"A STUDY OF CORD BLOOD ALBUMIN AS A PREDICTOR OF SIGNIFICANT NEONATAL JAUNDICE"

By

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ABSTRACT

BACKGROUND:

Neonatal Hyperbilirubinemia (NH) is the commonest abnormal physical finding during the first week of life. Over two third of newborn babies develop clinical jaundice. Newborns appear jaundiced when serum bilirubin is greater than 7 mg/dl .Significant neonatal jaundice is often used to define any level of bilirubin requiring intervention in the form of phototherapy or exchange transfusion.Early discharge of healthy term newborns after normal vaginal delivery has become a common practice because of medical reasons like prevention of nosocomial infections, economical constraints and social reasons. This recommendation is not appropriate for our country due to limited follow-up facilities in the community. So, early prediction of jaundice will help in timely discharge and prevent hospitalization of babies and mothers.

OBJECTIVES:

1 .To study the levels of CBA in term normal neonates.

2. To study the correlation between levels of CBA and significant neonatal jaundice requiring Interventions like phototherapy or exchange transfusion.

MATERIALS AND METHODS:

The study was conducted in 130 newborns .Cord blood albumin was collected in 130 newborns. At birth, 2 ml of cord blood sample was collected from normal newborns and analysed for albumin within 4-6 hours. All enrolled babies were followed for 3 days and clinical assessment for jaundice was done according to Kramer dermal scale. Total Serum Bilirubin (TSB) estimation was done for

neonates with evidence of clinical jaundice and the hour- specific values were plotted on Bhutani's chart.

METHOD OF STATISTICAL ANALYSIS:

The study was conducted on total of 130 newborns after obtaining a written consent from the parents. Proforma was filled for each newborn. Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Chi-square was used as test of significance. The data were analyzed using appropriate statistical software.

RESULTS:

- 130 newborns included in the study.
- Total serum bilirubin was collected in 100 newborns with clinical evidence of jaundice.
- The study cohort was divided into three groups based on cord blood albumin(CBA)levels. Group 1 consisted of neonates with CBA levels of < 2.8 g/dl, group 2 consisted of neonates with CBA levels ranging from 2.8 – 3.3 g/dl and group 3 consisted of neonates with CBA levels of > 3.3 g/dl.
- The mean cord blood albumin of 130 neonates was 3.42 and SD of 0.462.
- Out of 100 neonates, 19 received phototherapy for significant hyperbilirubinemia.
- There was a significant negative correlation between cord blood albumin levels and total serum bilirubin levels i.e. with an increase in total serum bilirubin levels there was a decrease in cord blood albumin levels.

CONCLUSION:

A significant p value and Negative Predictive Value, in the present study suggests that CBA levels of<2.8 g/dL can help to identify those newborns that are likely to require further evaluation and intervention. Babies with CBA levels of > 3.3 g/dl can be considered to be safer, with much lesser chances of developing significant NH in term neonates.

KEYWORDS: Cord Blood Albumin, Significant Neonatal Hyperbilirubinemia

ABBREVATIONS

AAP	:	American Academy of Paediatrics
BBB	:	Blood Brain Barrier
BF	:	Free Bilirubin
CBA	:	Cord Blood Albumin
CSA	:	Cord Serum Albumin
CBB	:	Cord Blood Bilirubin
COP	:	Colloid Osmotic Pressure
dL	:	decilitre
ETCO	:	End Tidal Carbon Monoxide
FFA	:	Free Fatty Acids
G	:	Gram
HDN	:	Hemolytic disease of newborn
IAP	:	Indian Academy of Pediatrics
mg	:	milligram
NH	:	Neonatal Hyperbilirubinemia
PT	:	Phototherapy
T3	:	Triiodothyronine
TcB	:	Transcutaneous Bilirubin
TSB	:	Total serum bilirubin.
UCB	:	Unconjugated Bilirubin
UDPGT	:	Uridine diphospho glucoronyl Transferase

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Introduction

INTRODUCTION

Neonatal Hyperbilirubinemia (NH) is the commonest abnormal physical finding during the first week of life. Over two third of newborn babies develop clinical jaundice.[1]Newborns appear jaundiced when serum bilirubin is greater than 7 mg/dl .Significant neonatal jaundice is often used to define any level of bilirubin requiring intervention in the form of phototherapy or exchange transfusion.[2]

Jaundice in the newborn period is a medical emergency because unconjugated hyperbilirubinaemia may cause bilirubin encephalopathy and its sequelae1.Early discharge of healthy term newborns after normal vaginal delivery has become a common practice because of medical reasons like prevention of nosocomial infections, economical constraints and social reasons.[3]

American Academy of Pediatrics *recommends that newborns who are* discharged within 48 hours should have follow-up visits between 24 and 72 hours and again between 72 and 120 hours for development of any significant jaundice.[4]This recommendation is not appropriate for our country due to limited follow-up facilities in the community. So, early prediction of jaundice will help in timely discharge and prevent hospitalization of babies and mothers.

Once formed, bilirubin is bound reversibly to serum albumin and when bilirubin albumin complex reaches the liver, a proportion of bilirubin is transferred across cell membrane of hepatocytes for conjugation and excretion. Albumin can bind bilirubin at a molar ratio of up to 1 or a maximum of up to 8.2 mg of bilirubin per gram of albumin. If serum albumin is low and binding of bilirubin is compromised there is a higher risk of bilirubin encepahalopathy.[5]

There are reports of cord blood bilirubin as a predictor of significant neonatal jaundice.[3,6-7] But there is paucity of literature on cord blood albumin as a predictor of significant jaundice.[8]

The present study was conducted to find out the critical value of cord blood albumin (CBA) in predicting subsequent development of significant neonatal jaundice in term normal neonates.

Objectives of the Study

OBJECTIVES OF STUDY:

1. To study the levels of CBA in term normal neonates.
2. To study the correlation between levels of CBA and significant neonatal jaundice requiring Interventions like phototherapy or exchange transfusion.

Review of Literature

REVIEW OF LITERATURE

A. History Review

Jaundice is a well-known clinical entity in the Indian Medicine (Ayurveda). Since the Vedic Era (1500 BC – 800 BC) this disease has been described. Jaundice has been mentioned among diseases in Atharvaveda. Ayurveda is based on "*Tridosha theory of disease*" – Vata (wind), Pitta (gall) and Kapha (mucus). Charaka Samhita (200AD) described one of the first references to skin icterus. Jaundice (kamale) is a specific condition, which arises due to aggravation of bile.Greek Medicine was based on four humors – phlegm, yellow bile, blood and black bile. Hippocrates (460-370 BC) "*Father of Medicine*" – made frequent references to jaundice as a serious Disease.[9]

Word "*bile*" is derived from latinbilis ("*bile*").Word '*Bilirubin*' and 'Biliverdin'- means "*red bile*" and "*green bile*" in Latin. Icterus derived from Greek "iketros", meaning "yellow colored", a word applied to a yellow bird as well.[10]

In 1654, Panaroli reported apparent case of hemolytic disease of the newborn.[11]

Erythroblastosisfetalis may well have been described in 1609 in France. A report by a midwife named Bourgeois described ahydropic infant girl who died 15 min after birth with severe jaundice of the placenta and blood.[12]

Juncker in 1724, speaks of true jaundice "*the icteric tinge which may be observed in infants, immediately after birth*" The latter, he says, is of no account and disappears spontaneously after the meconium is passed.[13]

The scientific description and study of the phenomenon of neonatal jaundice seems to have started in the second half of the 18th century. In 1785 Jean Baptiste

Thimote´eBaumes was awarded a prize from the University of Paris for his work describing the clinical course in ten jaundiced infants. The work by Jacques Hervieux, which he defended for his doctor of Medicine degree in 1847 was, in many respects, a landmark. Having dismissed most of the theories and work of his predecessors, a number of his clinical observations are still thought to be accurate even today.[14]

Clinical and Epidemiological Observations on Neonatal Jaundice:

The cause of neonatal jaundice is not known, but one can state that jaundice in the neonate is a manifestation of a recently established function that for a limited time exceeds its physiological limits.

- Neonatal jaundice is a physiological condition.
- Neonatal jaundice is, by itself, never fatal.
- Neonatal jaundice appears during the first 2 to 4 days of life and lasts for 1 to 2 weeks.
- It never reappears in the following months.
- There is a cephalocaudal progression in the appearance of jaundice and the extremities are always the last to be affected. When jaundice disappears, the order is reversed.
- Neonatal jaundice is very common; approximately two thirds of all infants are affected. The prognosis in the absence of complicating conditions is benign.
- Jaundice is not seen in foundlings who are wet-nursed, or in infants nursed by a woman who gave birth a long time ago.
- The most frequent complicating conditions are sclerodema, diarrhea, and thrush.

- Treatment consists of combating the complicating conditions. Isolated neonatal jaundice does not need treatment.
- In neonatal jaundice, the yellow color is found throughout the tissues of the body, including the brain.[14]

Hervieux described brain jaundice in 31 of 44 cases of neonatal jaundice. In all of these cases, clinical jaundice had been at its peak at the time of death. He described the intensity of the brain jaundice as variable. Some brains were quite uniformly stained, while in other brains some regions were more heavily stained than others. A peculiarity was that he found the cerebrospinal fluid to be jaundiced in all cases.[14]

In 1785 Jean Baptiste Thimote´e Baumes was awarded a prize from the University of Paris for his work describing the clinical course in 10 jaundiced infants. The first case was Baumes' own daughter, Justine. He believed that delayed meconium passage was a primary cause of neonatal jaundice, and espoused breast milk, particularly colostrum, from the infant's own mother as the best remedy for this problem.[14]

Dewees writes in his 1825 American text book "Jaundice in the newborn infant is but too often fatal, with whatever property or energy we may attempt to relieve it".[15]

In 1847, Virchow suggested that the basic cause of jaundice was excessive destruction of red blood cells during the first week of life. This observation provided the first experimental evidence for a link between bilirubin and heme.[16]

The first description of bilirubin staining of the brain of kernicteric newborn children is credited to Johannes Orth. Orth's report was based on the presence of yellow and red pigments and crystals in the organs of newborn infants. He presented data on 37 newborns, all of whom had evidence of pigment in their kidneys, and most others had small amounts of yellow pigment in all other organs. In one severe case which died only 2 days after birth, the brain was yellow, but more intense staining was noted in specific brain regions including the basal ganglia, hippocampus, cerebellum, and walls of the third and fourth ventricles. Examination of the brain microscopically by Orth, revealed that neurons in the basal ganglia contained yellow pigment whereas the surrounding glial components were not stained. This patient's skin was severely jaundiced, yet pallor was detected, leading Orth to state that the jaundice might have had a hematological cause.[17]

In the first edition of Holt's "The diseases of Infancy and Childhood" published in 1897, the clinical description of physiologic jaundice is entirely compatible with modern concepts.[18]

Christian Schmorl in Dresden was the first to coin the term "Kernicterus", whichmeant 'Jaundice of the nuclei'. In the paper published by Schmorl, 120 jaundiced newborn infants who died were autopsied. Of these, most (114) were described as having brain icterus of a diffuse yellow nature with "fat bodies" observed in some cases. The others (6) had "core icterus" in which only particular parts of the brains were yellow. These were mostly in "central ganglia" – basal ganglia, and in the "elongated ganglia" – medulla oblongata.

Microscopic study of these brains showed that the yellow pigment was selectively present in neurons in the nuclei. Schmorl also noted an absence of staining in the

glial component of these nuclei. It was due to the more intense staining of nuclei in the brains of newborn infants dying from jaundice that Schmorl coined the term "*kernicterus*". Schmorl may have also been the first to note that the yellow pigment in brain disappeared over time unless the tissue was preserved in formalin.[19]

The first use of the term "Erythroblastosisfetalis" was by Rautmann in 1912 in reference to anhydropic still born.[20]

Beneke, in 1907, was the first to suggest that septicemia might play an important role in icterus gravis neonatorum. He theorized that the pigmentation of brain tissue was caused by a peculiar attraction of bile pigments to ganglion cells leading to their necrosis, damage to the ganglion cells by the bile salts which then became pigmented or ischemic or the traumatic insult that allowed the cells to become pigmented. In 1908, Esch was the first to link the clinical findings of acute kernicterus with the characteristic neuropathological findings of kernicterus at autopsy of an infant who died with severe familial neonatal jaundice.[21]

In 1918, Dutch Biochemists, Van Den Bergh and Muller, observed that the serum from patients with hemolytic jaundice can be differentiated from the serum of patients with obstructive jaundice on the basis of chemical reactions. They observed that hemolytic serum did not react promptly with diazotized sulphanilic acid except in presence of alcohol while the other serum reacted with the reagent without alcohol.[22]

In 1932, Diamond and Colleagues found that generalized edema of the fetus, icterus gravis and congenital anemia of the newborn were in fact all part of a single condition, which they termed Erythroblastosis fetalis.[23]

In 1939, Landsteiner and Weiner, Levine and Stetson demonstrated the serological basis of maternal fetal blood group incompatibility and the identification of the Rh system of antigens.[24]

In 1944, Halbrecht coined the term "Icterus praecox" for jaundice which developed within 24 hours of birth.[25] In 1946 the technique of alternate removal and administration of blood for each transfusion by umbilical vein catheterization was introduced.Diamond and Allen in 1948 showed the effectiveness of exchange transfusion as a protection from Kernicterus.[26]

In 1952, Crigler and Najjar in the publication describing congenital familial non hemolytic jaundice with kernicterus defined a new disease. They advanced the understanding of kernicterus as a process related more too elevated unconjugated bilirubin levels than to specific blood group incompatibilities or even hemolysis.[27]

In 1955, Odell and associates demonstrated that albumin binding was essential for bilirubin to remain in the plasma. Substances such as sulfasoxazole, competed for albumin binding sites and displaced bilirubin, allowing greater movement of bilirubin into the tissues and extra vascular space. These observations ..contributed to greater understanding of factors that increased the risk of kernicterus.[21]

Cremer and associates from Rochform hospital in Essex, in 1958 published their report about the successful use of phototherapy for the treatment of neonatal jaundice. The sunshine's fading effect on the yellow skin color of jaundiced newborns was discovered accidentally by an observant nurse in 1956, who noticed that babies' uncovered parts were less yellow when compared to covered parts of body on exposure to sunlight. This prompted the first use of 'Cradle illumination machine.[28, 29] In 1965, Broughton and associates demonstrated that the serum

bilirubin levels of jaundiced infants can be reduced at best by irradiation with blue light.[30]

Nakamura and Lee, in the 1970's achieved a major advancement in measuring unbound free bilirubin, with an enzymatic method employing peroxidase and glucose oxidase.[31]

FETAL BILIRUBIN METABOLISM

Most unconjugated bilirubin formed by the fetus is cleared by the placenta into the maternal circulation. Formation of conjugated bilirubin is limited in the fetus because of decreased fetal hepatic blood flow, decreased hepatic ligandin and decreasedUridine diphosphoglucuronyltransferase (UDPGT) activity. UDPGT is detectable at 18 – 20 weeks. UDPGT levels in full term and preterm neonates are usually less than 0.1% of adult values. Adult value of this enzyme activity is demonstrable only by 6–14 weeks of postnatal life.[32]

Bilirubin is detected in normal amniotic fluid as early as 12 weeks of gestation, but usually disappears by 36- 37 weeks2. During the neonatal period, metabolism of bilirubin is in transition from the fetal stage during which placenta is the principal route of elimination of the lipid- soluble, unconjugated bilirubin to the adult stage, during which the water-soluble conjugated form is excreted from hepatic cells into the biliary system and gastrointestinal tract.[33]

C. Neonatal Bilirubin metabolism

Jaundice is the commonest abnormal physical finding during first week of life.

Sources of bilirubin

Bilirubin is derived from the breakdown of heme containing protein in the reticulo endothelial system.The major heme containing protein is red blood cell hemoglobin. This is the source of 75% of all bilirubin production.The other 25% of bilirubin is called early labeled bilirubin. It is derived from hemoglobin released by ineffective erythropoiesis in the bone marrow, from other heme containing proteins in tissues (e.g.: myoglobin, cytochromes, catalase, peroxidase) and from free heme.[2]

First step in bilirubin production involves removal of iron and protein moiety followed by the oxidative process, which is catalyzed by the enzyme microsomal hemeoxygenase and equimolar amount of carbon monoxide and biliverdin are formed. This enzyme hemeoxygenase is called the rate limiting enzyme in bilirubin metabolism. Biliverdin is then reduced to bilirubin by biliverdin reductase.

In step 2, extra hepatic bilirubin is bound to serum albumin and is delivered to the liver. Fraction of the unbound bilirubin in plasma may increase in severe hemolytic disease or when protein binding drugs displace bilirubin from albumin.

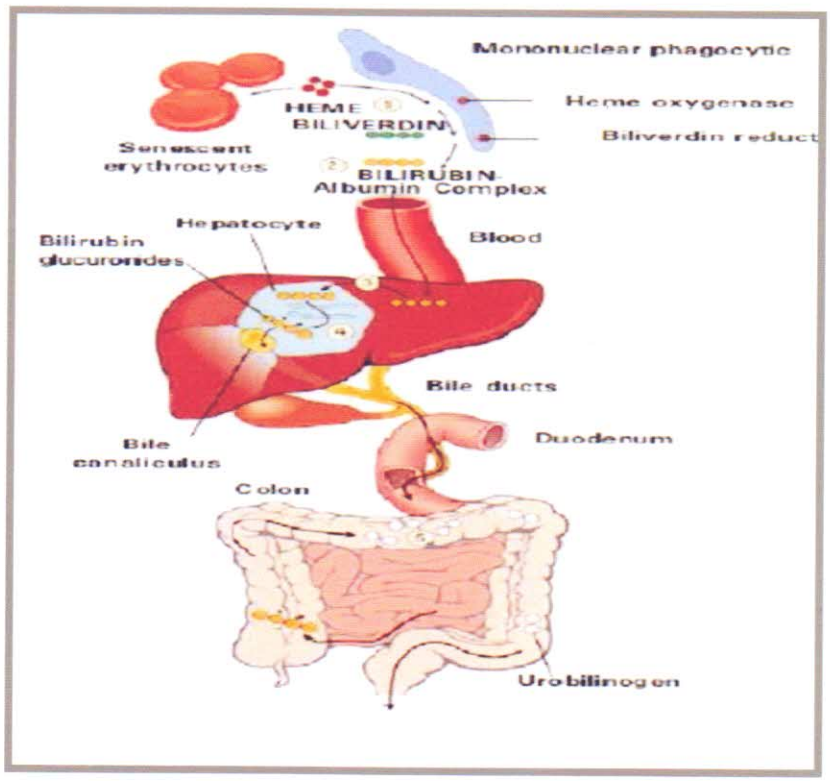
In step 3, the bilirubin albumin complex reaches the plasma membrane of hepatocytes; a proportion of bilirubin is transferred across the cell membrane of hepatocytes, where it binds to ligandin and probably other cytosolic-binding proteins.

In step 4, conjugation with one or two molecules of glucuronic acid by UDPGT enzyme in the endoplasmic reticulum occurs and this generates bilirubin monoglucuronides and diglucuronides, which are water soluble, and are readily excreted into the bile.In thenewborn, hepatic uptake, conjugation and excretion of

bilirubin is limited due to the transient deficiency of Y and Z acceptor proteins and UDPGT enzyme.

