேவையான அளவை விட 1.0-2.9 மிலி கிராம்/டெசி லிட்டர் அல்லது 3.0 மிலி கிராம்/டெசி லிட்டர் குறைந்ததும் ஒளிக்கதிர் சிகிச்சை நிறுத்தப்படும். பின்னர் மஞ்சள் காமாலை அளவு அதிகரிக்கிறதா என்பதை அறிய சீரம் பிளுரூபின் அளவு 6 மற்றும் 24 மணி நேரம் கழித்து அளவிடப்படும் .

பாதகங்கள்: உங்கள் குழந்தைக்கு ஒளிக்கதிர் சிகிச்சையை நிறுத்திய பின்னர் சீரம்

பிளூரூபின் அளவு அதிகரிக்கலாம். தேவைப்பட்டால் ஒளிக்கதிர் சிகிச்சை மீண்டும் துவங்கப்படும். அவ்வாறு சிகிச்சை அளிக்கப்பட்டால் ஒரு நாள் கூடுதலாக தங்க நேரிடலாம்.

நன்மைகள்: உங்கள் குழந்தைக்கு அளிக்கப்படும் ஒளிக்கதிர் சிகிச்சையின் காலம் குறைய வாய்ப்புள்ளது. அவ்வாறு குறைந்தால் மருத்துவமனையில் தங்கும் நேரம் குறைய வாய்ப்புள்ளது.

இந்த ஆய்விற்காக நீங்கள் அளிக்கும் தகவல்கள் மற்றும் இந்த ஆய்வில் கண்டறிய படும் தகவல்கள் இரகசியமாக வைக்கப்பட்டு உங்கள் அனுமதியுடன் மட்டுமே வெளியிடப்படும். ஆய்வு அறிக்கையில் உங்கள் குழந்தையைப்பற்றியோ அல்லது உங்களை பற்றியோ எந்த விபரமும் இடம் பெறாது.

இந்த ஆய்வில் உங்கள் குழந்தை பங்கேற்க அனுமதி அளிப்பதால் உங்கள் குழந்தைக்கும் இந்த மருத்துவமனைக்கும் இடையிலான உறவு எப்பொழுதும் பாதிக்கப்படாது. இந்த ஆய்வை பற்றிய உங்கள் சந்தேகங்களை என்னிடம் நீங்கள் கேட்கலாம். எதிர் காலத்தில் இந்த ஆய்வு பற்றி உங்களுக்கு கேள்வி எழுந்தால் எனது கைபேசி எண்ணிற்கு தாங்கள் அழைக்கலாம். எனது கைபேசி எண்: 8939462670

நீங்கள் விரும்பினால் இந்த ஒப்புதல் படிவத்தின் பிரதியை வைத்துக்கொள்ளலாம்.

கீழே நீங்கள் கையொப்பம் இடுவதன் வாயிலாக இந்த ஒப்புதல் படிவம் முழுவதும் படித்த பின்னர் இந்த ஆய்வில் உங்கள் குழந்தை பங்கு பெற அனுமதி அளிப்பதாக புரிந்து கொள்ளப்படுகிறது.

நீங்கள் உங்கள் குழந்தை ஆய்வில் பங்கு பெறும் அனுமதியை எந்த நிலையிலும் திரும்ப பெற்றுக் கொள்ளலாம். உங்கள் முடிவால் உங்கள் குழந்தையின் எதிர்கால மருத்துவ சிகிச்சையில் எந்த பாதிப்பும் ஏற்படாது.

குழந்தையின் பெயர் :

பொற்றோரின் கையொப்பம் / கை ரேகை ஆய்வாளரின் கையொப்பம்

தேதி :

மனித நெறிமுறைக் குழு அலுவலகத்தின் தொலைபேசி எண்: 0422 4345818

ABBREVIATIONS

AAP	:	American Academy of Paediatrics
ABE	:	Acute Bilirubin Encephalopathy
BAER	:	Brainstem auditory evoked respomse
BAMR	:	Bilirubin Albumin Molar Ratio
BBB	:	Blood Brain Barrier
CNS	:	Central Nervous System
CO	:	Carbon monoxide
COHb	:	Carboxy Hemoglobin
DCT	:	Direct Coombs Test
ETCO	:	End Tidal Carbon Monoxide
G6PD	:	Glucose 6 Phosphate Dehydrogenase
HO	:	Heme Oxygenase
HPLC	:	High Performance Liquid chromatography
IVIG	:	Intravenous Immunoglobulin
LED	:	Light Emitting Diodes
NICE	:	National Institute for Health and care Excellence
PGP	:	Phosphorylated glycoprotein
RBC	:	Red Blood Cells
UGT1A1	:	Uridine diphosphate- glucuronosyltransferase 1A1