In step 5, conjugated bilirubin is degraded to colorless urobilinogen by the intestinal bacterial flora. Conjugated bilirubin glucuronides are deconjugated by the intestinal β- glucuronidase enzyme and are recirculated in the blood and delivered to the liver for reconjugation through enterohepaticcirculation. Due to paucity of bacterial flora in the gut and over activity of intestinal β-glucuronidase enzyme, the conjugated bilirubin entering the duodenum is rapidly deconjugatedand are recirculated in the blood and delivered to the liver for reconjugation through enterohepaticcirculation.[34]

Figure 1: Bilirubin Metabolism and Elimination[34]



ALBUMIN:

A Major Protein in Human Plasma:

The name *"albumin"* refers to the white precipitate formed during the boiling of acidic urine. Albumin is a relatively small protein with a molecular mass of 66.3kDa and has a globular conformation, permitting equilibration across the vascular and glomerular basement membranes. Because of this and its high plasma concentration, albumin is a significant component of most extravascular body fluids, including CSF, interstitial fluid, urine and amniotic fluid.Normally, albumin is the most abundant and major human plasma protein from mid gestation until death, accounting for approximately 60% of the total plasma protein. About 40% of albumin is present in the plasma and the other 60% is present in the extracellular space. The liver produces 12 grams of albumin per day, representing about 25% of total hepatic protein synthesis and half of its secreted proteins.[35, 36]

Biochemical Properties of Albumin:

Human albumin consists of one polypeptide chain of 585 amino acids and 17 intra chain disulfide bonds, aligned in a multiple loop structure. Albumin is one of only a few plasma proteins with no carbohydrate side chains. It is a very stable protein with a high net negative charge at physiological pH and very high solubility in water. There is one free –SH group at position 34 that reacts completely with thiol compounds such as cysteine at physiological pH.[35]

Synthesis and Metabolism of Albumin:

Albumin is initially synthesized as a pre protein. Its signal peptide is removed as it passes in to the cisternae of the rough endoplasmic reticulum, and a hexapeptide at the resulting amino terminal is subsequently cleaved off further along the secretory pathway.

Albumin is synthesized primarily by the hepatic parenchymal cells except in early fetal life, when it is synthesized by the yolk sac. The synthetic reserve of the liver is enormous. The synthetic rate is controlled primarily by colloidal osmotic pressure (COP) and secondarily by protein intake. Synthesis is decreased by inflammatory cytokines, and release (but not synthesis) is decreased by hypokalemia. Catabolism of albumin occurs primarily by pinocytosis by all tissues, with lysosomal catabolism of the protein and use of the resulting free amino acids for synthesis of cellular proteins. The rate of pinocytosis is proportional to the local tissue metabolic rate.

Small amounts (10 % to 20 % of the total catabolized) are also lost in to the gastrointestinal tract and the glomerular filtrate. Nearly all the proteins in the glomerular filtrate is reabsorbed and catabolized by the proximal renal tubular cells, resulting in very low concentration in normal excreted urine. The normal plasma half-life of albumin is 19 to 21 days.[35, 36]

Functions of Albumin:

The primary function of albumin is considered to be the maintenance of COP in both the vascular and extravascular spaces. This is supported by the fact that its synthesis is regulated primarily by COP. If the plasma level of albumin falls, the

concentration in extravascular spaces rapidly equilibrates with plasma to compensate for this. The presence of many charged surface groups and many specific binding sites, both ionic and hydrophobic, gives albumin the ability to bind a large number of compounds. These include free fatty acids (FFA), phospholipids, cholesterol, metallic ions, amino acids, drugs, hormones and bilirubin, among many others. Albumin is essential for the metabolism and detoxification of many of these compounds. Albumin also binds many hormones, such as tri-iodothyronine (T3), but with lower affinity than other proteins.

Albumin also functions as an amino acid source for peripheral tissue. After ingestion and absorption of amino acid- containing foods, albumin transports them in to tissues. The synthesis of albumin by the liver increases after meals, apparently in an attempt to prevent loss or catabolism of essential amino acids. Complexing by albumin is essential for the transport of some amino acids across membranes, in particular the transport of tryptophan across the blood brain barrier (BBB).

Other important functions of albumin include: Albumin is an important component of plasma antioxidant activity. Albumin acts as a buffer, especially in nonphysiological conditions.

The binding of albumin to endothelial membrane associated glycoproteins increases capillary permeability to small proteins that are important for metabolism in the extravascular space.

Albumin inhibits leukotriene and actin production, thus reducing the inflammatory response of platelets and neutrophils.[35, 37]

Albumin in the Fetus and Newborn:

Synthesis of albumin appears at approximately the 7th-8th week in the human fetus and increases in inverse proportion to that of α-fetoprotein, which is the dominant fetal protein. Albumin concentrations are low in a neonate (~2.5 g/dL), reaching adult levels (~3.5 g/dL) after several months.[33]

During intrauterine life, oxygen tension in the blood is low, thereby generating only low amounts of radicals, which could damage albumin. The low oxygen tension is compensated for by the increased oxygen affinity of fetal hemoglobin. After birth, fetal hemoglobin is rapidly broken down, thereby releasing large amounts of bilirubin that should be transported off by albumin.[38]

During the beginning of the third trimester, fatty acid concentrations are low and will be of no burden to albumin. The surge in albumin synthesis would be expected just before term birth, as a preparation against an elevated radical exposure and for a higher transport load consisting of hemoglobin breakdown products and fatty acids, the latter found in high amounts in postnatal nutrition. In human preterm neonates, whole-body protein metabolic rates are higher when compared with neonates born at term. And also the antenatal steroids received by the mothers could down regulate albumin production in preterm neonates.[38]

Serum albumin is frequently utilized as an index of the hepatocyte's ability to carry out synthetic function. Because the half-life of albumin is 19–21 days, serum albumin may not reflect acute changes in liver synthetic ability.[39] Regarding reference ranges for serum albumin concentrations in preterm and term infants, very little evidence is available. Lower normal limit for serum albumin in term babies is 2.8gm/dl and mean serum albumin level at term is 3.1gm/dl37. In general, postnatal

albumin concentrations follow the gestational trend and increase with gestational Age.[39, 40]

Albumin-Bilirubin Binding:

Most indirect bilirubin is transported in plasma bound to albumin. Around 8.5- 10 mg of bilirubin will bind tightly to 1 g of albumin. Two terms used to describe albumin binding are capacity and affinity. Each molecule of albumin can bind at least two molecules of bilirubin. Each molecule of albumin has a certain number of binding sites available. The binding capacity of albumin depends on the number of these available binding sites. The tightness by which bilirubin is bound to sites available for binding is the affinity. The binding sites of albumin may be primary (tight or high affinity) or secondary (weak affinity). Each albumin molecule has one primary binding site and one or more secondary sites. If the primary site is saturated, there is a rapid increase in loosely bound or free bilirubin. Albumin binding capacity is lower in the neonate due to lower albumin levels and decreased albumin binding capacities.Competing substances easily displace bilirubin bound to secondary sites. Drugs such as sulfonamides, salicylate, chlorothiazide, ceftriaxone, rifampicin, certain x-ray contrast substances and sodium benzoate may displace bilirubin from albumin. Combination of drugs may exacerbate these effects.[37]

Albumin binding of bilirubin can be altered by pathologic events. Plasma free fatty acids compete with bilirubin for albumin binding sites. Hypothermia increases metabolism and catabolism of fatty acids, which may displace bilirubin from albumin. The amount of unbound indirect bilirubin may also be increased if there is more bilirubin than available albumin because of excess production of

bilirubin or decreased albumin. Serum pH per se may not alter binding but may influence deposition of unbound bilirubin in the central nervous system.[36, 37, 41]

In plasma, bilirubin binds to albumin and, as with drugs or hormones that bind to vascular proteins, it exits the vascular space and enters the tissues at a rate that is proportional to the non-albumin bound or free bilirubin concentration. Bilirubin combines with albumin in a second order process which is fast and has to be observed at low concentrations of the reactants and at low temperature. The primary binding is followed by a train of relaxations, usually analyzed in terms of consecutive, unidirectional, monomolecular reactions.[42]

Bilirubin-albumin binding has been studied using a variety of techniques, including fluorescent quenching, bilirubin fluorescence, circular dichroism, Sephadex gel filtration, optical rotary dispersion, dialysis, ultrafiltration, spectrophotometry, and enzymatic oxidation of bilirubin (peroxidase method)43. Bilirubin binds to albumin in an equimolar ratio. Free bilirubin is anticipated when the molar bilirubin- to- albumin

(B: A) ratio is > 0.844. Although 99.9% of unconjugated bilirubin in the circulation is bound to albumin, a relatively small fraction (only less than 0.1%) remains unbound (free bilirubin) and it can go into the brain across an intact BBB.[45]

According to the experimental studies, the concentration of free bilirubin is believed to dictate the biologic effects of bilirubin in jaundiced newborns, including its neuro-toxicity. The unbound or free bilirubin can easily cross the BBB. The risk of bilirubin toxicity will therefore be proportional to the plasma **"free"** bilirubin[8].

Causes of Unconjugated Hyperbilirubinemia:

A. Excessive production of bilirubin (hemolytic disease of newborn)

1. Red blood cell enzyme abnormalities:
    a. Pyruvate kinase deficiency
    b. Glucose 6-phosphate dehydrogenase deficiency
2. Blood Group Incompatibility (heterospecificity):
    a) ABO incompatibility
    b) Rh Isoimmunisation
    c) Minor blood group incompatibility

3.Red blood cell membrane defects:

    a) Hereditary Spherocytosis
    b) Elliptocytosis
    c) Poikilocytosis

4. Sepsis
5. Extra vascular blood
6. Polycythemia

B. Impaired conjugation or excretion:

1. Disorders of bilirubin metabolism:
    a) Gilbert disease
    b) Criggler-Najjar syndrome type- I
    c) Criggler-Najjar syndrome type- II (Arias Disease)
    d) Lucey- Driscoll syndrome
    e) Dubin Johnson syndrome
    f) Rotor syndrome

2. Hormonal Deficiency:
    a) Hypopituitarism
    b) Hypothyroidism
3. Enhanced enterohepatic circulation:
    a) Ileus
    b) Intestinal obstruction
    c) Pyloric Stenosis
    d) Meconium plugging
    e) Cystic fibrosis
4. Decreased breast feeding.[44]

Causes of Jaundice on the basis of Age of Onset:

Within 24 hours of birth:

- Rh and ABO incompatibility.
- Glucose 6-phosphate dehydrogenase deficiency.
- Pyruvate kinase deficiency.
- Infections: Bacterial, TORCH (T-toxoplasmosis, O-others, R-rubella, C-Cytomegalovirus, H -herpes simplex virus)
- Criggler-Najjar syndrome type- I.
- Drugs to mother –Vitamin K, salicylate, etc.

24-72 hours after birth:

- Physiological Jaundice • Rh and ABO incompatibility
- Polycythemia.

- Extra vascular bleed.
- Breast feeding Jaundice.
- Neonatal sepsis.
- Enhanced entero-hepatic circulation.

After 72 hours of birth:

- Neonatal sepsis.
- Enhanced entero-hepatic circulation.
- Extra vascular bleed
- Neonatal hepatitis.
- Hypothyroidism.
- Hypopituitarism.
- Galactosemia.
- Criggler-Najjar syndrome type – II.
- Gilbert disease.[46]

High Risk Factors of Jaundice:

- Prematurity.
- Low birth weight.
- Blood group incompatibility.
- Perinatal asphyxia.
- Infant of diabetic mother.
- Intrapartum use of oxytocin.
- Problem in breastfeeding.
- History of jaundice in previous siblings.
- Cephal hematoma or significant bruising. [1,2].

Clinical Assessment of Jaundice:

Although most adults are jaundiced when total serum bilirubin (TSB) exceeds 2.0 mg/dl, neonates characteristically do not appear jaundiced until the TSB exceeds 5.0 to 7.0 mg/dl. Jaundice in neonates becomes evident first on the face and progresses in a cephalo-caudal fashion with increasing hyperbilirubinemia.[44]

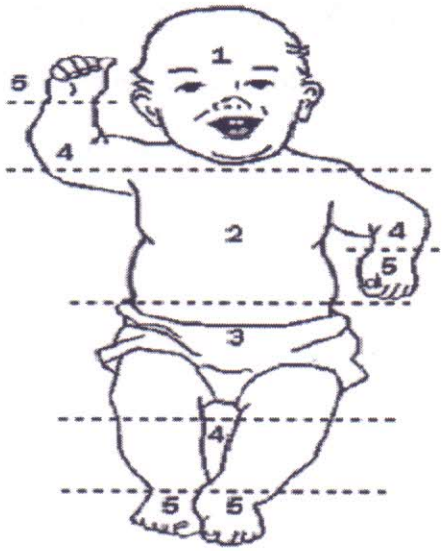
Clinicians should ensure that all infants are routinely monitored for the development of jaundice, and nurseries should have established protocols for the assessment of jaundice4.Jaundice should be assessed whenever the infant's vital signs are measured but no less than every 8 to 12 hours. In newborn infants, jaundice can be detected by blanching the skin with digital pressure, revealing the underlying color of the skin and subcutaneous tissue. The assessment of jaundice must be performed in a well-lit room or, preferably, in day light or at a window.[4] Jaundice is usually seen first in the face and progresses caudally to the trunk and extremities, but visual estimation of bilirubin levels from the degree of jaundice can lead to errors.[4]

Dermal staining of bilirubin may be used as a clinical guide to assess the level of jaundice which was described by Kramer.[47]A rough guide for level of dermal staining with level of bilirubin is depicted in Table 1. Kramer divided the infant into 5 zones.[47] - Figure 1.

Table 1: Kramer's dermal staining for clinical assessment of jaundice

Area of body	Level of bilirubin
Face	4-6 mg/ dl
Chest, upper abdomen	8-10 mg/dl
Lower abdomen, thighs	12-14 mg/dl
Arms, lower legs	15-18 mg/dl
Palms, soles	15-20 mg/dl

Figure 2: Kramer Dermal Zones



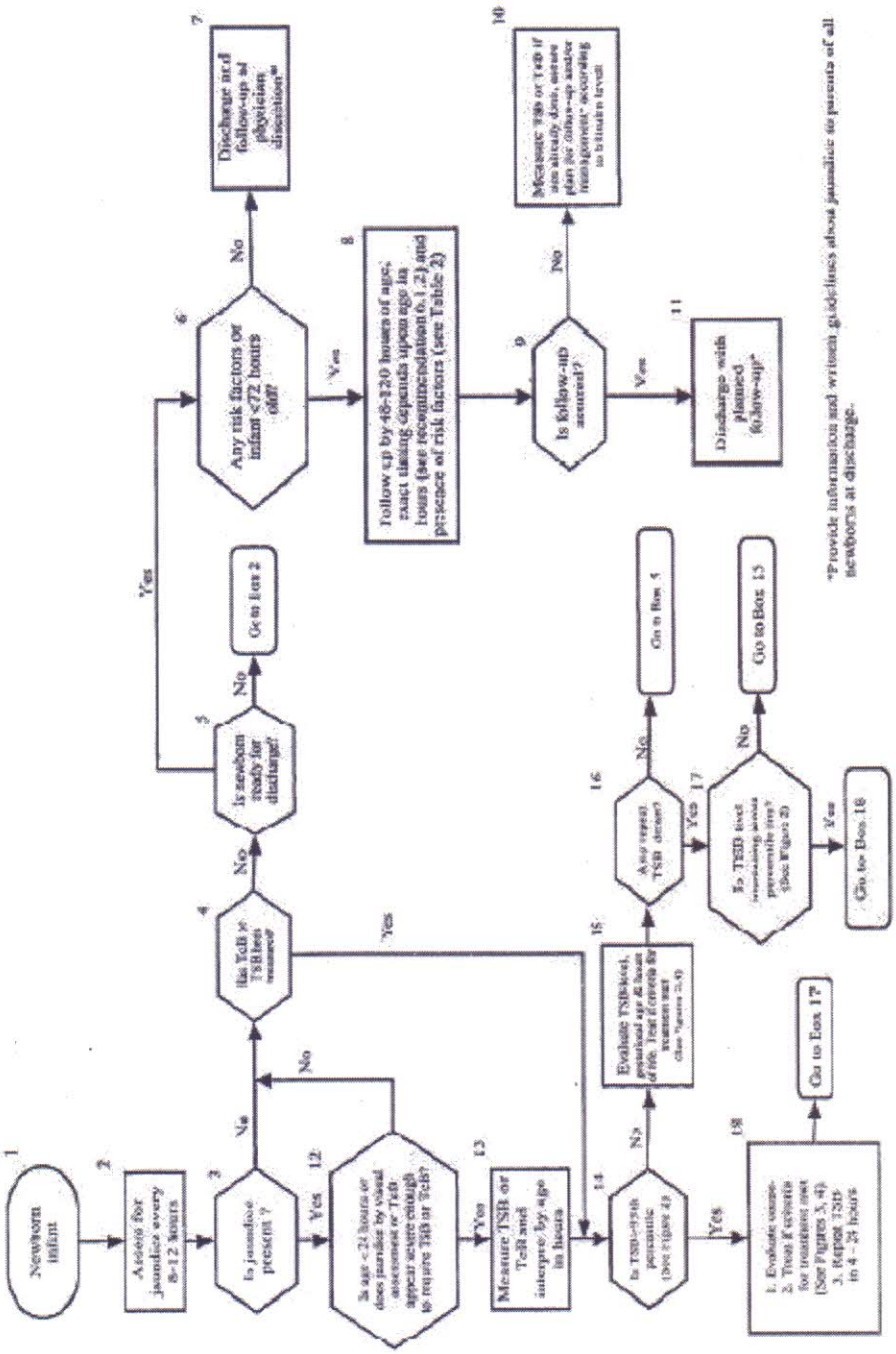
But physical examination alone is not a suitable measure for serum bilirubin estimation[1].

Approach to a Jaundiced Newborn:

- To identify "*high risk*" newborns at delivery likely to develop jaundice.
- Emphasize need for early, exclusive breast feeds and ensure adequacy of breast feeding.