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MASTER CHART

Direct Coomb's test	Hypoalbuminemia	G6PD	Septic screen	Acidosis	Asphyxia	AAP Risk category	SBR cut off for PT	SBR at start of PT	Age at starting PT	Target SBR to stop PT	SBR at stopping PT	Age at stopping PT	Hours after stopping	SBR after stopping PT 1	Hours after stopping	SBR after stopping PT 2	IV Fluid	IVIG	Exchange transfusion	Duration of PT	Repeat PT	Duration of Repeat PT	Readmission	Duration of Readmission	Total Duration of PT(Hr)	Totat duration of hospital	Outcome	Final group
0	0	2	2	0	0	2	15.5	16.2	72	14.5	13.5	84	6	13.5	62	15.1	0	0	0	14	0	0	0	0	12	122	1	1
1	0	2	2	0	0	3	12.0	13.2	54	9.0	7.5	95	6	6.9	NA	NA	0	0	0	35	0	0	0	0	35	103	1	2
0	0	2	2	0	0	3	15.0	16.2	105	12.0	11.7	113	6	8.2	NA	NA	0	0	0	16	0	0	0	0	16	134	1	2
0	0	2	2	0	0	2	15.0	15.6	80	12.0	10.6	96	7	10.6	NA	NA	0	0	0	16	0	0	0	0	16	129	1	2
1	0	2	2	0	0	3	10.0	16.3	31	9.0	10.9	93	6	10.4	NA	NA	0	0	0	61	0	0	0	0	61	114	1	1
0	0	2	2	0	0	2	15.0	17.2	72	14.0	11.4	95	6	13.0	NA	NA	0	0	0	17	0	0	0	0	17	104	1	2
0	0	2	2	0	0	3	13.0	14.3	75	12.0	11.2	93	6	11.8	14	12.8	0	0	0	28	0	0	0	0	28	121	1	1
0	0	2	2	0	0	3	14.5	16.5	70	11.5	11.4	88	6	13.4	NA	NA	0	0	0	18	0	0	0	0	18	106	1	2
0	0	2	2	0	0	2	18.0	18.3	146	17.0	14.3	157	6	12.2	NA	NA	0	0	0	11	0	0	0	0	11	22	1	2
1	0	2	2	0	0	2	13.0	13.0	48	10.0	9.4	64	6	9.2	14	9.9	0	0	0	16	0	0	0	0	16	93	1	2
1	0	2	2	0	0	2	14.0	15.2	52	13.0	11.5	60	6	11.5	NA	NA	0	0	0	8	0	0	0	0	8	79	1	1
0	0	2	2	0	0	2	14.5	14.7	56	11.5	12.0	76	6	11.1	NA	NA	0	0	0	20	0	0	0	0	20	95	1	2
0	0	2	2	0	0	2	14.5	17.0	68	13.5	13.8	88	6	12.2	NA	NA	0	0	0	20	0	0	0	0	20	97	1	1
1	0	2	2	0	0	2	13.0	13.9	53	10.0	10.5	93	NA	NA	NA	NA	0	0	0	40	0	0	0	0	40	93	2	2
0	0	2	2	0	0	2	15.3	18.5	78	14.3	11.7	92	6	11.1	36	16.4	0	0	0	14	0	0	0	0	14	105	1	2
0	0	2	2	0	0	2	14.5	16.0	63	11.5	11.4	92	6	10.4	19	11.6	0	0	0	29	0	0	0	0	29	115	1	2
0	0	2	2	0	0	1	17.5	17.6	74	16.5	15.8	82	6	14.8	15	15.6	0	0	0	8	0	0	0	0	8	100	1	1
0	0	2	0	0	0	3	12.5	14.9	76	9.5	9.3	96	6	7.7	22	9.3	0	0	0	20	0	0	0	0	20	92	1	2
0	0	2	2	0	0	2	16.5	18.9	117	13.5	12.5	137	5	13.1	24	16.5	0	0	0	20	0	0	0	0	20.0	48.0	2	2
0	0	2	2	0	0	2	15.5	15.6	76	12.5	12.3	85	6	11.7	NA	NA	0	0	0	9	0	0	0	0	9	98	1	2
0	0	2	2	0	0	1	15.0	15.3	47	14.0	13.4	60	6	12.6	NA	NA	0	0	0	13	0	0	0	0	13	73	1	1
0	0	2	2	0	0	1	17.0	19.3	76	14.0	13.2	97	6	12.7	NA	NA	0	0	0	24	0	0	0	0	24	120	1	2
0	0	2	2	0	0	3	13.0	16.0	70	10.0	8.9	98	7	8.9	NA	NA	0	0	0	28	0	0	0	0	28.0	117.0	1	2