- Assess clinical condition (well or ill).
- Evaluate jaundice with post-natal age in hours.
- Ascertain birth weight & gestation.
- Perform systematic evaluation – history and physical examination.
- Decide whether jaundice is physiological or pathological.
- If physiological and baby well, only observation is required.
- If deeply jaundiced, look for signs of bilirubin encephalopathy (lethargy, poor feeding, shrill cry, asymmetric Moro reflex, hypertonia, opisthotonus or convulsions)
- If bilirubin is in pathological range as per Kramer dermal zones, perform lab tests.
- Initiate appropriate measures to reduce elevated bilirubin.
- Ensure appropriate follow up for jaundice.
- Counsel parents.[46]

Figure 3: Algorithm for the Management of Jaundice in Newborns[32]



Complications of Neonatal Jaundice:

Bilirubin encephalopathy refers to the clinical manifestations of the effects of bilirubin on the central nervous system (CNS),whereas kernicterus refers to the neuropathologic changes that are characterized by pigment deposition in specific areas of the CNS such as basal ganglia, pons and cerebellum.[10]

Bilirubin encephalopathy is a multifactorial process that requires a critical level of free bilirubin, access to the brain across the BBB and presence of susceptible nerve cells. The severity and duration of hyperbilirubinemia, the maturity of the structures involved, the binding capacity of albumin, the physiologic environment, the cell membrane composition and metabolic state probably are all critical to the development of neurodysfunction.[33]

Entry of bilirubin into the brain:

The mechanism by which uncojugated bilirubin enters the brain and damages it is unclear. Several hypotheses regarding entrance of bilirubin into the brain have been proposed.One hypothesis is the lipophilic nature of free bilirubin, in equilibrium with bound bilirubin, has access to tissues. Thus, any increase in the amount of free bilirubin or reduction in the amount or binding capacity of albumin could increase the level of unbound bilirubin within the brain tissue, saturating membranes and causing precipitation of bilirubin acid within the nerve cell membrane. Second hypothesis is based on close examination of the chemical nature of bilirubin in solution and seeks to explain the increased risk in acidotic infants. In this theory, the rate of tissue uptake of bilirubin depends on both the concentration of albumin-bound bilirubin and the pH, with low pH enhancing precipitation and

tissue uptake.Third theory suggests that bound bilirubin enters the brain mainly through a damaged BBB. Recent studies suggest that unconjugated bilirubin is a substrate for P-glycoprotein (P-gp) and that the BBB P-gp may play a role in limiting the passage of bilirubin into the CNS. P-gp is an ATP – dependent integral plasma membrane transport protein that translocates a wide range of substrates across biologic membranes.[10]

Factors that increase susceptibility to Neurotoxicity associated with Hyperbilirubinemia:

Asphyxia, Hyperthermia, Septicemia, Hypoalbuminemia, Acidosis, Calorie deprivation, Prolonged Hyperbilirubinemia, Low birth weight, Young gestational age, Excessive hemolysis.[10]

Bilirubin toxicity at cellular level:

- Four possible mechanisms have been proposed:
- Interruption of normal neurotransmission
- Mitochondrial dysfunction
- Cellular and intracellular membrane impairment
- Interference with enzyme activity.[10]

Clinical features of Acute Bilirubin Encephalopathy:

Early: Lethargy, poor feeding, high pitched cry, hypotonia.

Intermediate: Irritability, opisthotonus, seizures, apnea, oculogyric crisis, hypertonia, retrocollis.

All infants who survive this phase develop chronic bilirubin encephalopathy (clinical diagnosis of kernicterus).

Advanced phase: Pronounced opisthotonus, shrill cry, apnea, seizures, coma and death.[2]

Chronic bilirubin encephalopathy (kernicterus):

It is marked by athetosis, athetoid cerebral palsy,partial or complete high frequency sensorineural hearing loss, paralysis of upward gaze, dental dysplasia and intellectual deficits.[2]

Predicting Encephalopathy and Reversibility of damage:

Brainstem Evoked Auditory Response (BEAR): Because auditory pathway of the newborn is particularly vulnerable to insult from the bilirubin, BEAR testing has been suggested as a tool that could identify or predict early effects of hyperbilirubinemia. Studies have shown increased bilirubin concentrations with changes in the amplitude and latency of these responses. BEAR is accurate and noninvasive and assesses the functional status of the auditory nerve in the brainstem pathway.[10] In a study of 50 full term infants with moderate hyperbilirubinemia, the latency of BEAR waves lV and V was longer than in those infants with lower TSB levels (Shapiro and Nakamura, 2001).[41].BEAR testing could be used to screen hyperbilirubinemic full-term and premature infants for sensorineural hearing loss and could be incorporated into the assessment of need for exchange transfusions.[49.50]

Infant Cry Analysis - It has been shown that with moderately elevated TSB levels, there is interference with neural conduction, as demonstrated by the BEAR, and changes in neural function in adjoining pathways, with resultant effects on the vocal cords (increased tension on phonation).[10]

Nuclear Magnetic Resonance (NMR) Techniques – Both imaging and spectroscopy, have been proposed as a rapid, noninvasive measure of impending or actual brain cell injury in the face of hyperbilirubinemia.[10]

Laboratory Evaluation of Jaundiced Newborn:

These tests are individualized to a newborn to know the cause for NH. Even after detailed investigations, the cause of NH remains uncertain in about one-third of cases.

Investigation list is as follows:

I. **Maternal:** Blood grouping and Indirect Coombs Test (ICT) to test for iso-immune hemolytic disease, serology to rule out syphilis.

II. Infant:

- Total serum bilirubin (TSB) and or transcutaneous bilirubin.
- Blood grouping, Rh typing and Direct Coomb test (DCT) to test for iso-immune hemolytic disease.
- Hemoglobin and Hematocrit: Anemia suggests hemolytic disease and large entrapped hemorrhage.
- Polycythemia causes jaundice.
- Reticulocyte count is elevated in hemolytic anemia.

- Red cell morphology – by peripheral blood smear
- Red cell fragmentation seen in disseminated intravascular coagulation (DIC)
- Spherocytes suggests ABO incompatibility or Hereditery Spherocytosis.
- Platelet count is decreased in infections.
- White blood cell count less than 5,000 cells/cumm or Band to Total Neutrophil ratio (BNR) > 0.2 suggest infection.
- Urine analysis for reducing substance to diagnose galactosemia.
- Screening of G6 PD deficiency.
- Serum protein and albumin to estimate albumin binding capacity and reserve albumin binding site.
- pH
- Protein binding {2,4 hydroxy benzene azobenzoic acid (HABA), salicylates} These tests help to measure the quantity of binding of bilirubin in the serum of jaundice infants.[12]

Criterion for physiological jaundice:

- Type of bilirubin – Indirect bilirubin,
- Direct bilirubin never more than 2mg/dl or less than 15% of total bilirubin,
- Appearance - after 36 hours of age,
- Rate of rise of bilirubin – less than 5mg / dl/day,
- Severity of jaundice – Usually does not exceed 15 mg/dl,
- Natural course – Peak TSB levels seen between 3rd – 5th days of life in term neonates and 3rd – 7th day in preterm and disappears by 2 weeks.
- Clinical condition – Healthy newborn.[51]

Pathological jaundice is suspected in the newborn with:

- Clinical jaundice in the first 24 hours of life.
- TSB > 15 mg/dl
- Rate of TSB increase > 0.2 mg/dl/hr or 5mg/dl/day.
- Direct serum bilirubin > 2mg/dl or > 15% of total bilirubin
- Clinical jaundice ersisting for > 2 weeks.[51]

Treatment of Neonatal Hyperbilirubinemia:

The aim of the therapy is to ensure that serum bilirubin is kept at a safe level and brain damage is prevented. NH is a medical emergency and delay in its management can lead to irreversible brain damage and death.Reduction of serum bilirubin levels and prevention of neurotoxicity can be achieved by phototherapy, exchange transfusion and pharmacotherapy. Exchange blood transfusion remains the single most effective and reliable method to lower the bilirubin when it approaches critical levels.[1]

Principles of treatment in jaundiced neonates according to 2011, Indian Academy of Pediatrics (IAP) and National Neonatology Forum (NNF) guidelines are:

- Treatment decisions are based on total serum bilirubin.
- Gestation is more important than birth weight of the baby. A higher cut off can be used for a small for date baby.
- Post-natal age in hours should be considered when deciding treatment .
- Sick baby refers to presence of asphyxia, hypothermia, sepsis, acidosis, hypoxia, hypercapnia and evidence of haemolysis.[46].

- Guidelines for Phototherapy and Exchange transfusion in hospitalized infants of 35 or more weeks' gestation are depicted in Fig. 4 and Fig. 5 respectively.[4]

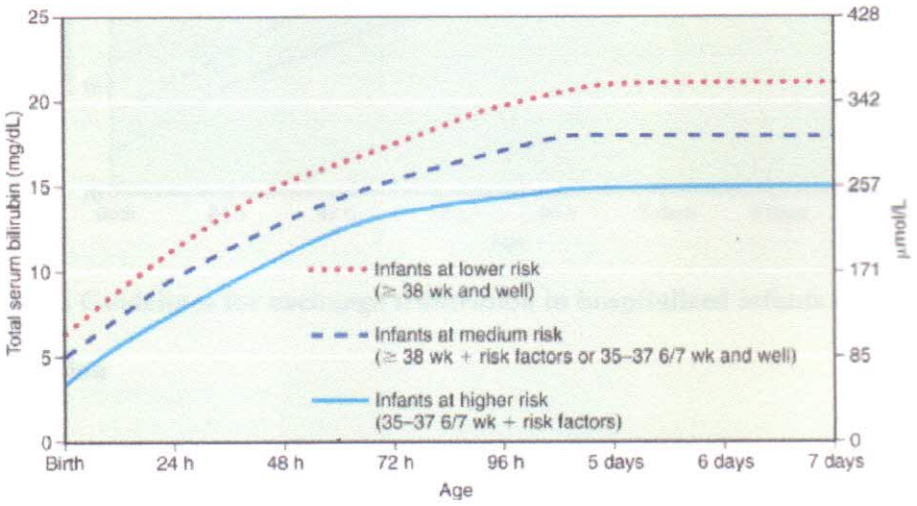


Fig. 4: Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation

Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.

Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured). For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 wk.

It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dl (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.[33]

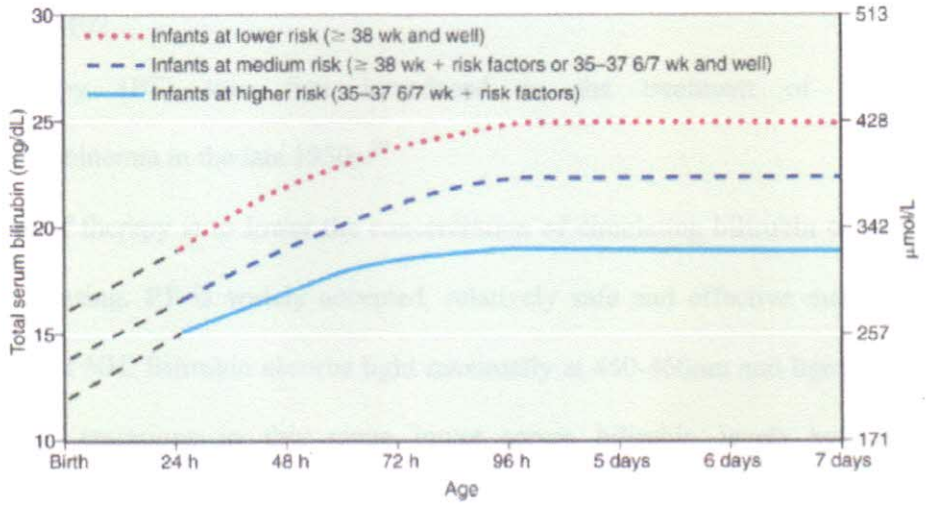


Fig. 5: Guidelines for exchange transfusion in hospitalized infants of 35 or more weeks' gestation

- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥ 5 mg/dl (85 μmol/L) above these lines.
- Risk factors – isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis,acidosis.
- Measure serum albumin and calculate B/A ratio.
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.[33]

Phototherapy:

Phototherapy (PT) was first introduced in the treatment of neonatal hyperbilirubinemia in the late 1950s.[29]

The goal of therapy is to lower the concentration of circulating bilirubin or keep it from increasing. PT is widely accepted, relatively safe and effective method for treatment of NH. Bilirubin absorbs light maximally at 450-460nm and light sources with peak emissions in this range lower serum bilirubin levels by several mechanisms.

Photo oxidation:

Photo oxidation of bilirubin into water soluble colorless form of bilirubin is very slow and ineffective.[2]

Configurational photoisomerization:

Here E-isomers (4Z 15E, 4E 15E, 4E 15Z) which are more polar water soluble diazo negative compounds are produced. E isomers are nontoxic and after 8-12 hours of phototherapy they constitute about 25% of total serum bilirubin.[2]

Structural isomerization:

It is the production of stable water soluble structural isomers of bilirubin like lumirubin. These photo catabolites are readily excreted in bile, feces and to a lesser extent in urine. The conversion of bilirubin to lumirubin is irreversible and it cannot be reabsorbed. It is most important pathway for the lowering of serum bilirubin levels and strongly related to the dose of phototherapy used in the range of 6 to 12 $\mu w/cm^2/nm^2$.

Procedure of phototherapy

The narrow spectral blue light is most effective for phototherapy but it interferes with proper observation of the infant. White day light fluorescent lamps are quite effective and commonly used in our country. Blue and white tubes phototherapy units are also available.

Nude infant is exposed to a portable or fixed light source kept at 45cm from the skin. Distance between the baby and phototherapy unit can be reduced to 10-15 cms to provide effective and more intensive phototherapy.During phototherapy eyes must be shielded to prevent retinal damage and a diaper should be kept on to cover the genitals. For effective phototherapy, the minimal spectral irradiance or 'flux' of 4 to 6 μw/cm2/nm is available and maintained at the level of the infant's skin.[51]

Care of a Newborn receiving Phototherapy:

- The eyes should be covered during phototherapy.
- Breast feeding on demand is continued. More frequent breast feeds or 10-20% extra intravenous fluids are provided.
- Adequacy of hydration is checked by urine colour and frequency, skin turgor, mucous membrane and weight.
- Assess and record urine and stool pattern.
- Frequent change of posture is necessary.
- Temperature is monitored every 3-4 hrs, Avoid hypo or hyperthermia.
- Daily baby is weighed.
- TSB is measured every 12hrs or 4-6 hourly if severely jaundiced.
- Monitor for adverse effects of phototherapy: dehydration, loose stools, hyperthermia/ Hypothermia, erythematous rash and bronze baby syndrome.[51]

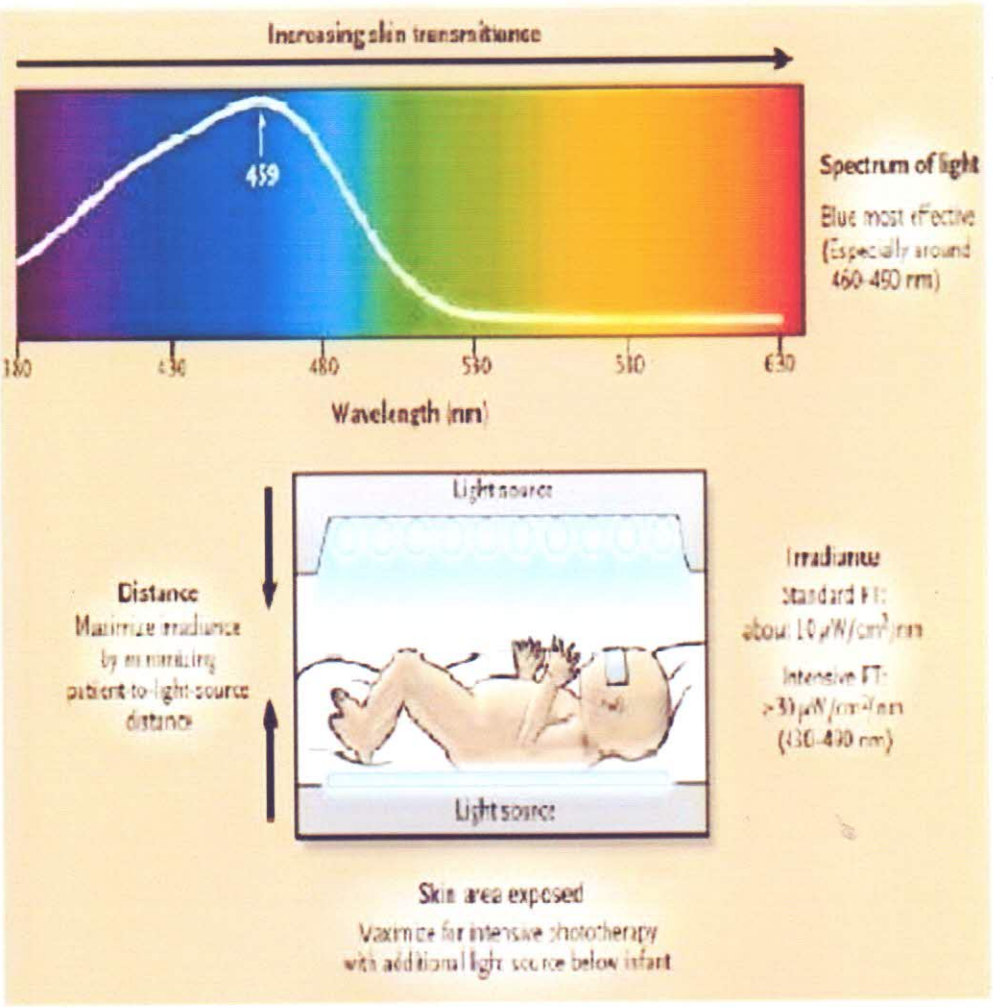


Fig 6: Important factors in efficacy of phototherapy.[52]

Side effects of PT:

- Passage of loose green stools because of transient lactose intolerance and irritant effect of photo-catabolites causes increased colonic secretory losses.
- Hyperthermia
- Irritability
- Dehydration
- Flea bite rash on the trunk or extremities

- Risk of opening up to patent ductus arteriosus in preterm babies.
-
- Hypocalcemia due to secretion of melatonin from pineal gland.
- Bronze baby syndrome – Infants with parenchymal liver disease with biliary obstruction, due to excessive accumulation of bilifucin (Polymerized form of lumirubin) imparting brownish discoloration to the skin.
- Theoretically increased risk of skin malignancy later in life.
- Exposure to light may disturb the circadian rhythm of the sex hormones thus having potential implications on onset of puberty and disturbances in future sex behaviuor.[2, 33]

Exchange Transfusion:

Exchange transfusion is the most rapid method for lowering serum bilirubin concentrations. This treatment is rarely needed when intensive phototherapy is effective. The procedure removes partially haemolysed and antibody-coated erythrocytes and replaces them with uncoated donor red blood cells that lack the sensitizing antigen53. Need for exchange transfusion is based on level of unconjugated serum bilirubin, gestational maturity, postnatal age, existence of or otherwise perinatal distress factors and the cause of jaundice.[2]

Choice of blood

- Group Rh negative blood in emergency situations.
- Fresh (<7 days old) type O cells with AB plasma to ensure that no anti-A and anti-B antibodies are present.

- In non-immune hyperbilirubinemia, blood is typed and cross matched against the plasma and red cells of the infant. Exchange transfusion usually involve double the volume of the infant's blood and is known as a two volume exchange (160 ml/kg). This replaces 87% of infant's blood volume with new blood.[2]

Technique

a. Exchange transfusion is done by push pull technique through the umbilical vein inserted only as far as required to permit the free blood exchange.

b. Iso-volumetric exchange transfusion –Simultaneously pulling blood out of the umbilical artery and pushing new blood in the umbilical vein may be better tolerated in small sick or hydropic infants.

c. Exchange transfusion can be accomplished through central venous line placed through the anticubital fossa or into the femoral vein through the saphenous vein.

In push pull method, blood is removed in aliquots that are tolerated by the infant. Usually 5ml for neonates weighing <1500gms, 10ml for neonatesweighing 15002500gms, 15ml for 2500- 3500gms and 20ml for >3500gms.The recommended time for the exchange transfusion is 1 hour.[2]

Complications of Exchange transfusion:

- Hypocalcaemia and Hypomagnesemia: The citrated blood used binds ionic calcium and magnesium.