0	0	2	2	0	0	1	18.0	21.5	83	17.0	16.1	98	6	14.5	58	16.0	0	0	0	15	0	0	0	0	15	107	1	1
0	0	2	2	0	0	1	17.5	17.9	79	16.5	16.0	92	6	14.4	NA	NA	0	0	0	13	0	0	0	0	13	101	1	1
0	0	2	2	0	0	2	15.5	17.1	82	14.5	11.4	96	6	11.2	NA	NA	0	0	0	14	0	0	0	0	14	100	1	2
0	0	2	2	0	0	3	15.0	19.6	126	12.0	10.2	150	6	12.2	NA	NA	0	0	0	24	0	0	0	0	24	173	1	2
0	0	2	2	0	0	1	17.0	17.1	76	14.0	12.8	94	5	12.5	30	15.4	0	0	0	18	0	0	0	0	18	145	1	2
1	0	2	2	0	0	2	15.0	15.1	75	12.0	10.2	90	6	9.7	NA	NA	0	0	0	15	0	0	0	0	15.0	100.0	1	2
0	0	2	2	0	0	1	16.0	16.2	69	15.0	13.4	84	6	13.2	36	16.0	0	0	0	15	0	0	0	0	15	95	1	1
0	0	2	2	0	0	1	16.5	16.7	63	15.5	12.9	79	6	12.3	30	13.2	0	0	0	14	0	0	0	0	14	89	1	2
0	0	2	2	0	0	2	15.0	15.7	66	12.0	10.8	86	5	10.9	NA	NA	0	0	0	20	0	0	0	0	20	100	1	2
0	0	2	2	0	0	2	15.0	15.5	70	12.0	12.4	NA	N/A	N/A	NA	NA	0	0	0	7	0	0	0	0	7	71	2	3
0	0	2	2	0	0	2	14.5	16.3	60	13.5	13.4	79	6	13.1	NA	NA	0	0	0	19	0	0	0	0	19	75	1	1
0	0	2	2	0	0	2	15.0	16.9	75	14.0	12.9	83	7	11.0	NA	NA	0	0	0	8	0	0	0	0	8	102	1	1
1	0	2	2	0	0	2	15.0	16.4	72	12.0	12.0	94	6	10.1	25	11.2	0	0	0	22	0	0	0	0	22	115	1	2
0	0	2	2	0	0	2	15.0	15.9	71	14.0	12.3	85	6	12.7	12	13.2	0	0	0	14	0	0	0	0	14	100	1	1
0	0	2	2	0	0	2	15.5	15.7	85	12.5	11.9	106	6	10.4	NA	NA	0	0	0	21	0	0	0	0	21	114	1	2
0	0	2	2	0	0	2	14.3	14.4	63	11.3	11.2	83	6	11.4	52	14.6	0	0	0	20	0	0	0	0	20	92	1	2
1	0	2	2	0	0	2	15.5	17.7	77	14.5	14.4	96	7	13.3	26	14.3	0	0	0	19	0	0	0	0	19	124	1	1
0	0	2	2	0	0	1	18.0	18.5	97	15.0	14.3	111	7	13.9	11	14.2	0	0	0	14	0	0	0	0	14	123	1	2
0	0	2	2	0	0	2	17.0	18.1	102	16.0	15.1	113	7	13.1	23	13.6	0	0	0	9	0	0	0	0	9	149	1	1
0	0	2	2	0	0	2	14.5	14.5	65	11.5	10.8	91	6	11.0	15	10.7	0	0	0	26	0	0	0	0	26	111	1	2
0	0	2	2	0	0	2	15.5	16.5	77	14.5	13.5	91	6	12.3	14	13.2	0	0	0	14	0	0	0	0	14	105	1	1
0	0	2	2	0	0	1	17.0	17.1	75	14.0	12.6	93	7	11.6	24	13.4	0	0	0	18	0	0	0	0	18	124	1	2
0	0	2	2	0	0	2	15.0	16.0	74	14.0	12.5	87	6	10.6	12	11.8	0	0	0	13	0	0	0	0	13	98	1	1
0	0	2	2	0	0	1	17.0	17.1	82	14.0	14.0	97	N/A	N/A	N/A	N/A	0	0	0	20	0	0	0	0	20	98	2	2
1	0	2	2	0	0	3	12.0	13.0	72	9.0	8.4	87	6	9.7	28	9.3	0	0	0	15	0	0	0	0	15	120	1	2
0	0	2	2	0	0	1	19.5	20.5	96	18.5	16.8	113	7	14.9	28	16.2	0	0	0	17	0	0	0	0	17	148	1	1
0	0	2	2	0	0	2	15.5	18.7	82	14.5	13.3	97	6	12.5	10	12.5	0	0	0	15	0	0	0	0	15	105	1	1
0	0	2	2	0	0	2	15.0	17.5	68	14.0	13.6	80	6	12.6	12	11.5	0	0	0	12	0	0	0	0	12	95	1	1
0	0	2	2	0	0	2	13.0	22.6	50	10.0	9.8	98	6	13.5	21	16.7	0	0	0	48	1	28	0	0	76	192	1	2