- Hypoglycemia: High glucose content of (CPD) Citrate Phosphate Dextrose (300mg/dl) stimulates insulin secretion and causes hypoglycemia 1-2 hours after exchange.
- Acid base balance: Citrate in CPD blood is metabolized to alkali resulting in late metabolic alkalosis.
- Hyperkalemia: Potassium levels may be greatly elevated in stored packed RBC's.
- Cardiovascular: Perforation of vessels, embolisation, vasospasm, thrombosis, infarction, arrhythmia, volume overload, arrest.
- Bleeding: Thrombocytopenia, deficient clotting factors.
- Infections: Bacteremia, hepatitis, CMV, HIV, West Nile virus and malaria.
- Hemolysis: Hemoglobinemia, hemoglobinuria and hyperkalemia caused by overheating of the blood have been reported.
- Graft-versus-host disease: This is prevented by using irradiated blood.
- Miscellaneous: Hypothermia, hyperthermia and possibly necrotizing enterocolitis.[2]

Pharmacological management:

Phenobarbitone:

Barbiturates have been shown to induce the maturation of microsomal enzymes, ligandin (Y-acceptor protein) and UDPG-T, thus improving the uptake, conjugation and excretion of bilirubin by the liver.

Phenobarbitone in a single dose of 10 mg/kg by intra muscular route or 5mg/kg/day in two divided doses orally for 3 days is indicated in cases of cord serum bilirubin level of > 2.5 mg/dl, early onset of jaundice due to any cause,

difficult or Instrumental delivery, oxytocin induced delivery with bruising and cephalohematoma.[1]

Clofibrate:

It is a potent enhancer of glucurony ltransferase. It is more efficacious but it is slow in its action and takes several days to show the beneficial effect.[1]

Agar:

It is a sea weed extensively used in processing of food. In dose of 250 mg 6th hourly orally, it binds conjugated bilirubin in the gut and blocks the enterohepatic circulation. Its use is unpredictable and variable.[1]

Cholestyramine:

In dose of 1.5 mg/kg/day in 4 divided doses, by mixing in milk feeds has been shown to enhance fecal exertion of bilirubin and thus blocking enterohepatic circulation. Infant should be watched for constipation, intestinal obstruction and hyperchloremic acidosis.[1]

Orotic acid:

It is a metabolic precursor of uridine diphosphate glucuronic acid and thus promotes the conjugation of bilirubin. Its ability is limited and cost is prohibitive.[1]

Tin-mesoporphyrin (SnMP):

Metalloporphyrins (Tin and Zinc) are structural analogs of heme and they inhibit heme-oxygenase. It diminishes the production of bile pigments by competitive inhibition. Heme-oxygenase is a rate limiting enzyme in heme metabolism. Tin mesoporphyrin (6 μmol/kg/single dose IM) has been shown to significantly reduce bilirubin production. It is associated with high incidence of photosensitive skin reactions and potential risk of hepatic and renal toxicity.[2]

Albumin infusion:

When administered (1 gm/kg), half an hour before exchange transfusion it facilitates more effective removal of bilirubin and also improves the bilirubin binding capacity of the baby. Use is avoided in babies with congestive cardiac failure because of risk of overloading the circulation. Rarely used due to exorbitant cost and risk of transmission of viral infections.[2]

Inhibiting hemolysis:

Intravenous immunoglobulin (500-1000 mg/kg) is used to reduce bilirubin levels in infants with iso-immune hemolytic disease. The immunoglobulins act by occupying the Fc receptors of reticulo-endothelial cells, thereby preventing them from taking up and lysing antibody coated red blood cells.[2]

Preventive and suggestive measures:

- Drugs known to aggravate jaundice or block the bilirubin binding sites on albumin should be withheld.
- Vitamin K in large doses should be avoided.

- Perinatal distress factors such as hypoxia, acidosis, hypothermia, and hypoglycemia should be prevented or adequately managed.
- Uses of phenolic detergents are avoided in nursery as they may enhance the jaundice in the babies.[2]

Adequate feeding:

Early feeding augments colonization of the gut and reduces the enterohepatic circulation. Effective evacuation of meconium is associated with elimination of conjugated bilirubin and stercobilin.[2]

Prediction of Neonatal Hyperbilirubinemia:

Jaundice appears in 60% of term newborns and 80% of preterm infants by the first week of life. Up to 4% of term newborns who are readmitted to the hospital during their first week of life, approximately 85% are readmitted for jaundice.Of all conditions found to account for readmission to the hospital within first 14 days, hyperbilirubinemia and others like dehydration / failure to thrive are susceptible to some kind of intervention that might prevent readmission.In order to reduce hospital cost, most healthy term babies delivered by vaginal route without any complication are discharged from hospital within 48 hours or less. These babies may develop neonatal jaundice which may be missed or delay in recognition if the follow up is not done.

Concern of pediatrician regarding the early discharge are reports of bilirubin induced brain damage occurred in healthy term infants even without hemolysis. This is addressed by predicting the newborns developing significant neonatal jaundice

early at birth.NH is a cause of concern for the parents as well as for the pediatricians.[54]Severe jaundice, and even kernicterus, can occur in some full-term healthy newborns with no apparent hemolytic, jaundice in the first 24 hours, or any causes other than breastfeeding hyperbilirubinemia.[55]

Friedman and Spitzer suggested that shorter hospital stays, decreased vigilance in diagnosing jaundice and lack of physician compliance with the guidelines may account for re-emergence of severe hyperbilirubinemia and kernicterus56. In the last two decades, there have been several articles published on re-emergence of

kernicterus in full term infants.[57, 58, 59]

The current list of identified risk factors to recognize infants who are likely to require treatment for hyperbilirubinemia is not adequate. While jaundice per se is not always preventable, nonetheless, early detection of threatening bilirubin levels permits initiation of phototherapy and prevents higher risk and higher cost exchange transfusion therapy or kernicterus. Early discharge complicates the ability to measure both the level of serum bilirubin and the rate of increase.[60]

The trend towards shorter hospital stay was evident even before the recent influence of insurance and managed care plans. In the past decade, however this trend has increased rapidly.[61]

Hyperbilirubinemia is the commonest cause for readmission to the hospital after earlydischarge. [61]

Palmer et al, in 1983 presented a reviewed jaundiced newborn infants during a 10-year period up to 1980. Neonates with serum bilirubin level of 9 or more were included in this study. Of 41,057 live births, 4,406 (10.7%) infants had

hyperbilirubinemia. The most common aetiological factor was prematurity (19.9%) followed by ABO iso-immunisation (7.1%); sepsis (3.4%); Rhesus iso-immunisation (2.7%); bruising (2.2%); multifactorial (1.0%) and glucose-6phosphate dehydrogenase deficiency (0.5%). Treatment was not undertaken in 2,855 (64.7%) infants while 1419 (32.2%) infants received phototherapy alone, 122 (2.7%) infants received both exchange transfusion and phototherapy and 10 (0.2%) infants received exchange transfusion alone. Of the infants which required exchange transfusion, 50.0% had Rhesus iso-immunisation, 28.0% had ABO iso-immunisation, 10.6% had jaundice of prematurity and the remaining were due to a variety of causes.[62]

Rosenfeld, in 1986 analyzed a group of 108 full-term newborns based on their risk of developing severe hyperbilirubinemia and concluded that babies with an umbilical cord blood bilirubin level of lower than 2 mg/100 ml had a 4% chance of developing significant jaundice, in comparison with a 25% chance presented by the ones with levels higher than 2 mg/100ml. In addition, the latter group also had a higher chance of needing to undergo phototherapy.[63]

Rataj et al, in 1994 studied the usefulness of measuring bilirubin levels in cord blood for predicting hyperbilirubinemia in newborns and reported that 89% of the infants with cord bilirubin above 2.5 mg% became jaundiced while only 2.4% of newborns had jaundice whose cord bilirubin levels were under 1 mg%.[64]

Bhutanivk et al, in1999 generated a percentile based bilirubin normogram using hour specific pre discharge TSB levels from a racially diverse group of term healthy newborns in the absence of ABO or Rh incompatibility, who did not require phototherapy before 60 hours of age and of whom 60% were breastfed. Post discharge TSB levels were measured by a hospital based bilirubin assay within 3

days after discharge in a supervised program. The risk for significant hyperbilirubinemia (TSB greater than 17 mg/dl) for infants with a pre-discharge TSB above the 95th percentile (high risk zone) was 57%, for infants with TSB between the 75th and 95th percentiles (high intermediate risk) it was 13%, for infants with TSB between the 40th and 75th percentiles (low intermediate risk zone) it was 2.1%, and for infants below 40th percentiles (low risk) it was zero. This study showed that universal policy of measuring pre-discharge serum bilirubin would facilitate targeted intervention, follow-up and also helps to reduce the potential risk for kernicterus development.[65]

A study done by David K Stevenson et al (2001), to predict hyerbilirubinemia, by measuring End Tidal Carbon monoxide (ETCO), failed to improve the predictive ability of an hour-specific bilirubin normogram. But the combination of measuring serum total bilirubin with ETCO as early as around 30 hours of life, helps in identifying increased bilirubin production (eg. hemolysis) or decreased elimination of bilirubin (eg. conjugation defect) and hence helps in determining early follow-up for problems like pathological jaundice or late anemia.[66]

Agarwal et al. (2002) in his editorial has stated that in 220 infants who were exclusively breastfed, clinically detectable jaundice was present in 164(77%) and hyperbilirubinemia occurred in 22(10.3%) infants. Study predicted that infants with total serum bilirubin levels lesser than 6 mg/dl at 24±6 hours would not develop hyperbilirubinemia.[67]

Bernaldo et al (2004) predicted that Blood incompatibility between mother and child was a predictor for the appearance of hyperbilirubinemia that required

treatment. Considering a cut-off point of 2.0 mg/dl, 53% of the newborns who had greater unconjugated bilirubin levels in cord blood would reach levels requiring phototherapy by the third day of life. In addition, they also concluded that the presence of mother/child blood group incompatibility was statistically significant for the occurrence of unconjugated bilirubin serum levels that were indicative of phototherapy treatment during the same three-day period.[68]

In 2012, a study was conducted by Sajjadian et al to show the significance of transcutaneous bilirubin measurement in preterm neonates to predict significant hyperbilirubinemia. This study concluded that there was significant correlation between transcutaneous bilirubin (TcB) and TSB in preterm cases even in ill neonate or who were receiving phototherapy. This method could be used for determination of bilirbin level in preterm neonates and also could reduce the number of painful blood sampling.[69]

A study conducted by Izi Mayer et al in 2014, showed that twelfth hour capillary total biluribin levels, over the cutoff values (3.55 mg/dl in newborns with 1,000 - 1,499 g birth weight and 4.55 mg/dl in newborns with 1,500-2,000 g birth weight) for the prediction of significant hyperbilirubinemia, have a good prediction of hyperbilirubinemia and is helpful in reducing the risk of bilirubin induced neurological dysfunction or kernicterus by starting early treatment.[70]

In 2011, Sahu et al measured cord serum albumin (CSA) to predict significant neonatal jaundice. Forty healthy term newborns were included in the study and were divided it into 3 groups based on CSA. They showed that 82% of neonates who had albumin le.ss than 2.8 g/dl developed hyperbilirubinemia requiring PT and 12% needed exchange transfusionET.At higher levels of albumin

(2.8-3.3 gm/dl), 40% needed PT while neonates with cord blood albumin levels of>3.3gm/dl did not need any intervention for hyperbilirubinemia. Hence they concluded that cord albumin more than 3.3g/dl was probably safe for early discharge of babies.[8]

In 2013, Trivedi et al measuredcord serum albumin (CSA) levels and correlated with cord serum total bilirubin (CSTB) and cord serum unconjugated bilirubin (CSUB) levels to recognize the risk factor for hyperbilirubinemia in neonates. A total of 605 healthy term babies were included and followed up for the first 7 days of life for development of significant NH.Out of 605 neonates, 205(33.88%) developed significant NH. Jaundice was present during first seven days of the life in 73.6% of newborns with CSUB of >2.0mg/dl. Among 205 babies who developed significant NH, 58.53% (120) had CSA levels of < 2.8g/dland 28.78% (59) of babies with CSA in the range of 2.8-3.5g/dl also developed significant NH.

However in 12.68% (26) of babies,there was significant NH withCSA levels of >3.5g/dl. This study concluded that cord serum albumin gives additional clue in visualizing possibility of significant NH.[71]

Venkatamurthy M et al (2014) showed a significant relationship between cord blood albumin and neonatal hyperbilirubinemia in term infants. The study showed that cord serum albumin level of ≤2.8 g/dl at birth had a greater risk of predicting the development of neonatal hyperbilirubinemia.[72]

Materials & Methods

MATERIALS AND METHODS:

The present study is a prospective study carried out over a period of three years from February 2012 to February2015, at R.L.Jalappa Hospital and Research Centre, a constituent of Sri Devraj Urs Medical College, Kolar. The study cohort consists of 130 randomly selected eligible term newborns.

The study was approved by the Institutional Ethics Committee of Sri Devraj Urs Medical College.

INCLUSION CRITERIA:

- Term normal newborns
- Babies delivered by normal vaginal route
- Babies delivered by caesarean section
- Birth weight $\geq$ 2.5kg
- APGAR Score $\geq$ 7/10 at 5 minutes

EXCLUSION CRITERIA

- Preterm neonates
- Rh incompatibility/ ABO incompatibility
- Neonatal sepsis
- Birth trauma
- Cephal hematoma
- Bruising/ Ecchymosis
- Birth asphyxia
- Respiratory distress

METHOD OF COLLECTION OF DATA

An informed consent was obtained from the parents of the newborns before enrolling them in the study. Demographic profile and relevant information pertaining to the study was collected by using structured proforma, by interviewing the mother and also from mother's case sheet.

Gestational age was assessed by New Ballard score.

At birth, 2 ml of cord blood sample was collected from normal newborns and analysed for albumin within 4-6 hours by dry chemistry auto analyzer Bromocresol green method.[73]

All enrolled babies were followed for 3 days and clinical assessment for jaundice was done according to Kramer dermal scale.[47]

Total Serum Bilirubin (TSB) estimation was done for neonates with evidence of clinical jaundice and the hour- specific values were plotted on Bhutani's chart .[65]

Significant hyperbilirubinemia was defined as > 13.5mg/dl at 36 hrs of life, > 15 mg/dl at 48 hrs of life and >16.5 mg/dl at 54 hrs of life.[65]

Venous blood sample was collected in a plain vial for total bilirubin estimation and precautions were taken to keep the vials away from light by wrapping them with aluminium foil to prevent photocoagulation. The sample was centrifuged, serum separated and stored till analysis at 2 -8 degree °C. Serum bilirubin was estimated by diazotized sulfanilic test. Throughout the procedure, all Precautions were taken to avoid pre analytical, analytical and post analytical errors. Daily internal quality assurance was run and promptly external quality was confirmed for all the parameters that were included .The quality of the parameters were confirmed with Bio RAD USA And all the parameters were within ± SD. Sample rerun was done in case of doubtful cases.

METHODS:

Parameter	Sample	Methodology	Test	Instrument
Blood Group and Rh	Arteriove nous whole blood finger prick	Antisera	The red cells contain different types of agglutinogens (antigens) and plasma contains agglutinins (antibodies). The red cells of the subject are allowed to react with commercially made agglutinins (anti sera). The presence or absence of clumping of red cells in different agglutinins determines the blood groups.	S tan diagnostics
Cord blood Albumin	Supernatant of Blood	Bromocresol green (BCG)	When albumin binds with BCG in a suitable buffer, pH 4.154.25, an intense blue colored albumin-BCG complex is formed. Albumin+ BCG to form Albumin-BCG complex which is greenish colour.[73]	Johnson and Johnson vitros 250Drychemistr y analyzer which works on the principle reflectance photometry
Total bilirubin	Serum of venous blood	Diazotized sulfanilic test	Bilirubin reacts with diazotized sulfanilic acid to produce azobilirubin which is quantified by drychemistry analyzer which works on both direct and indirect bilirubin couple with diazo in the presence of cetremide. The terms 'direct' and 'indirect' are approximately equivalent to conjugated and unconjugated fractions respectively.[74]	Johnson and Johnson vitros 250 Drychemistry analyzer which works on the principle reflectance Photometry.

Fig 7: Johnson and Johnson vitros 250 Drychemistry analyzer

Fig 8: Antisera bottles with slides showing A+ blood group of neonate

Serum bilirubin estimation was done only in 100 newborns with clinical jaundice.

Statistical analysis:

Categorical data was represented in the form of frequencies and proportions. Chi-square was used as test of significance. Continuous data was represented as mean and standard deviation.

Correlation was done to find the relationship between two quantitative variables. P value <0.05 was considered as statistically significant.

Results

RESULTS

The study was conducted on total of 130 newborns after obtaining a written consent from the parents. Proforma was filled for each newborn. Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Chisquare was used as test of significance. The data were analyzed using appropriate statistical software .

General details of the Newborns

Table 2: Gender distribution of newborns

	Frequency	Percent
Female	58	44.6
Male	72	55.4
Total	**130**	**100.0**

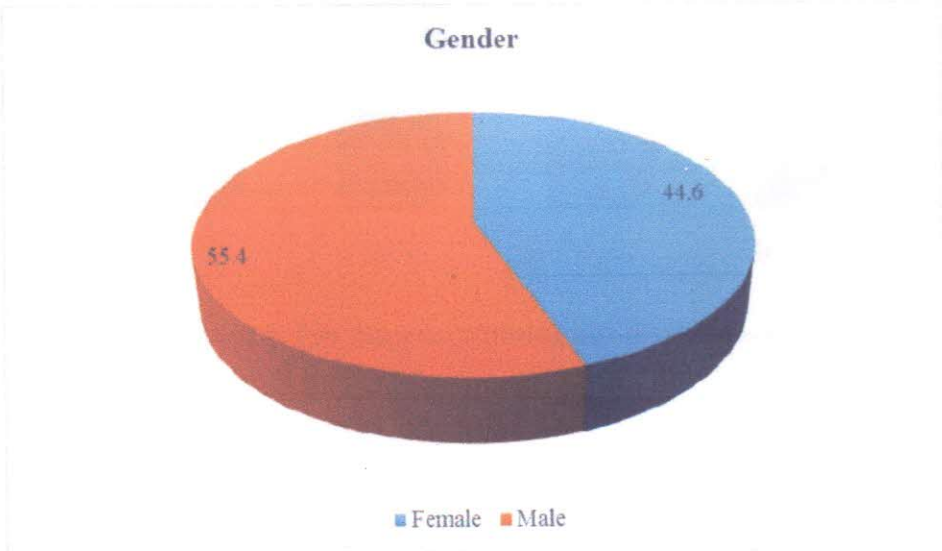


Figure 9: Pie diagram showing gender distribution of newborns

In the study, it was observed that 58(44.6%) newborns were females and72 (55.4%) were males - Table 2& Fig 9

Table 3: Distribution of mothers according to age

Age Group	Frequency	Percent
<20yrs	27	20.8
21 to 25yrs	72	55.3
26 to 30yrs	27	20.8
>30yrs	4	3.1
Total	**130**	**100**

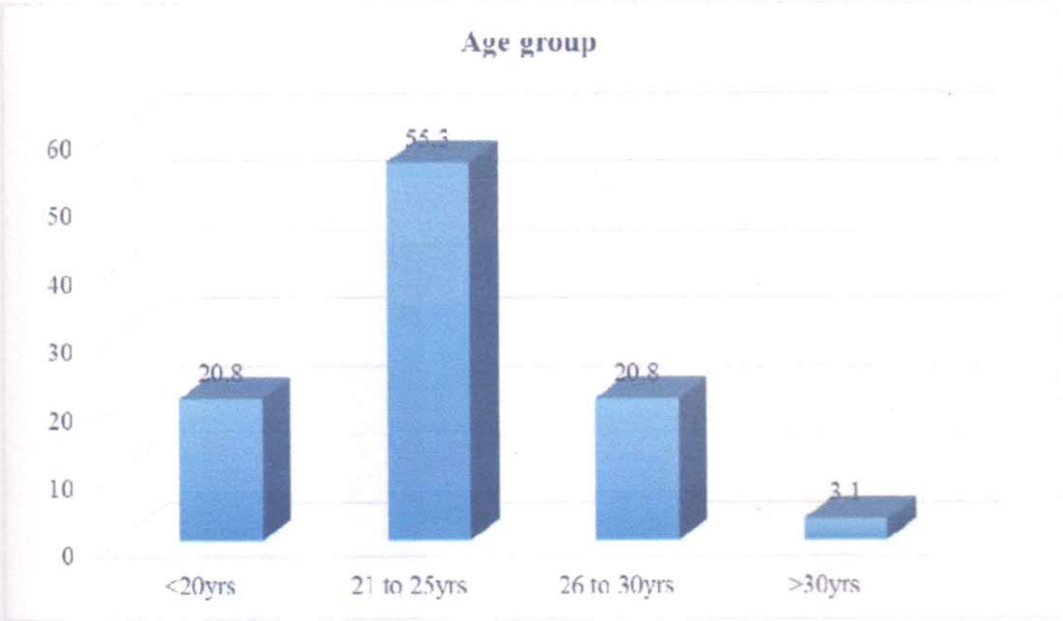


Figure 10: Bar diagram showing age distribution of mothers

In the study, majority (55.3%) of mothers were in the age group of 21 to 25 yrs, followed by 20.8% each in 26 to 30 yrs and < 20 yrs age groups. Only 3.1% belonged to the age group of >30yrs - Table 3 & Fig 10.

Table 4: Distribution of mothers according to gravida status

		Frequency	Percent
Gravida	**1**	53	40.8
	2	58	44.6
	3	11	8.5
	4	4	3.1
	5	1	0.8
	6	3	2.3
	Total	130	100.0

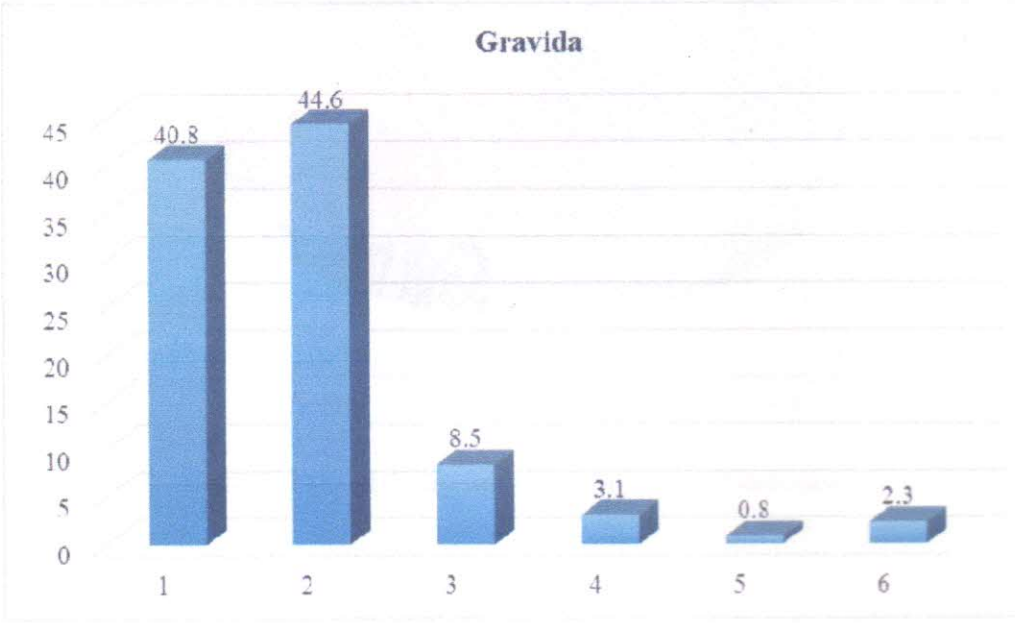


Figure 11: Bar diagram showing gravida status of mothers

In the study, 40.8% of mothers were primigravida while 59.2% were multigravida - Table 4 & Fig 11.

Table 5: Distribution of mothers according to mode of delivery

		Frequency	Percent
Mode of delivery	Normal	57	43.8
	Emergency LSCS	50	38.5
	Elective LSCS	23	17.7
	Total	130	100.0

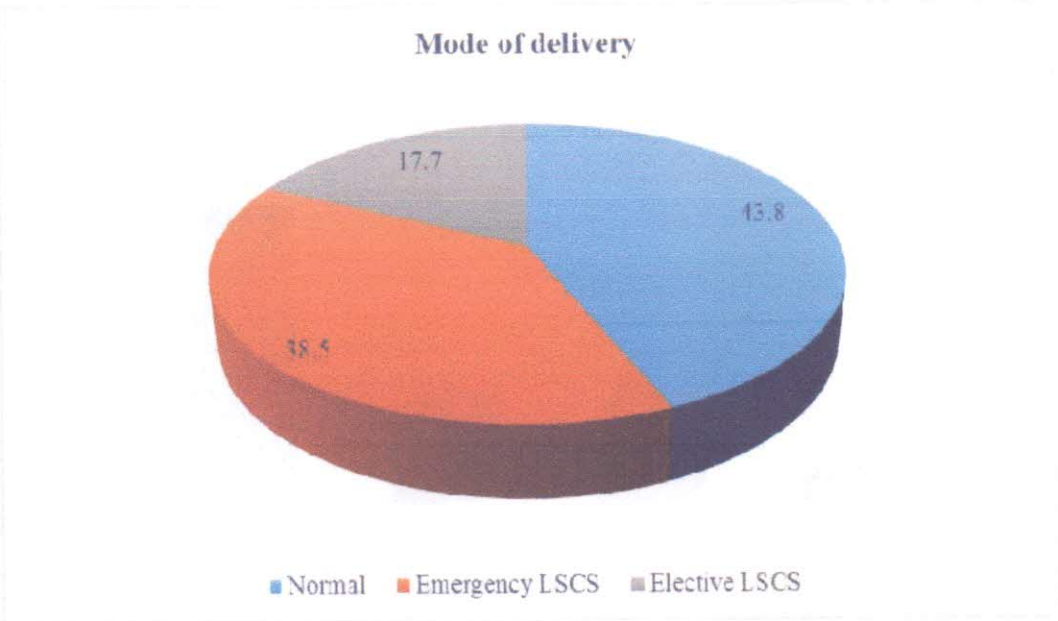


Figure 12: Pie diagram showing Mode of delivery

Table 5 & Fig 12 show that majority (43.8%) of mothers had normal vaginal delivery while 38.5% and 17.7% underwent emergency LSCS and elective LSCS respectively.

Table 6: Distribution of mothers according to blood group

		Frequency	Percent
Blood group & Rh typing	O+ve	74	57
	A+ve	25	19.2
	B+ve	25	19.2
	AB+ve	6	4.6
	Total	**130**	**100.0**

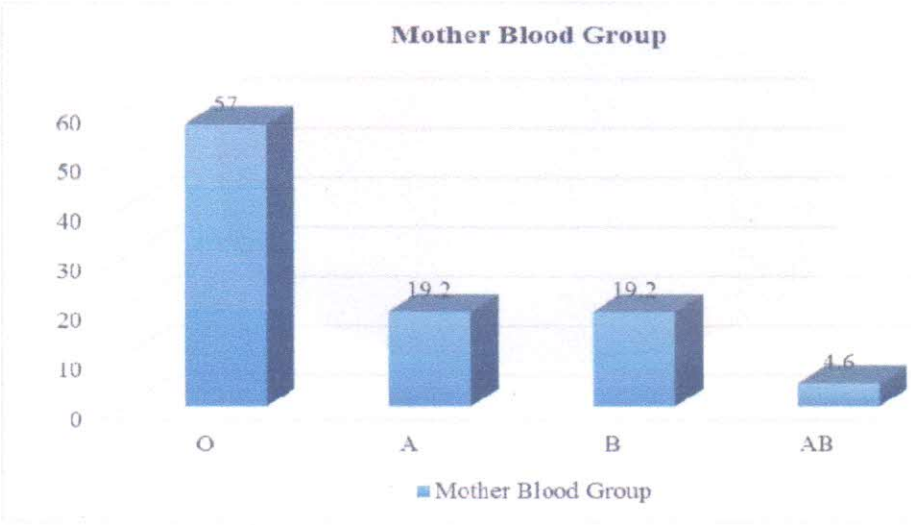


Figure 13: Bar diagram showing Blood group of Mother

Table 6 and Fig 13 depict the distribution of mothers according to blood grouping and Rh typing. Majority (57%) of mothers belonged to O positive group while 4.6% belonged to AB positive group.Mothers with A & B positive groups showed an equal distribution of 19.2%.

Table 7: Distribution of newborns according to birthweight

	Frequency	Percent
2.5 to 3.0 kg	90	69.2
3.0 to 3.5 kg	31	23.8
>3.5 kg	9	6.9
Total	**130**	**100.0**

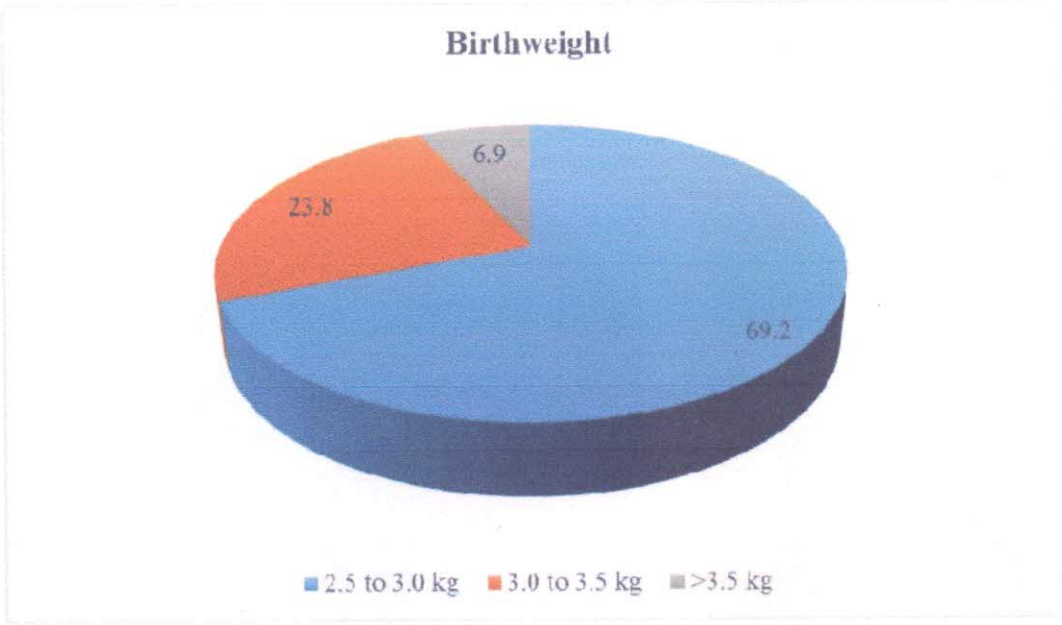


Figure14: Pie diagram showing birth weight of newborns

Mean birth weight of babies was 2.91 ± 0.32 kg. It was observed that majority (69.2%) of newborns weighed between 2.5 and 3 kg, followed by 23.8% who weighed between 3 and 3.5 kg while 6.9% of newborns weighed >3.5kg. Table 7 and Fig 14

Objective specific tables:

Table 8: Distribution of cord blood albumin levels of newborns

			Frequency	Percent
Cord blood albumin(g/dl)	<2.8	Group 1	10	7.7
	2.8 to 3.3	Group 2	49	37.7
	>3.3	Group 3	71	54.6
	Total		130	100.0

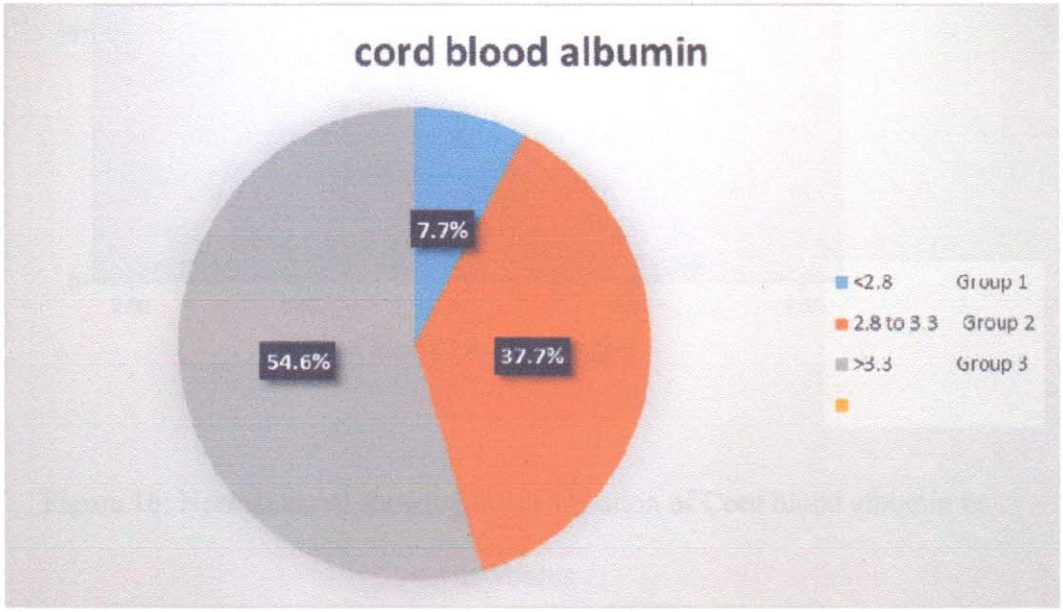


Figure 15: Pie diagram showing cord blood albumin levels

In the present study it was observed that mean cord albumin level was 3.41 ± 0.46 g/dl. Cord albumin levels of >3.3g/dl was present in 71 (54.6%) newborns (group 1), while in 49 (37.7%) newborns the cord blood albumin levels were in the range of 2.8 and 3.3 g/dl (group 2). Cord blood albumin levels of < 2.8 g/dl was present in 10 (7.7%) of newborns - Table 8 &Fig 15.

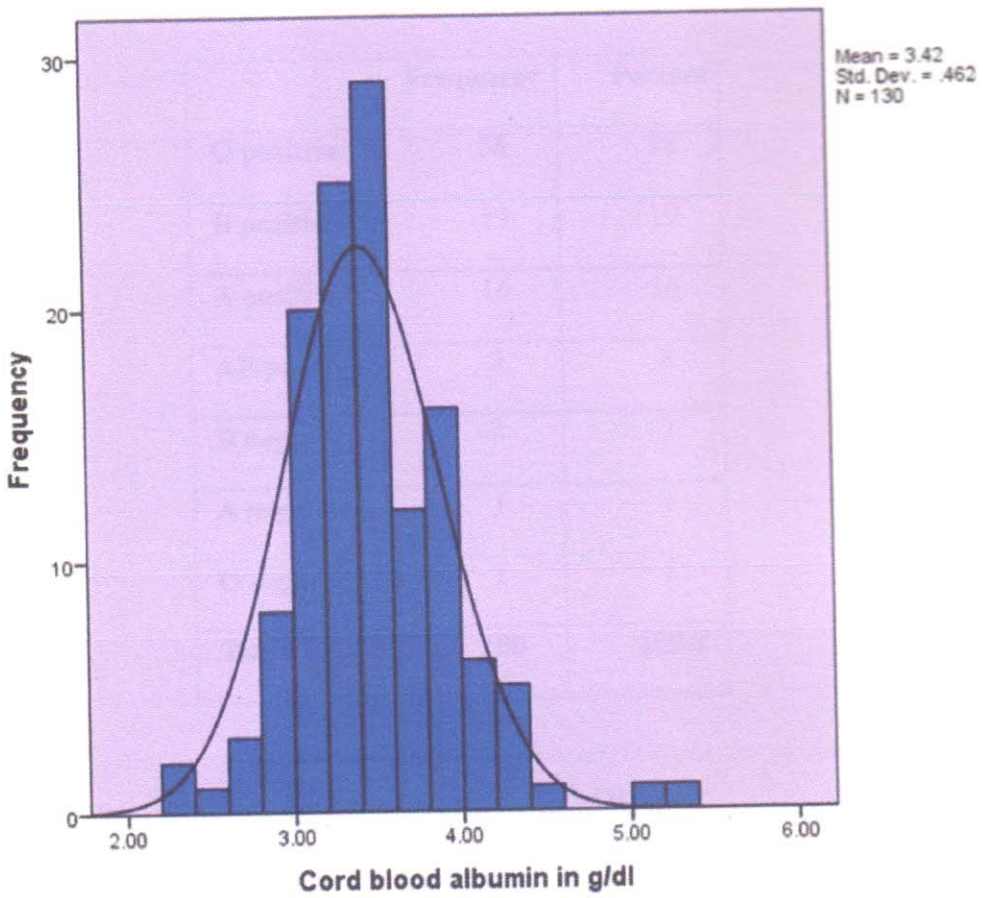


Figure 16: Normal curve showing the distribution of Cord blood albumin in newborns

Figure 16 depicts distribution of cord blood albumin levels in newborns with a mean of 3.42 and SD of 0.462 (n=130).

Serum bilirubin estimation was done only in 100 newborns with clinical jaundice.