0	0	2	2	0	0	1	16.5	19.5	69	13.5	13.5	90	6	11.6	NA	NA	0	0	0	21	0	0	0	0	21	99	1	2
0	0	2	2	0	0	1	18.0	19.7	77	15.0	12.7	91	7	10.5	25	11.5	0	0	0	14	0	0	0	0	14	122	1	2
0	0	2	2	0	0	2	17.0	18.3	103	14.0	13.3	118	7	13.1	12	12.2	0	0	0	15	0	0	0	0	15	130	2	2
0	0	2	2	0	0	2	13.5	14.0	56	10.5	10.4	96	6	10.7	25	12.2	0	0	0	40	0	0	0	0	40	144	1	2
0	0	2	2	0	0	1	16.0	16.2	65	15.0	14.8	80	8	13.6	NA	NA	0	0	0	15	0	0	0	0	15	108	1	1
0	0	2	2	0	0	2	15.0	17.3	70	14.0	12.9	85	6	11.9	12	15.9	0	0	0	15	0	0	0	0	15	112	1	1
0	0	2	2	0	0	2	15.0	16.0	63	14.0	12.5	78	6	10.6	12	11.8	0	0	0	13	0	0	0	0	13	98	1	1
0	0	2	2	0	0	2	14.5	14.7	63	11.5	10.5	84	6	9.5	15	11.2	0	0	0	21	0	0	0	0	21	107	1	2
0	0	2	2	0	0	1	17.0	17.9	68	16.0	15.8	77	6	14.7	25	14.1	0	0	0	9	0	0	0	0	9	109	1	1
0	1	2	0	0	0	3	15.0	15.5	126	12.0	NA	135	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	withdrawn	3
0	0	2	2	0	0	2	15.0	16.1	72	12.0	10.0	92	6	9.3	28	10.3	0	0	0	20	0	0	0	0	20	101	1	2
0	0	2	2	0	0	1	17.0	17.5	69	16.0	15.1	89	6	14.7	13	15.8	0	0	0	20	0	0	0	0	20	98	1	1
0	0	2	2	0	0	3	14.0	15.5	83	13.0	11.9	98	6	12.4	31	13.7	0	0	0	14	0	0	0	0	15	143	1	1
1	0	2	2	0	0	2	13.5	20.4	51	12.5	11.5	72	6	11.5	25	13.7	0	0	0	21	0	0	0	0	21	148	1	1
0	0	2	2	0	0	2	16.0	16.1	72	15.0	14.8	80	8	13.6	25	11.9	0	0	0	8	0	0	0	0	8	101	1	2
0	0	2	2	0	0	2	14.0	14.3	63	11.0	10.6	79	6	10.2	25	12.0	0	0	0	16	0	0	0	0	16	107	1	2
0	0	2	2	0	0	1	17.5	18.2	100	16.5	14.9	109	6	14.2	13	13.6	0	0	0	9	0	0	0	0	9	126	1	1
0	0	2	2	0	0	2	14.0	15.9	76	11.0	10.3	95	6	8.9	25	11.0	0	0	0	21	0	0	0	0	19	123	1	2
0	0	2	2	0	0	1	17.3	17.3	73	14.3	13.6	81	5	11.4	12	12.4	0	0	0	8	0	0	0	0	8	96	1	2
1	0	2	2	0	0	2	14.5	15.7	63	13.5	12.7	79	6	10.2	22	9.6	0	0	0	16	0	0	0	0	16	94	1	1
0	0	2	2	0	0	2	14.5	17.4	58	13.5	13.5	75	7	13.7	20	12.6	0	0	0	17	0	0	0	0	17	87	1	1
0	0	2	2	0	0	2	17.0	17.1	92	14.0	13.0	116	9	11.9	22	10.1	0	0	0	24	0	0	0	0	24	120	1	2
0	0	2	2	0	0	2	17.0	18.5	83	16.0	14.4	104	6	13.6	20	15.1	0	0	0	21	0	0	0	0	21	132	1	1
0	0	2	2	0	0	2	16.5	16.8	72	13.5	12.3	94	6	11.5	20	13.4	0	0	0	22	0	0	0	0	22	126	1	2
0	0	2	2	0	0	2	17.0	17.5	95	14.0	12.2	117	6	10.9	16	11.1	0	0	0	22	0	0	0	0	22	142	1	2
0	0	2	2	0	0	2	14.5	16.4	68	13.5	13.4	76	6	11.5	12	11.8	0	0	0	8	0	0	0	0	8	93	1	1
0	0	2	2	0	0	2	15.0	15.4	70	12.0	11.4	88	7	10.4	23	11.8	0	0	0	18	0	0	0	0	18	116	1	2
0	0	2	2	0	0	1	16.5	21.6	66	15.5	10.7	89	6	10.3	21	9.2	0	0	0	23	0	0	0	0	23	117	1	2
0	0	2	2	0	0	2	18.0	18.2	110	17.0	16.4	118	8	13.7	20	15.5	0	0	0	8	0	0	0	0	8	30	1	1
0	0	2	2	0	0	1	18.0	18.4	84	15.0	14.0	93	6	12.7	20	13.4	0	0	0	9	0	0	0	0	9	114	1	2
0	0	2	2	0	0	1	16.5	20.5	66	15.5	14.6	74	6	12.6	29	16.5	0	0	0	8	0	0	0	0	8	112	1	1
0	0	2	2	0	0	3	12.5	15.0	64	9.5	9.5	95	7	9.1	15	8.8	0	0	0	31	0	0	0	0	31	111	1	2
0	0	2	2	0	0	3	12.5	15.1	66	9.5	9.0	90	8	10.8	29	10.5	0	0	0	24	0	0	0	0	24	120	1	2
0	0	2	2	0	0	2	13.5	15.0	57	12.5	11.9	72	8	11.4	20	13.0	0	0	0	15	0	0	0	0	15	97	1	1
0	0	2	0	0	0	2	15.0	19.2	56	12.0	11.8	85	6	12.7	28	15.7	0	0	0	29	0	0	0	0	29	133	1	2
0	0	2	2	0	0	2	15.0	16.8	71	14.0	13.1	85	7	12.9	15	13.8	0	0	0	14	0	0	0	0	14	99	1	1
0	0	2	2	0	0	2	14.5	14.6	71	13.5	13.4	81	6	12.7	23	14.7	0	0	0	10	0	0	0	0	10	106	1	1
0	0	2	2	0	0	2	15.0	16.5	71	12.0	10.9	85	6	10.0	17	12.2	0	0	0	14	0	0	0	0	14	122	1	2
0	0	2	2	0	0	2	15.0	15.5	71	12.0	9.8	86	7	9.9	24	12.7	0	0	0	15	0	0	0	0	15	117	1	2
0	0	2	2	0	0	1	17.5	18.9	76	14.5	14.0	99	6	13.2	23	15.8	0	0	0	23	0	0	0	0	23	151	1	2
0	0	2	1	0	0	2	14.0	14.3	64	13.0	12.3	78	6	11.2	10	11.0	0	0	0	14	0	0	0	0	14	91	1	1
0	0	2	2	0	0	3	13.0	14.1	72	12.0	11.3	86	6	10.9	NA	NA	0	0	0	14	0	0	0	0	14	94	1	1
0	0	2	2	0	0	2	15.0	16.0	76	14.0	13.1	91	6	11.6	12	11.1	0	0	0	15	0	0	0	0	15	104	1	1
0	0	2	2	0	0	2	15.0	15.9	73	14.0	13.5	82	6	13.0	14	14.5	0	0	0	9	0	0	0	0	9	101	1	1
0	0	2	2	0	0	1	15.0	16.3	68	12.0	11.6	88	6	10.8	29	10.6	0	0	0	20	0	0	0	0	20	119	1	2
0	0	2	2	0	0	1	16.5	17.7	66	13.5	12.2	86	N/A	N/A	N/A	N/A	0	0	0	20	0	0	0	0	20	90	2	2
0	0	2	0	0	0	2	14.5	14.5	71	11.5	10.9	86	7	9.1	12	9.7	0	0	0	15	0	0	0	0	15	100	1	2
0	0	2	0	0	0	2	14.0	15.3	57	11.0	9.9	90	6	10.8	12	11.8	0	0	0	33	0	0	0	0	33	106	1	2
0	0	2	2	0	0	2	15.2	15.9	72	12.2	11.9	87	6	9.8	12	11.0	0	0	0	15	0	0	0	0	15	99	1	2
0	0	2	2	0	0	2	15.0	16.2	75	14.0	12.7	88	6	11.2	NA	NA	0	0	0	13	0	0	0	0	13	99	1	1
0	0	2	0	0	0	1	17.0	18.9	68	16.0	14.3	81	6	14.4	29	15.4	0	0	0	13	0	0	0	0	13	140	1	1
0	0	2	2	0	0	2	16.5	16.5	90	15.5	13.3	99	6	11.4	13	10.3	0	0	0	9	0	0	0	0	9	120	1	2
0	0	2	2	0	0	2	15.2	17.8	77	14.2	12.7	97	6	12.1	18	13.5	0	0	0	20	0	0	0	0	20	121	1	1
0	0	2	2	0	0	2	16.0	16.4	86	15.0	13.8	94	7	13.0	23	14.7	0	0	0	7	0	0	0	0	8	131	1	1
0	0	2	2	0	0	1	17.5	20.4	85	14.5	13.0	104	6	11.7	22	13.4	0	0	0	19	0	0	0	0	19	128	1	2
0	0	2	2	0	0	2	15.2	15.9	74	12.2	11.7	88	6	9.8	12	10.6	0	0	0	14	0	0	0	0	14	102	1	2
0	0	2	0	0	0	2	14.5	18.3	64	11.5	11.3	110	6	11.9	32	9.6	0	0	0	46	0	0	0	0	46	116	1	2
0	0	2	2	0	0	2	15.0	17.4	74	14.0	12.6	89	6	12.4	32	13.4	0	0	0	15	0	0	0	0	15	125	1	1