Table 9: Distribution of blood groups of newborns

	Frequency	Percent
O positive	58	58
B positive	19	19
A positive	16	16
AB positive	3	3
B negative	2	2
A negative	1	1
O negative	1	1
Total	**100**	**100.0**

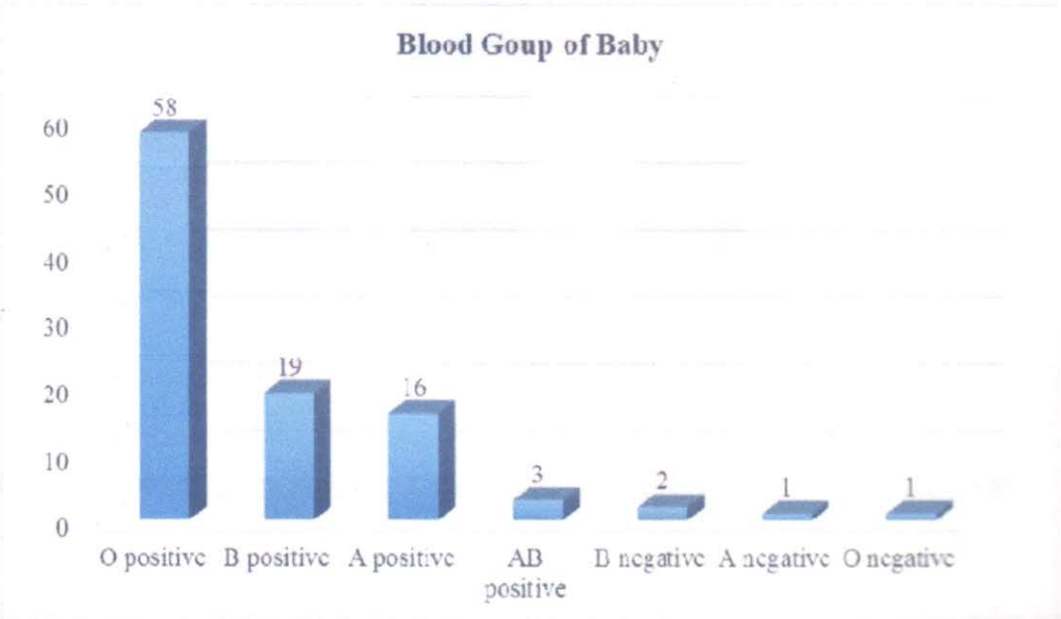


Figure 17: Bar diagram showing blood group of newborns

In the study, blood group of majority (58%) of newborns was O positive, followed by B positive in 19% and A positive in 16% - Table 9 &Fig 17

Table10: Distribution of neonates according to total serum bilirubin levels

		Frequency	%
Total serum bilirubin (mg/dl)	**<10**	23	23
	10 to 14	59	59
	14.1 to 17	17	17
	>17	1	1
Total		**100**	

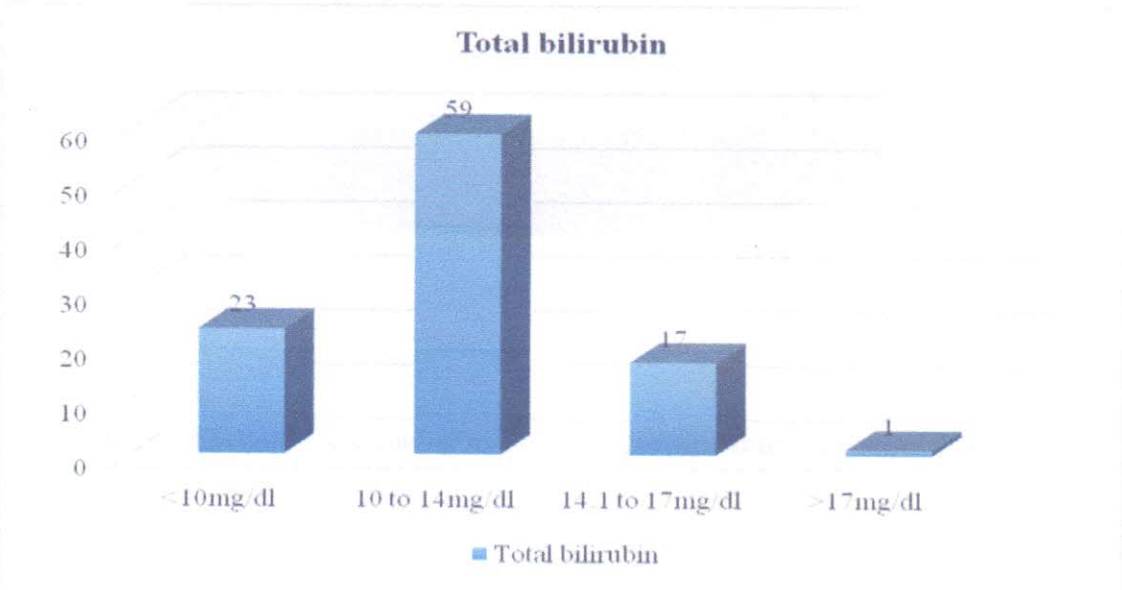


Figure 18: Bar diagram showing Total serum bilirubin levels in newborns (n=100)

Table 10 & Fig 18 depict the distribution of newborns according to total serum bilirubin levels. It Was found that majority (59%) of newborns with jaundice had total serum bilirubin levels between 10 and 14 mg/dl while only 1% had levels above 17mg/dl.In 17% of newborns total serum bilirubin levels ranged between 14.1 and 17 mg/dl.

Table 11: Distribution of phototherapy requirement for Neonatal Hyperbilirubinemia

Phototherapy	No. of patients	%
No	81	81.0
Yes	19	19.0
Total	100	100.0

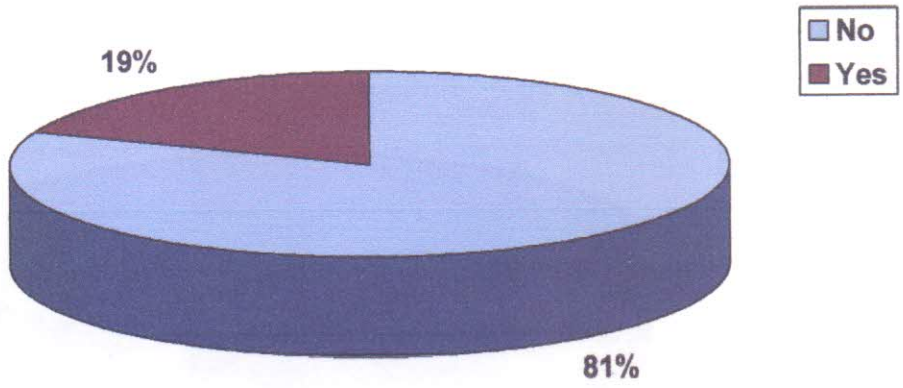


Figure 19: Pie diagram showing neonatal hyperbilirubinemia requiring phototherapy

Significant hyperbilirubinemia requiring phototherapy was present in 19 newborns as depicted in Table 11 & Fig 19

Table 12: Distribution of exchange transfusion requirement for neonatal hyperbilirubinemia

Exchange transfusion	No. of patients	%
No	100	100.0
Yes	0	0.0
Total	100	100.0

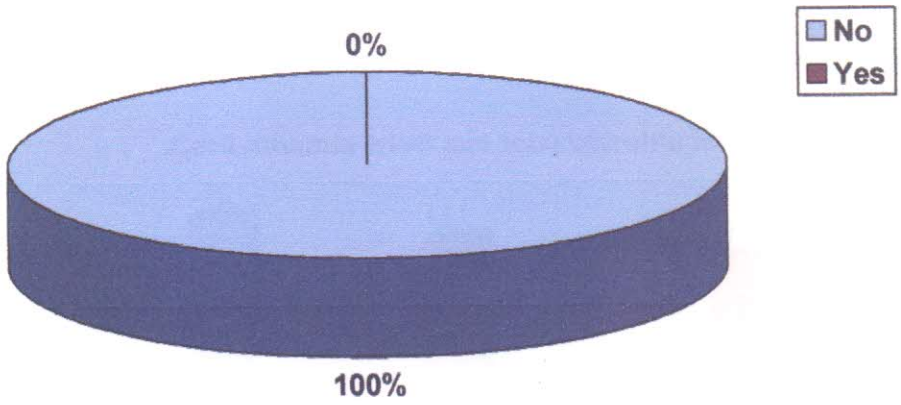


Figure 20: Pie diagram showing neonatal hyperbilirubinemia requiring exchange transfusion

Table 12 & Fig 20 show that none of the newborns in the study group required exchange transfusion.

Table 13: Association between cord blood albumin levels and total serum bilirubin levels

		Bilirubin(mg/dl)				Total
		<10	10 to 14	14.1 to 17	>17	
Cord blood albumin (g/dl)	**<2.8**	1 (10)	2 (20)	7 (70)	0	10
	2.8 to 3.3	3 (8.6)	23 (65.7)	8 (22.9)	1 (2.9)	35
	>3.3	19 (34.5)	34 (61.8)	2 (3.6)	0	55
Total		**23**	**59**	**17**	**1**	**100**

X 2 = 34.87, df =6, p <0.00001**

Figures in parentheses indicate percentage

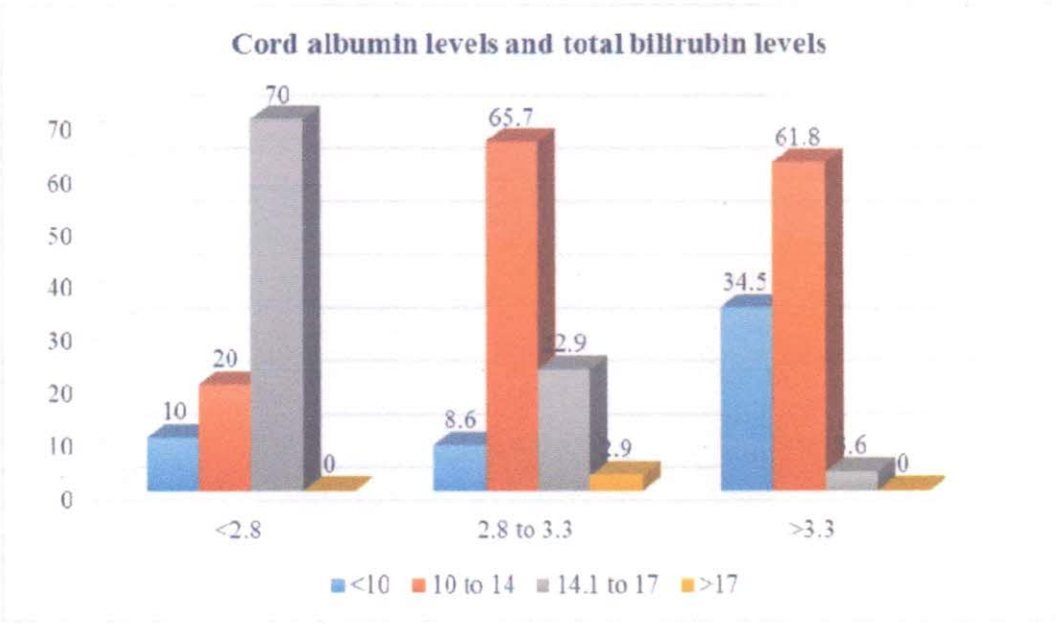


Figure 21: Bar diagram showing association between cord blood albumin and total serum bilirubin levels

In the present study it was observed that with decrease in cord blood albumin levels there was increase in total bilirubin levels. This observation was statistically significant - Table 13 & Fig 21.

Table 14: Correlation between Cord blood albumin levels and total serum bilirubin

		Cord blood albumin (g/dl)	Total serum Bilirubin(mg/dl)
Cord blood albumin g/dl	**Pearson Correlation**	1	-0.484**
	Sig. (2-tailed)		<0.0001**
	N	100	100
**. Correlation is significant at the 0.01 level (2-tailed).			

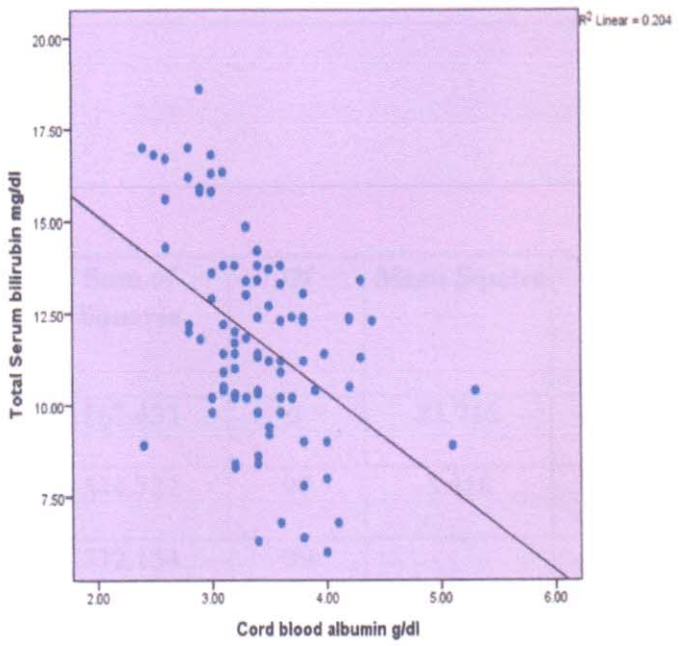


Figure 22: Scatter plot showing Correlation between Cord blood albumin and Total serum bilirubin

In the study, it was observed that there a was highly significant negative correlation between cord Albumin levels and total serum bilirubin i.e. with increase in total serum bilirubin there was a Decrease in cord blood albumin levels and vice versa - Table 13 &Fig 22

Table 15: Comparison of mean serum bilirubin levels with respect to cord blood albumin levels

Cord blood albumin (g/dl)	N	Total serum Bilirubin(mg/dl)	
		Mean	Std. Deviation
<2.8	10	14.67	2.77
2.8 to 3.3	35	12.56	2.60
>3.3	55	10.71	2.12
Total	**100**	**11.75**	**2.68**

ANOVA					
	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	167.433	2	83.716	14.908	<0.0001**
Within Groups	544.722	97	5.616		
Total	712.154	99			

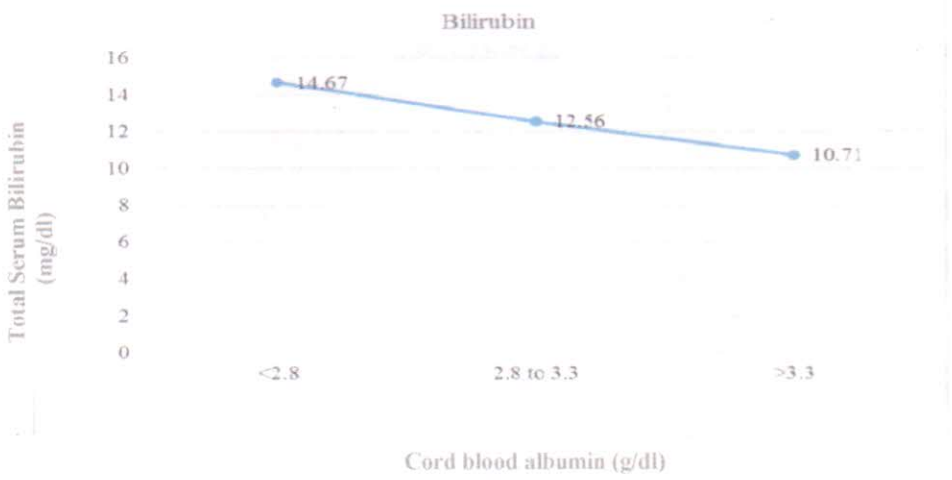


Figure 23: Line diagram showing Bilirubin levels with respect to Cord blood albumin

In the study it was observed that, among newborns with cord blood albumin levels of <2.8mg/dl, mean serum bilirubin was 14.67± 2.77. In 2.8 to 3.3 g/dl group, mean bilirubin was 12.56 ± 2.60 and in >3.3 g/dl group the mean serum bilirubin was 10.71 ± 2.12. This difference in mean serum bilirubin levels among different cord blood albumin groups was highly significant statistically as shown by ANOVA test i.e., total serum bilirubin levels increased with decrease in cord blood albumin. Hence this confirms the correlation - Table 15 & Fig 23.

Table 16: Association between cord blood albumin levels and phototherapy

		Phototherapy				Total
		No	%	Yes	%	
Cord blood albumin (g/dl)	<2.8	0	0	10	100	10
	2.8 to 3.3	26	74.3	9	25.7	35
	>3.3	55	100	0	0	55
Total		**81**		**19**		**100**

Chi-Square Tests			
	Value	df	p value
Pearson Chi-Square	56.56	2	<0.0001**

In the study, it was observed that when cord blood albumin was >3.3 g/dl, none of the newborns received phototherapy.Out of 35 newborns with cord blood albumin levels between 2.8 and 3.3 g/dl, 9 (25.7%) neonates received phototherapy while all the 10 (100%) newborns with albumin <2.8 g/dl received phototherapy. This observation was highly significant statistically. There was significant association with decrease in cord blood albumin and phototherapy treatment in newborns - Table 16 & Fig 24

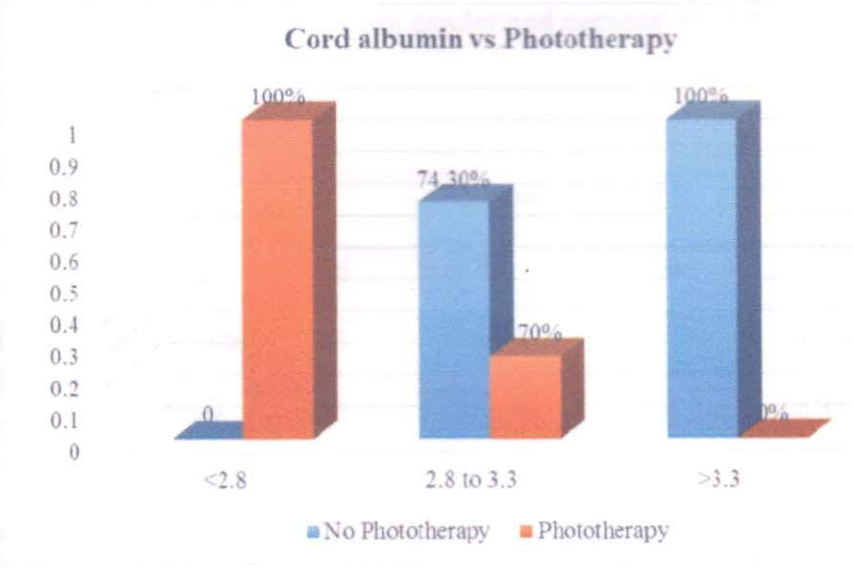


Figure 24: Bar diagram showing association between cord albumin and phototherapy

Table 17: Total Bilirubin values among subjects with neonatal hyperbilirubinemia requiring phototherapy

	N	Mean	Std. Deviation
Day 2 Total Bilirubin	4	11.675	1.9822
Day 3 Total Bilirubin	15	16.3293	0.93841

In the study it was observed that the number of newborns who received phototherapy on day 2 were 4 with the mean bilirubin value of 11.6.And the number of newborns who received phototherapy on day 3 were 15 with the mean bilirubin of 16.3.Table 17.

Table 18: Association between gender and neonatal hyperbilirubunemia requiring phototherapy

		Phototherapy				Total
		No	%	Yes	%	
Gender of neonates	Female	38	46.9%	6	31.6%	44
	Male	43	53.1%	13	68.4%	56
Total		81		19		100

X 2 = 1.53, df =2, p = 0.465

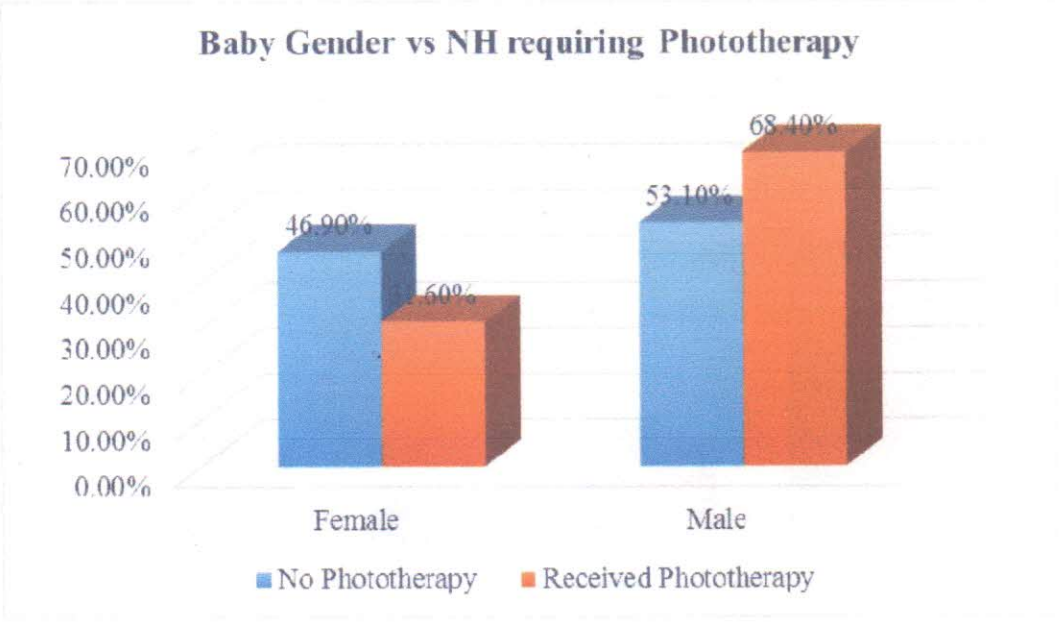


Figure 25: Bar diagram showing association between gender and phototherapy received

In the study, it was observed that among 19 subjects who received phototherapy, majority were males (68.4%). But there was no significant association - Table 18 & Fig 25.