0	0	2	2	0	0	1	15.5	20.6	82	12.5	11.8	110	6	11.3	NA	NA	0	0	0	28	0	0	0	0	28	43	1	2
0	0	2	2	0	0	3	13.0	16.4	75	12.0	10.6	105	6	10.5	18	11.5	0	0	0	30	0	0	0	0	30	124	1	1
0	0	2	2	0	0	2	15.0	15.0	76	12.0	10.5	98	6	11.1	24	12.7	0	0	0	22	0	0	0	0	22	125	1	2
0	0	2	2	0	0	3	14.0	15.8	88	13.0	12.8	110	6	12.0	24	13.3	0	0	0	22	0	0	0	0	22	139	1	1
0	0	2	2	0	0	1	17.5	18.4	81	14.5	12.8	97	7	10.8	29	14.4	0	0	0	16	0	0	0	0	16	107	1	2
0	0	2	2	0	0	2	14.5	14.5	64	13.5	13.4	77	6	13.1	20	10.2	0	0	0	13	0	0	0	0	13	85	1	1
0	0	2	2	0	0	2	17.5	17.5	102	14.5	13.9	111	6	11.0	32	12.7	0	0	0	9	0	0	0	0	9	149	1	2
1	0	2	2	0	0	2	13.0	18.3	49	12.0	10.9	76	NA	NA	NA	NA	0	0	0	27	0	0	0	0	27	94	2	1
0	0	2	2	0	0	1	19.5	21.5	93	18.5	16.9	102	6	14.7	24	16.1	0	0	0	9	0	0	0	0	9	139	1	1
0	0	2	2	0	0	1	19.5	20.7	100	16.5	16.3	115	6	12.2	25	12.9	0	0	0	15	0	0	0	0	15	139	1	2
0	0	2	0	1	0	2	15.2	18.5	73	14.2	14.1	86	7	12.5	32	11.0	0	0	0	13	0	0	0	0	13	97	1	1
0	0	2	2	0	0	2	18.0	19.5	119	17.0	16.1	135	6	14.8	12	14.9	0	0	0	16	0	0	0	0	16	144	1	1
0	0	2	2	0	0	1	17.0	17.1	93	14.0	13.4	114	6	12.8	22	13.6	0	0	0	15	0	0	0	0	15	152	1	2
0	0	2	2	0	0	2	18.0	18.7	149	15.0	13.3	163	7	13.1	22	13.8	0	0	0	14	0	0	0	0	14	40	1	2
0	0	2	2	0	0	2	14.2	14.4	62	13.2	9.1	76	6	8.7	26	10.3	0	0	0	14	0	0	0	0	14	110	1	2
0	0	2	2	0	0	2	15.5	15.5	76	12.5	11.9	96	6	11.5	24	11.7	0	0	0	20	0	0	0	0	20	124	1	2
0	0	2	2	0	0	2	14.0	14.6	53	11.0	11.2	NA	N/A	NA	NA	NA	0	0	0	19	0	0	0	0	19	84	2	3
0	0	2	2	0	0	1	17.0	21.4	74	16.0	15.7	101	6	16.5	18	16.8	0	0	0	27	0	0	0	0	27	121	1	1
0	0	2	2	0	0	3	13.0	14.6	69	12.0	11.3	83	6	11.8	27	13.6	0	0	0	14	1	18	0	0	32	190	1	1
0	0	2	2	0	0	1	16.5	16.5	64	13.5	11.6	78	6	10.2	24	9.7	0	0	0	14	0	0	0	0	14	106	1	2
0	0	2	2	0	0	2	14.5	14.5	67	11.5	9.6	81	6	7.0	NA	NA	0	0	0	14	0	0	0	0	14	90	1	2
1	0	2	2	0	0	2	14.5	18.1	66	13.5	11.2	87	6	10.0	24	11.2	0	0	0	21	0	0	0	0	21	111	1	2
0	0	2	2	0	0	2	16.0	17.5	84	13.0	13.0	104	6	12.8	24	13.1	0	0	0	20	0	0	0	0	20	133	1	2
0	0	2	1	0	0	3	14.0	14.1	97	11.0	10.6	106	6	8.4	24	9.8	0	0	0	9	0	0	0	0	9	122	1	2
0	0	2	2	0	0	2	15.0	16.1	71	14.0	12.0	85	7	12.8	27	16.4	0	0	0	14	0	0	0	0	14	143	1	2
0	0	2	2	0	0	1	16.0	16.8	69	15.0	13.4	78	6	13.8	15	14.4	0	0	0	9	0	0	0	0	9	97	1	1
0	0	2	1	0	0	2	16.5	16.5	88	13.5	10.7	101	7	9.8	12	10.7	0	0	0	13	0	0	0	0	13	114	1	2
0	0	2	2	0	0	1	16.0	16.4	63	15.0	14.8	77	6	15.8	18	17.9	0	0	0	14	0	0	0	0	14	111	1	1
0	0	2	2	0	0	1	18.0	19.6	114	17.0	16.7	123	6	12.5	24	11.7	0	0	0	9	0	0	0	0	9	135	1	2
0	0	2	0	0	0	2	14.0	15.4	58	13.0	13.0	93	6	11.6	16	13.5	0	0	0	35	1	24	0	0	59	244	1	1
0	0	2	2	0	0	1	15.5	17.3	77	12.5	11.0	90	6	10.9	24	11.1	0	0	0	14	0	0	0	0	14	118	1	2
0	0	2	2	0	0	2	15.0	17.2	70	14.0	13.2	84	7	12.8	31	16.2	0	0	0	14	0	0	0	0	14	95	1	1
0	0	2	2	0	0	2	13.4	1.4	58	10.4	9.7	86	6	10.1	18	12.3	0	0	0	28	0	0	0	0	28	126	1	2
0	0	2	2	0	0	2	18.0	20.7	94	15.0	13.9	108	7	11.9	25	11.7	0	0	0	14	0	0	0	0	14	48	1	2
0	0	2	2	0	0	1	18.7	18.7	86	17.7	15.5	94	6	13.6	24	15.1	0	0	0	8	0	0	0	0	8	118	1	2
0	0	2	2	0	0	2	14.0	16.2	62	13.0	11.8	77	7	10.9	22	12.3	0	0	0	15	0	0	0	0	15	106	1	1
0	0	2	2	0	0	1	18.0	20.0	76	17.0	13.5	90	7	12.7	28	15.1	0	0	0	14	0	0	0	0	14	124	1	2
0	0	2	2	0	0	2	16.5	16.9	70	13.5	12.7	84	6	13.5	26	17.7	0	0	0	14	1	22	0	0	36	167	1	2
0	0	2	2	0	0	2	15.0	18.5	77	12.0	11.5	92	6	11.1	NA	NA	0	0	0	15	0	0	0	0	15	102	1	2
0	0	2	2	0	0	2	16.5	17.3	85	15.5	14.9	94	7	11.6	36	13.8	0	0	0	9	0	0	0	0	9	110	1	1
1	0	2	2	0	0	3	13.0	15.7	73	12.0	9.8	87	6	9.9	NA	NA	0	0	0	14	0	0	0	0	14	97	1	2
0	0	2	2	0	0	1	17.0	18.5	71	14.0	14.0	81	6	13.0	10	15.6	0	0	0	10	0	0	0	0	10	122	1	2
0	0	2	2	0	0	3	13.5	13.5	85	10.5	10.1	101	6	9.8	19	10.7	0	0	0	16	0	0	0	0	16	121	1	2
0	0	2	2	0	0	3	13.0	15.6	53	12.0	11.8	79	6	11.7	19	11.6	0	0	0	26	0	0	0	0	26	102	1	1
0	0	2	2	0	0	2	14.5	16.0	70	11.5	9.2	91	6	9.9	24	10.4	0	0	0	21	0	0	0	0	21	120	1	2
0	0	2	2	0	0	1	17.0	17.5	73	16.0	15.2	81	6	12.7	22	12.4	0	0	0	8	0	0	0	0	8	98	1	1
0	0	2	1	0	0	2	15.0	15.2	79	14.0	13.6	87	6	11.5	25	9.9	0	0	0	8	0	0	0	0	8	126	1	1
0	0	2	0	0	0	3	13.5	14.8	73	12.5	10.4	89	7	10.6	24	11.0	0	0	0	16	0	0	0	0	16	118	1	2
0	0	2	0	0	0	3	12.5	13.9	64	9.5	9.4	97	6	9.3	12	9.7	0	0	0	33	0	0	0	0	33	110	1	2
1	0	2	2	0	0	2	14.2	14.6	61	11.2	10.7	94	6	10.8	13	9.3	0	0	0	33	0	0	0	0	33	107	1	2
0	0	2	1	0	0	2	17.5	17.8	74	14.5	11.8	89	6	10.6	26	12.3	0	0	0	15	0	0	0	0	15	132	1	2
0	0	2	2	0	0	2	14.5	15.8	71	13.5	12.6	97	6	10.4	18	10.9	0	0	0	30	0	0	0	0	30	121	1	2
0	0	2	2	0	0	2	14.5	15.0	64	11.5	10.3	81	6	9.2	24	10.4	0	0	0	17	0	0	0	0	17	107	1	2
0	0	2	2	0	0	3	13.5	13.8	85	10.6	10.1	100	6	10.5	20	12.8	0	0	0	11	0	0	0	0	11	127	1	2
0	0	2	2	0	0	2	15.0	17.1	72	12.0	10.9	84	6	9.4	23	9.1	0	0	0	22	0	0	0	0	22	121	1	2
0	0	2	1	0	0	2	15.0	19.1	65	12.0	11.5	87	6	10.5	NA	NA	0	0	0	22	0	0	0	0	22	97	1	2
0	0	2	2	0	0	1	17.5	21.2	73	16.5	13.5	87	6	14.8	12	13.8	0	0	0	14	0	0	0	0	14	102	1	2
0	0	2	2	0	0	2	15.5	15.6	79	14.5	13.8	88	6	12.4	16	12.9	0	0	0	9	0	0	0	0	9	104	1	1
0	0	2	0	0	0	2	15.5	16.4	77	12.5	12.1	92	6	10.9	24	11.2	0	0	0	15	0	0	0	0	15	123	1	2