Table 19: Association between maternal blood group and phototherapy received

		Phototherapy				Total
		No	%	Yes	%	
Maternal Blood group	A+ve	16	19.8	3	15.8	19
	AB+ve	4	4.9	0	0	4
	B+ve	17	20.9	3	15.8	20
	O+ve	44	54.4	13	68.4	57
Total		**81**		**19**		**100**

X 2 = 1.81, df =3, p = 0.61

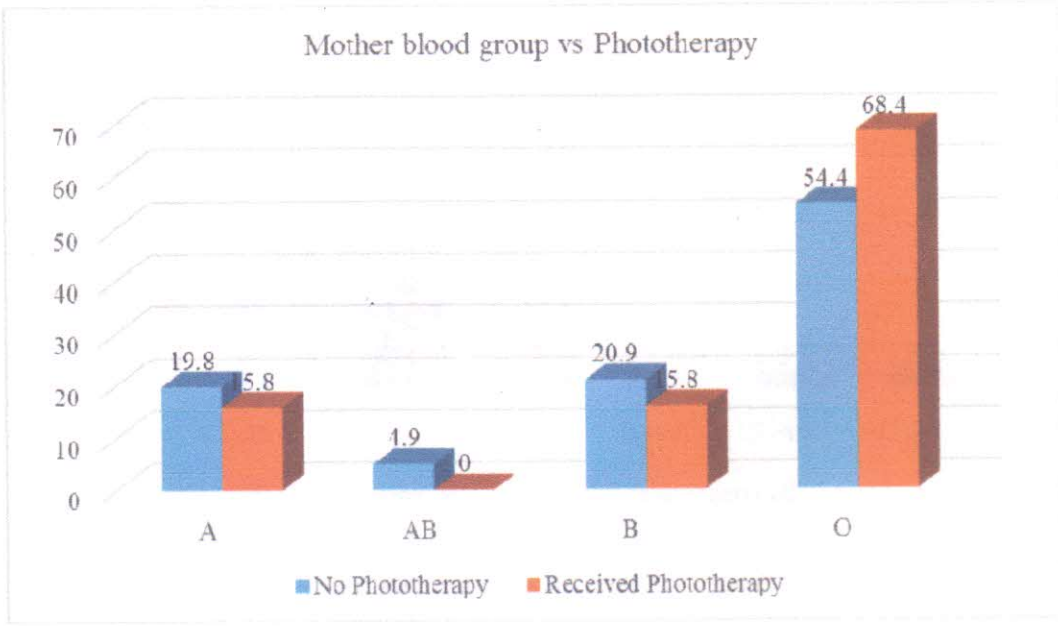


Figure 26: Bar diagram showing association between maternal blood group and phototherapy received

In the study it was observed that among 19 subjects who received phototherapy, majority (68.4%) were born to mothers belonging to O +ve blood group. But there was no significant association between maternal blood group and phototherapy received - Table 19& Fig 26.

Table 20: Association between blood group of newborns and phototherapy received

		Phototherapy				Total
		No	%	Yes	%	
Blood group of newborns	O	51	63	7	36.9	58
	B	14	17.3	5	26.3	19
	A	12	14.9	4	21.1	16
	AB	1	1.2	2	10.5	3
	B –ve	1	1.2	1	5.2	2
	A –ve	1	1.2	0	0	1
	O –ve	1	1.2	0	0	1
Total		**81**		**19**		**100**

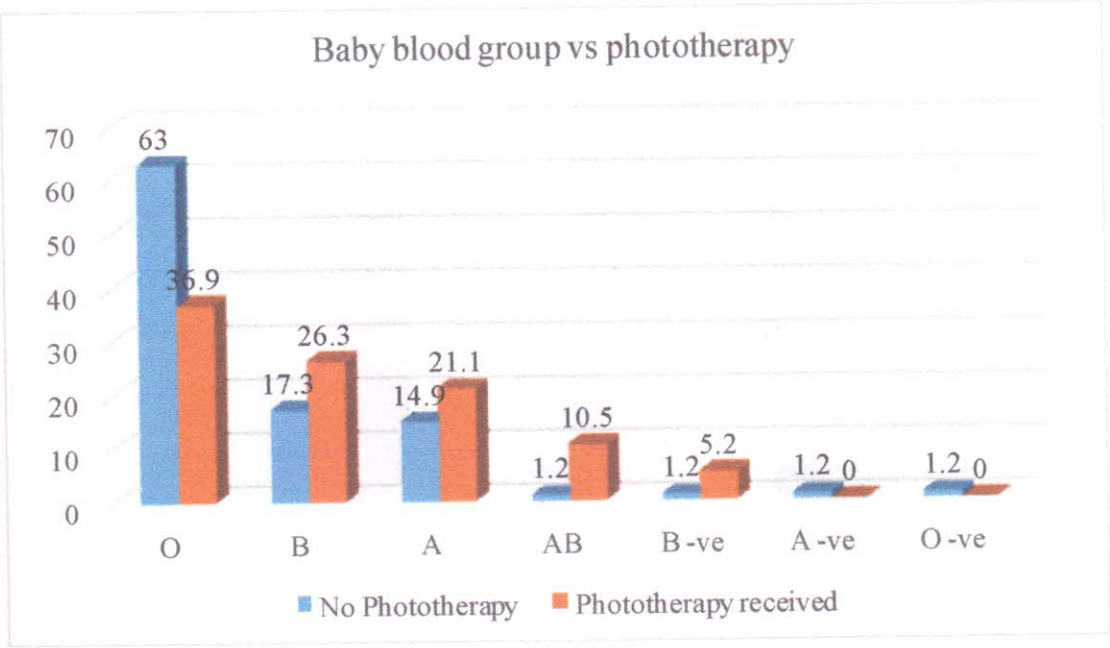


Figure 27: Bar diagram showing association between blood group of newborns and phototherapy

In the present study among 19 subjects who underwent phototherapy, 36.9% had O +ve blood group, while 26.3%, 21.1% , 10.5% and 5.2% had B +ve, A +ve, AB +ve and B-ve blood groups respectively. However there was no statistical significance between blood groups of newborns and phototherapy received- Table 20 & Fig 27.

Table 21: Showing association between birth weight and phototherapy received

		Phototherapy				Total
		No	%	Yes	%	
Birth weight	**2.5 to 3.0 kg**	53	65.5	15	78.9	68
	3 to 3.5 kg	23	28.4	4	21.1	27
	>3.5 kg	5	6.1	0	0	5
Total		**81**		**19**		**100**

X 2 = 1.894, df =2, p = 0.388

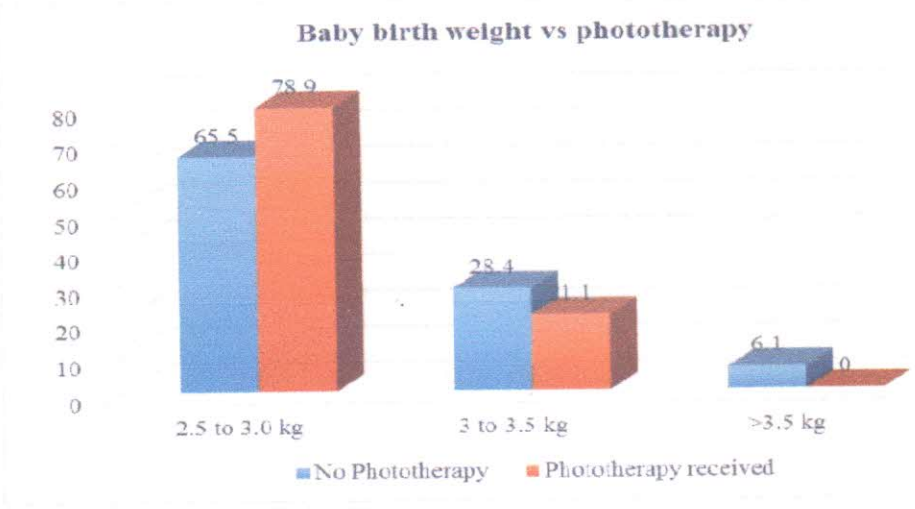


Figure 28: Bar diagram showing association between birth weight and phototherapy

In the study it was observed that among 19 subjects who underwent phototherapy 78.9% weighed between 2.5 and 3.0 kg while 21.1% weighed between 3 and 3.5 kg. There was no significant association between birth weight and phototherapy. Table 21 & Fig 28

All the babies were discharged from hospital.

Discussion

DISCUSSION

Albumin is the major binding protein in the human neonate. Low production of albumin will lower its transport and binding capacity.[75] Albumin binds to potentially toxic products like bilirubin and antibiotics. Bilirubin binds to albumin in an equimolar ratio. Free bilirubin is anticipated when the molar bilirubin-to-albumin (B: A) ratio is >0.8.It is the free bilirubin which can cross the BBB. There is no precise data to correlate a specific bilirubin value or albumin value with neurotoxicity. The clinical manifestations of acute bilirubinencephalopathy can be insidious and progress rapidly to severe and life threatening illness. Kernicterus is the chronic sequela of acute bilirubin encephalopathy. The incidence of kernicterus is unknown.[76] Unconjugated hyperbilirubinemia is a potentially correctable cause and kernicterus is preventable.[77]

The decision to treat hyperbilirubinemia is based on the infant's history, course, physical findings, serum bilirubin levels and risk benefit analysis.[78]

In this present study, we assessed the cord blood albumin level as as screening tool for the risk of subsequent NH.

Cord blood albumin (CBA) levels:

In the present study, cord blood albumin level of term neonates was measured and the mean level was 3.41 ± 0.46. Majority (71/130) of neonates had CBA levels of > 3.3 g/dl while only 10 neonates had CSA levels of < 2.8 g/dl in our study. However, in studies conducted by Sahuet al[8]and Venkatamurthy et al [72] on term neonates, majority of neonates had CSA levels of < 2.8 g/dl which is in disagreement with the findings of our study – Table 22. The source of cord blood albumin is from the mother's circulation which probably reflects the nutritional status of mothers.

Table 22: Comparison of cord blood albumin levels

Cord blood albumin (g/dl)	Present Study	Sahu et al[8]	VenkatamurthyM et al[72]
< 2.8	**10**	17	81
2.8 – 3.3	**49**	15	53
>3.3	**71**	08	40
Total	**130**	40	174

Out of 130 neonates, only 100 neonates with clinical evidence of jaundice were subjected to serum bilirubin estimation. However in studies conducted by other authors [8, 71, 72] all the neonates were investigated for serum bilirubin.

Sex of newborns:

Table 23: Comparison of gender predilection and NH

Studies	Male	Female	p Value
Present study	**56**	**44**	**0.465**
Amar Taksande et al[79](2005)	118	82	0.323
Rostami et al[80](2005)	300	343	>0.05
VenkatamurthyM et al[72] (2014)	98	76	0.899

In the present study, there was no significant correlation (p 0.465) between TSB levels and the sex of the newborn. A study done by Amartaksande et[79] al on 200 newborns with 82 males and 118 females also did not found any correlation between the sex of the neonate and NH. Similarly, studies conducted by Rostamiet al[80] and

VenkatamurthyM et al[72]did not find any correlation between NH and the sex of the newborns. The observations of the above studies are in conformity with the findings of our study - Table 23. Hence the present study infers that the TSB is independent of the sex of the newborns.

However, Trivedi et al [71] reported a higher incidence of NH among male babies which is not in agreement with the findings of the present study.

Birth weight of newborns:

Table 24: Comparison of birth weight with NH

Studies	Year of study	No. of cases	P value
Present study	**2014**	**100**	**0.388**
Rudy Satrya et al[3]	2009	88	0.402
Onwuanaku et al [81]	2011	278	0.002

There was no significant association between birth weight and NH in the present study – Table 20. Rudy Satryaet al[3], in a study on 88 newborns, showed that there was no association (p 0.885) between birth weight and NH among term newborns which is similar to our study. However, Onwuanakuet al[81], in their study on term newborns found a significant association between birth weight and NH among term newborns which is not in conformity with our study – Table 24.

Association between the cord blood albumin levels and NH:

Table 25: Association of CBA levels and NH

Studies	Year	Total no of cases	No of case with NH	Cord blood albumin (CBA) levels in g/dl			P value
				Group1	Group 2	Group 3	
Sahu et al[8]	2011	40	20	14(<2.8)	6 (2.8-3.3)	0 (>3.3)	<0.001
Trivedi et al [71]	2013	605	205	120 (≤ 2.8)	59 (2.8-3.5)	26 (>3.5)	<0.05
Present study	**2015**	**100**	**19**	**10(< 2.8)**	**9(2.8-3.3)**	**0 (>3.3)**	**<0.001**

(P value <0.05 is significant).

Sahu et al[8] showed that 70% (14/20) newborns who developed significant NH had CSA levels of< 2.8 g/dl, 30% (6/20) had CSA levels in the range of 2.8-3.3 g/dl and none of newborns with CSA levels of >3.3g/dl developed NH which was statistically significant with p value of <0.001.

Trivedi et al[71] studied a total of 605 newborns of whom 205 developed significant NH. There was statistical significance with CSA level and NH, with p value of <0.05.

In the present study, 100 newborns were included and 19developed NH. The study cohort was grouped into Group 1, Group 2 and Group 3 based on CBA levels of< 2.8 g/dl, 2.8 - 3.3g/dl and >3.3 g/dl respectively. In groups 1 and 2, 52.6% (10/19) and 47.3% (9/19) developed NH respectively. In Group 3, none of the neonates with CBA levels of >3.3 g/dl developed NH.

The present study results correlated well with the observations of Sahuet al8 and Trivedi et al[71] – Table 25.

Thus, CSA level appears as a risk indicator in predicting NH. Hence this study indicates that CSA level <2.8g/dl is a high risk factor for future development of NH and CSA level > 3.3 g/dl is probably safe for early discharge.

In the present study it was observed that 10 newborns who had cord blood albumin levels of <2.8 g/dl had significant NH and received phototherapy. At higher levels of albumin (2.8-3.3g/dl), 25.7% needed intervention for hyperbilirubinemia while newborns with cord blood albumin levels of >3.3 g/dl did not require any intervention.

Studies and literatures have shown that neonates have an immature liver function as compared to that of adults. As a result, there is decreased production and synthesis of all the major proteins in the newborns. The decrease in the production of various proteins means that there is a decrease in the production of albumin, which has a major role in the conjugation of bilirubin. Albumin acts a carrier protein for the transport of bilirubin, which eventually helps in the transfer of bilirubin to the liver where conjugation occurs. This process is interrupted due to decreased albumin levels in newborns. The impact is more so in preterm newborns, who have an even decreased albumin levels.

In the present study, it was found that there was a significant association between cord blood albumin values and the tendency to develop significant neonatal hyperbilirubinemia requiring intervention. Albumin levels indicate the synthetic function of liver and bilirubin is an indicator of the excretory function of the liver. Due to the immaturity of liver in newborns, both the synthetic and excretory function may be affected.

This study concludes that there is a correlation between cord blood albumin and serum bilirubin levels, thereby showing that the synthetic function of liver can have an impact on its excretory function, the end product being bilirubin. Hence cord blood albumin can be used as a 'surrogate marker' for screening the newborns for development of neonatal hyperbilirubinemia.

Conclusion

CONCLUSION:

Mean CBA level among term newborns is 3.41 ± 0.46

Sex of the neonate was not associated with neonatal hyperbilirubinemia.

A significant p value and Negative Predictive Value, in the present study suggests that CBA levels of<2.8 g/dL can help to identify those newborns that are likely to require further evaluation and intervention. Babies with CBA levels of > 3.3 g/dl can be considered to be safer, with much lesser chances of developing significant NH in term neonates.

In association with other resources that are already available, this proposal may help in assuring safer early discharge. It means that the prediction test developed by us can be applied to the neonates of local rural population.

LIMITATIONS OF THE STUDY:

- Small sample size.
- Only healthy neonates were taken for the study.
- Thus, prediction of NH will have widespread implications especially in a rural setup where there are limited resources and fewer hospital beds. Evaluation of CBA being cost effective can be safely implemented in daily clinical practice, along with the presently available laboratory tests, for a better outcome in newborns developing hyperbilirubinemia.

Summary

SUMMARY

- The study group consisted of 130 randomly selected term normal newborns delivered at R. L. Jalappa Hospital and Research Centre. The study period was from February 2012 to February 2015.
- Cord blood was collected at birth and albumin estimation was done within 4-6 hours of collection of blood.
- All the neonates were followed up daily for evidence of clinical jaundice by Kramer's dermal scoring up to day 3 of post-natal life.
- In neonates with clinical jaundice, total serum bilirubin estimation was done.
- Total serum bilirubin levels were plotted on Bhutani's chart and those neonates with significant hyperbilirunemia received intervention in the form of phototherapy.
- The study cohort was divided into three groups based on cord blood albumin (CBA) levels. Group 1 consisted of neonates with CBA levels of < 2.8 g/dl, group 2 consisted of neonates with CBA levels ranging from 2.8 – 3.3 g/dl and group 3 consisted of neonates with CBA levels of > 3.3 g/dl.
- The mean cord blood albumin of 130 neonates was 3.42 and SD of 0.462.
- Clinical jaundice was present in 100 neonates for whom serum bilirubin estimation was done.
- Out of 100 neonates, 19 received phototherapy for significant hyperbilirubinemia.
- There was no significant association between gender of neonates and significant hyperbilirubinemia.

- There was no significant association between birth weight of neonates and significant hyperbilirubinemia.
- There was no significant association between blood group of neonates, maternal blood groups and significant hyperbilirubinemia.
- There was a significant negative correlation between cord blood albumin levels and total serum bilirubin levels i.e. with an increase in total serum bilirubin levels there was a decrease in cord blood albumin levels.
- Hence, cord blood albumin levels < 2.8 g/dl is a cost effective method for early discharge of newborns.

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Annexures

ANNEXURES

PROFORMA

A Study of cord blood albumin as a predictor of significant neonatal jaundice

Maternal Data:

1)Name of Mother: ……..

2)Age: ……..