0	0	2	2	0	0	1	18.0	18.7	86	15.0	14.8	95	6	14.6	16	14.7	0	0	0	9	0	0	0	0	9	112	1	2
0	0	2	1	0	0	2	17.5	17.9	62	14.5	11.8	88	7	10.9	26	12.8	0	0	0	15	0	0	0	0	15	132	1	2
0	0	2	1	0	0	2	16.5	16.8	86	15.5	14.8	95	6	15.8	32	16.6	0	0	0	9	0	0	0	0	9	144	1	1
0	0	2	2	0	0	2	13.0	15.3	54	12.0	11.1	74	6	10.0	23	9.5	0	0	0	20	0	0	0	0	20	100	1	1
0	0	2	2	0	0	2	17.5	17.6	129	14.5	12.3	144	6	10.8	24	12.1	0	0	0	15	0	0	0	0	15	42	1	2
0	0	2	2	0	0	1	17.5	18.3	77	14.5	14.2	85	7	13.5	15	13.8	0	0	0	8	0	0	0	0	8	42	1	2
0	0	2	2	0	0	2	15.0	15.6	68	14.0	13.7	83	6	12.1	25	12.4	0	0	0	15	0	0	0	0	15	114	1	1
0	0	2	2	0	0	3	13.0	14.2	72	10.0	8.7	87	6	9.2	24	10.5	0	0	0	15	0	0	0	0	15	121	1	2
0	0	2	2	0	0	2	12.4	14.2	47	11.4	11.3	73	6	14.0	24	12.9	0	0	0	26	0	0	0	0	26	110	1	1
0	0	2	2	0	0	2	18.0	19.4	115	15.0	14.5	150	6	13.8	26	15.5	0	0	0	20	0	0	0	0	43	165	1	2
0	0	2	2	0	0	2	15.0	16.0	69	14.0	13.3	79	6	10.5	16	10.5	0	0	0	10	0	0	0	0	10	98	1	1
0	0	2	2	0	0	2	16.5	17.0	83	13.5	13.5	97	6	13.2	30	14.7	0	0	0	14	0	0	0	0	14	25	1	2
0	0	2	2	0	0	3	13.0	14.9	70	12.0	9.7	85	7	8.8	26	8.7	0	0	0	15	0	0	0	0	15	123	1	2
0	0	2	2	0	0	2	16.0	17.8	80	15.0	14.2	100	6	12.9	20	12.6	0	0	0	20	0	0	0	0	20	108	1	1
0	0	2	2	0	0	1	18.0	18.6	78	15.0	14.6	93	6	14.4	30	15.2	0	0	0	15	0	0	0	0	15	128	1	2
0	0	2	2	0	0	3	13.5	14.9	65	12.5	12.1	80	6	11.8	27	11.8	0	0	0	15	0	0	0	0	15	94	1	1
0	0	2	2	0	0	1	15.0	16.6	53	12.0	11.2	79	12	11.8	24	12.2	0	0	0	26	0	0	0	0	26	104	1	2
0	0	2	2	0	0	3	12.0	15.8	51	9.0	8.9	71	6	10.1	24	12.1	0	0	0	20	0	0	0	0	20	99	1	2
0	0	2	1	0	0	2	15.0	15.1	147	12.0	10.8	196	6	11.4	36	10.8	1	0	0	49	0	0	0	0	49	232	1	2
0	0	2	2	0	0	2	15.0	15.3	77	12.0	11.0	93	6	9.2	21	11.6	0	0	0	16	0	0	0	0	16	146	1	2
0	0	2	2	0	0	2	16.5	17.3	85	15.5	14.7	93	6	15.1	38	14.6	0	0	0	8	0	0	0	0	8	132	1	1
0	0	2	2	0	0	3	12.5	13.9	64	11.5	11.2	85	6	9.8	26	12.9	0	0	0	21	0	0	0	0	21	112	1	1
0	0	2	2	0	0	2	18.0	20.2	124	15.0	13.1	138	6	11.6	25	12.0	0	0	0	14	0	0	0	0	14	146	1	2
0	0	2	1	0	0	2	13.5	14.8	56	10.5	10.4	80	6	10.2	22	13.2	0	0	0	24	0	0	0	0	24	105	1	2
0	0	2	0	0	0	2	15.0	17.5	64	12.0	12.0	87	6	12.9	30	15.0	0	0	0	23	0	0	0	0	23	138	1	2
0	0	2	2	0	0	1	15.5	16.5	55	14.5	14.2	71	8	13.9	26	14.7	0	0	0	16	0	0	0	0	16	104	1	1
0	0	2	2	0	0	2	15.0	15.7	70	14.0	13.6	78	7	11.2	17	12.0	0	0	0	8	0	0	0	0	8	97	1	1
0	0	2	2	0	0	1	16.0	19.5	62	15.0	13.1	75	8	13.4	13	13.9	0	0	0	13	0	0	0	0	13	91	1	1
0	0	2	2	0	0	2	16.5	21.4	94	15.5	13.4	107	6	13.8	23	14.7	0	0	0	13	0	0	0	0	13	144	1	2