3)Address: ……

4)Obstetric Score: G…… P…… A …….. D……

5)Blood Group:

6)LMP: …… EDD: ……

7)Gestational age (weeks) by USG ……

8)Maternal illness : Yes/No

If Yes, specify ……

9)Maternal Drugs : Yes/No

If Yes,specify ……..

10)Family history of Hemolytic Disease : Yes/No

If Yes, specify ……..

11)Mode of delivery : NVD/caesarean section ……

B.Neonatal Data:

1) Name: …….. 2) IP No: ……..

3) DOB ……. 4) TOB …… 5) SEX …….

6) Apgar score: 1 min ..... 5 min .....

7) Gestational Age(Ballard scoring): .....

8) Birth Weight (gms): .....

9) AGA|SGA|LGA : .....

10) Feeding History:

Breast feed|Formula|Cow's milk|Buffalo's milk: .....

Time of initial feeding(hrs) : .....

Frequency of feeding(per day): .....

C Evidence of icterus (Kramer dermal staining)

Day 1 (Hours Of appearance) : .....Face|Chest|Upper abdomen|Lower abdomen|Thighs| arms|Lowerlegs|Palms|Soles

Day 2(Hours Of appearance): .....Face|Chest|Upper abdomen|Lower abdomen|Thighs|Arms|Lowerlegs|Palms|Soles

Day 3 (Hours Of appearance): .....Face|Chest|Upper abdomen|Lower abdomen|Thighs |Arms|Lowerlegs|Palms|Soles

D INVESTIGATIONS

1) Blood Group: .....
2) PCV : .....
3) Cord blood Albumin (mg/dl) .....
4) Serum bilirubin(mg/dl) .....
5) DCT: Positive/Negative

Age of neonate (hrs)	Serum Bilirubin levels (mg/dl)
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....

6)DCT : positive/negative

E <u>OUTCOME</u>

1)Requiring Phototherapy Yes/No

If Yes ,age of neonate (hrs) when started .....

2)Total Duration of Phototherapy .....

3) Requiring Exchange Transfusion Yes/No

If yes ,age of neonate (hrs) when performed .....

Discharged with Advice|DAMA|Death

.....

KEY TO MASTER CHART

BW	:	Birth weight (in kgs)
CBA	:	Cord Blood Albumin (in g/dL)
DOB	:	Date of Birth
ET	:	Exchange Transfusion
F	:	Female
GA	:	Gestational Age (in weeks)
GID	:	Gestation in Days
IP no.	:	Inpatient number
M	:	Male
TOD	:	Type of Delivery
N	:	No
PT	:	Phototherapy
SI NO	:	Serial Number
TSB	:	Total Serum Bilirubin (in mg/dl)
Y	:	Yes
PCV	:	Packet Cell Volume
BG	:	Blood Group
CBA	:	Cord Blood Albumin
Oxy	:	Oxytocin
Miso	:	Misoprostol

MASTER CHART

Slno	Mother Name	Baby sex	IP No	DOB	Maternal data								BW	CBA	BG	PCV	TSB in mg/dl	PT	ET	OUTCOME
					Age	Gravida	Inductionoflabour	Bloodgroup	GA	GID	TOD	GRAVIDA								
1	B/O PADMAMMA	M	913364	24/5/13	20	2	No	B	41WKS AND 2 DAY	289	EmergencyLSCS	2	3.11	3.2	B	58.9	10.3/0.02	no	NO	DISCHARGED
2	B/OARUNA	F	913327	23/5/13	25	2	No	A	40WKS AND 4 DAYS	284	EmergencyLSCS	2	3.2	3.4	A	50.5	6.3/0.03	no	no	DISCHARGED
3	B/O ASHARANI	M	913359	24/513	22	2	No	O	38 WKSAND 5 DAYS	271	Normal	3	2.78	2.6	O	52	14.3/0.28	yes	no	DISCHARGED
4	B/O MANJULA	M	913342	23/5/13	19	1	No	O	4O WKS AND 3 DAYS	283	EmergencyLSCS	2	2.87	3.4	O	60.3	11 .4/0.02	no	no	DISCHARGED
5	B/O ARATHIBAI	M	913928	25/5/13	24	1	No	O	38 WKSAND 2 DAYS	268	Normal	3	2.86	2.4	O	54.5	15.8/0.01	yes	no	DISCHARGED
6	B/O ANUPAMA	M	377399	30/8/13	22	2	No	O	38 WKS AND 4 DAYS	270	ElectiveLSCS	1	3.42	3	AB	51.8	12.2/0.02	yes	NO	DISCHARGED
7	B/O KARISHMA	F	913940	25/5/13	24	2	No	B	40 WKS	280	EmergencyLSCS	2	2.5	3.4	B	51.7	10.3 /0.02	no	no	DISCHARGED
8	B/O SHABANA	F	945024	41556	30	4	No	O	39 WKS AND 1 DAY	274	ElectiveLSCS	1	2.9	3.6	O	51.3	6.8/0.02	no	no	DISCHARGED
9	B/O SUGUNA	F	946953	15/9/13	25	1	No	O	39 WKS AND 3 DAYS	276	Normal	3	2.5	3.4	O	58.5	9.8/0.03	no	no	DISCHARGED
10	B/O SUJATHA	M	946960	16/9/13	22	2	Miso	A	39 WKS AND 5 DAYS	278	Normal	3	2.7	3.3	O	59.2	10.2/0.1	no	no	DISCHARGED
11	B/O NAZHAPASHA	F	379087	16/9/13	20	2	Oxy	O	40 WKS	280	Normal	3	2.9	3.4	B NEGATIVE	60.2	12.4/0.02	no	no	DISCHARGED
12	B/O AYESHA	F	378954	14/9/13	22	2	Miso	O	40 WKS	280	Normal	3	2.9	3.5	O	54.5	12.7/0.1	no	no	DISCHARGED
13	B/O AMRUTHA	M	379264	16/9/13	24	2	Miso	O	40 WKS	280	Normal	3	2.78	2.8	O	52.5	14.2/0.03	yes	no	DISCHARGED
14	B/O SURKYA BEGUM	M	947724	19/9/13	25	4	Oxy	O	40 WKS	280	Normal	3	2.7	3.6	A	56.7	9.8/0.4	no	no	DISCHARGED
15	B/O BHAGYA LAKSHMI	M	948074	21/9/13	30	3	No	O	39 WKS AND 3 DAYS	276	EmergencyLSCS	2	3.19	3.5	O	60.2	11.2/0.03	no	no	DISCHARGED
16	B/O REKHA	M	948440	22/9/13	23	1	No	O	41 WKS AND 1 DAY	288	EmergencyLSCS	2	3.1	3.2	A	58.2	12.0/0.03	NO	NO	DISCHARGED
17	B/O SOWMYA	M	987095	41700	23	1	Oxy	A	37WKS AND 4 DAYS	263	Normal	3	2.5	2.6	O	56.7	16.7/0.01	YES	NO	DISCHARGED
18	B/O KAMALAKSHI	M	987601	41731	30	3	No	B	39 WK AND 4 DAYS	277	ElectiveLSCS	1	3.08	3.1	O	60.1	10.4/0.02	NO	NO	DISCHARGED
19	B/O MANJULA	F	987590	41731	22	4	Miso	A	37WKS AND 4 DAYS	263	Normal	3	3.38	3.1	O	60.4	12.2/0.03	NO	NO	DISCHARGED
20	B/O SYEDA SHABANA	M	988237	41792	25	G5	No	B	39 WKS AND 5 DAYS	278	ElectiveLSCS	1	3.02	3.3	B	50.1	13.0/0.2	NO	NO	DISCHARGED

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21	B/O KAMAKSHI	M	988317	41822	22	1	Oxy	O	42 WKS AND 1 DAY	295	Normal	3	2.8	2.4	B	50.1	17.0/0.2	**YES**	NO	DISCHARGED
22	B/O PREMA	M	988883	41853	20	1	Oxy	B	40 WKS AND 3 DAYS	283	Normal	3	2.6	3.1	O	60.1	10.9/0.1	NO	NO	DISCHARGED
23	B/O PARVATHI	F	988934	41853	22	2	Miso	O	37 WKS	259	Normal	3	2.61	3.4	B	54.5	12.4/0.03	NO	NO	DISCHARGED
24	B/O SARITHA	F	988640	41853	23	3	Miso	O	39 WKS AND 6 DAYS	279	Normal	3	2.98	3.8	O	53.4	7.8/0.4	NO	NO	DISCHARGED
25	B/O MADHAVI	M	988953	41884	21	1	Oxy	B	40 WKS	280	Normal	3	2.5	3.6	O	50.4	12.3/0.01	NO	NO	DISCHARGED
26	B/O CHIKKAREDDAMMA	F	988645	41853	25	3	Oxy	O	38WKS 5 DAYY	271	Normal	3	2.83	3.2	A	60.2	10.3/0.03	NO	NO	DISCHARGED
27	Blo MANORANJINI	M	99245	20/1/15	19	1	No	O	41 wks AND 3DAY	290	EmergencyLSCS	2	3.1	4.4	B	60.4	12.3/0.03	NO	no	DISCHARGED
28	B/O SALMA SULTHANA	F	100893	23/1/15	20	2	No	O	38WKS 6 DAY	271	ElectiveLSCS	1	2.72	3	B	56.8	15.8/0.04	YES	NO	DISCHARGED
29	B/O MAMATHA	F	96077	24/1/15	24	1	Oxy	B	39 WKS	273	Normal	3	2.8	4.3	O	50.4	11.3/0.03	NO	no	DISCHARGED
30	B/O TEJASHWINI	M	100952	23/1/15	21	1	No	O	40 WKS	280	EmergencyLSCS	2	2.55	4.2	O	56.5	10.5/0.02	NO	NO	DISCHARGED
31	B/O LALITHA BAI	M	28333	21/1/15	35	3	Oxy	B	38 WKS	266	Normal	3	2.53	3.8	O	50.4	6.4/0.06	NO	no	DISCHARGED
32	B/O KAVYA	M	28763	24/1/15	20	1	Miso	B	37 WKS	259	Normal	3	2.9	3.5	O	60.2	13.7/0.1	NO	NO	DISCHARGED
33	B/O KAVITHA	F	28762	24/1/15	20	2	No	A	39 WKS AND 5 DAYS	278	EmergencyLSCS	2	2.84	5.1	O	51.2	8.9/0.02	no	no	DISCHARGED
34	B/O TULASAMMA	F	28786	24/1/15	20	1	Miso	O	38 WKS AND 2 DAYS	268	Normal	3	2.7	2.9	B	64.2	15.9/0.03	**YES**	NO	DISCHARGED
35	B/O ANITHA	M	28808	24/1/15	26	1	Oxy	A	40 WKS AND 3 DAYS	283	Normal	3	2.6	3.4	O	58.2	10.4/0.02	NO	NO	DISCHARGED
36	B/O NAGAVENI	F	101415	25/1/15	22	2	No	O	41 WKS AND 5 DAYS	292	ElectiveLSCS	1	2.9	5.3	B	54.5	10.4/0.6	NO	NO	DISCHARGED
37	B/O MANJULA	M	101468	25/1/15	24	3	No	O	40 WKS	280	EmergencyLSCS	2	3	3.7	O	57.8	12.4/0.3	NO	NO	DISCHARGED
38	B/O SALMASULTHANA	F	101417	25/1/15	27	2	No	O	37 WKS AND 4 DAYS	263	ElectiveLSCS	1	2.5	3.6	B	60.2	13.3/0.02	NO	NO	DISCHARGED
39	B/O LAVANYA	F	28830	25/1/15	23	2	No	A	37 WKS	259	ElectiveLSCS	1	2.6	3.1	AB	52.8	13.8/0.02	NO	NO	DISCHARGED
40	B/O SARITHA	F	101504	25/1/15	23	3	Oxy	B	39 WKS AND 2 DAYS	275	Normal	3	2.86	3.9	O	55.4	10.4/0.02	NO	NO	DISCHARGED
41	B/O SWETHA	M	101515	26/1/15	23	2	No	NO	41 WKS AND 6 DAYS	293	EmergencyLSCS	2	3	3.4	O	53.4	13.4/0.02	NO	NO	DISCHARGED
42	B/O GAYATHRI	M	101516	26/1/15	19	1	No	O	38 WKS AND 4 DAYS	270	EmergencyLSCS	2	2.6	4.3	B	59.4	13.4/0.02	NO	NO	DISCHARGED
43	B/O SUMA	M	98979	24/1/15	23	1	Oxy	A	40 WKS	280	Normal	3	2.8	4.2	O	56.7	12.4/0.1	no	no	DISCHARGED
44	B/O VEENA	F	101848	26/1/15	33	2	No	O	39 WKS AND 6 DAYS	279	EmergencyLSCS	2	3.48	3.4	B	54.5	8.4/0.02	no	NO	DISCHARGED
45	B/O RADHA	F	102976	29/1/15	26	2	Miso	A	40 WKS AND 2DAYS	282	Normal	3	2.7	3.4	O	52.4	13.8/0.03	no	no	DISCHARGED

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46	B/O ARUNA	M	103278	29/1/15	22	1	No	O	38 WKS AND 4 DAYS	270	EmergencyLSCS	2	2.97	3.98	B	56.4	11.4/0.02	NO	NO	DISCHARGED
47	B/O SARASWATHI	M	103386	30/1/15	25	2	No	B	41 WKS AND 2 DAYS	289	EmergencyLSCS	2	3.02	3.8	O	60	12.4/0.04	no	no	DISCHARGED
48	B/O CHANDRIKA	F	103384	30/1/15	23	2	No	O	37 WKA AND 1 DAY	260	EmergencyLSCS	2	2.77	4	O	50.4	8.0/0.1	no	no	DISCHARGED
49	B/O MAMATHA	F	103764	30/1/15	24	2	Oxy	O	39 WKS AND 3 DAYS	276	ElectiveLSCS	1	2.88	3.2	O	58.7	13.8/0.1	no	no	DISCHARGED
50	B/O AMARAVATHI	M	103391	30/1/15	22	1	Oxy	O	39 WKS AND 5 DAYS	278	Normal	3	3.25	2.8	B	52.5	16.2/0.01	yes	NO	DISCHARGED
51	B/O BHAVYA	F	29446	30/1/15	20	1	Miso	O	42 WKS AND 2 DAY	296	Normal	3	3.8	3.1	B	56.7	10.5/0.3	no	NO	DISCHARGED
52	B/O RAJESHWARI	M	103772	31/1/15	25	1	Oxy	A	41 WKS AND 2 DAYS	289	Normal	3	2.6	2.9	A	52.6	18.6/0.01	yes	NO	DISCHARGED
53	B/O KEMPAMMA	F	103769	31/1/15	28	3	No	O	41 WKS	287	Normal	3	2.5	3.4	O	50.8	9.8/0.1	no	no	DISCHARGED
54	B/O SHASHIKALA	M	104310	42006	26	2	No	O	40 WKS	280	Normal	3	3.24	4.2	O	60.1	12.33/0..02	NO	no	DISCHARGED
55	B/O CHANDRAKALA	F	105252	42065	23	2	No	O	39 WKS	273	ElectiveLSCS	1	3.42	4	A	56.8	9.0/0.02	no	NO	DISCHARGED
56	B/O SUSHAMA	F	104954	42065	27	2	Oxy	A	42 WK	294	Normal	3	3.4	4	O	59	6.0/0.1	no	NO	DISCHARGED
57	B/O LAKSHMI	M	104960	42065	27	2	Miso	B	38 WKS	266	Normal	3	2.96	3.6	O	58.9	10.9/0.02	no	no	DISCHARGED
58	B/O MANJULA	F	109479	13/2/15	28	2	Oxy	O	39 WKS	273	Normal	3	2.8	2.8	A	60.2	12.0/0.02	yes	no	DISCHARGED
59	B/O JOTHI	M	108974	42310	22	1	No	AB	40 WKS AND 2 DAYS	282	ElectiveLSCS	1	2.9	2.9	O	53.8	11.8/0.6	no	no	DISCHARGED
60	B/O VARALAKSHMI	M	108714	42310	24	2	No	B	38 WKS AND 5 DAYS	271	EmergencyLSCS	2	3.6	3.3	A	58.4	13.38/0.2	no	no	DISCHARGED
61	B/O MUNIYAMMA	M	108983	42310	25	2	No	B	40 WKS AND 5 DAYS	285	EmergencyLSCS	2	2.76	3	O	50.2	16.8/0.2	YES	no	DISCHARGED
62	B/O VARALAKSHMI	F	109488	42340	20	2	Oxy	O	38 WKS AND 6 DAYS	272	Normal	3	2.7	3.4	O	50.2	14.2/0.01	no	no	DISCHARGED
63	B/O JAMRUDH	M	109456	42340	20	2	Miso	O	40 WKS AND 3 DAYS	283	EmergencyLSCS	2	3.24	3.2	O	50.6	11.4/0.03	no	no	DISCHARGED
64	B/O VARALAKSHMI	F	109488	42340	20	2	Oxy	O	38 WKS AND 6 DAYS	272	Normal	3	2.7	3.4	O	50.2	14.2/0.01	no	no	DISCHARGED
65	B/O GEETHA	M	109970	13/2/15	28	2	Miso	O	39 WKS AND 4 DAYS	277	Normal	3	3.6	3.9	A	56.8	10.4/ 0.02	no	no	DISCHARGED
66	B/O DEEPA	M	109787	13/2/15	22	2	Oxy	O	38WKS AND 6 DAYS	272	Normal	3	2.6	3	A	54.8	15.8/0.01	YES	NO	DISCHARGED
67	B/O MAMATHA	F	109957	13/2/15	26	2	No	O	39 WKS AND 3 DAYS	276	EmergencyLSCS	2	2.58	3.8	B	59.8	11.2/0.03	NO	no	DISCHARGED
68	B/OROOPA	F	110939	16/2/15	20	1	No	O	38 WKS AND 6 DAYS	272	EmergencyLSCS	2	3.6	3.8	A NEG	54.8	9/0.01	no	no	DISCHARGED
69	B/O MUNIRATHNAMMA	M	110840	16/2/15	30	1	No	A	40 WKS AND 3 DAYS	283	EmergencyLSCS	2	2.61	3.6	O	53.4	9.8/0.01	NO	NO	DISCHARGED
70	B/O BHAGYAMMA	M	110978	16/2/15	30	2	No	B	38 WKS AND 3 DAYS	269	ElectiveLSCS	1	3.1	3.1	B	50.2	16.34/0.02	YES	no	DISCHARGED

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71	B/O AKSHITHA	M	111005	16/2/15	20	1	No	O	4O WKS AND 4 DAYS	284	EmergencyLSCS	2	3.11	3.3	B	51.8	11.83/0.01	no	NO	DISCHARGED
72	B/O ANITHA	M	110465	16/2/15	18	1	Miso	O	41 WKS AND 2 DAYS	289	EmergencyLSCS	2	2.78	3.6	O	54.8	13.8/0.02	NO	NO	DISCHARGED
73	B/O GAYATHRI	F	110935	16/2/15	22	1	Oxy	A	40 WKS AND 2 DAYS	282	Normal	3	2.85	3	A	56.8	16.3/0.8	yes	NO	DISCHARGED
74	B/O NOORJHAN	M	111025	17/2/15	30	6	Oxy	O	39 WKS	273	ElectiveLSCS	1	3.68	3.3	O NEG	51.6	14.86/0.01	no	NO	DISCHARGED
75	B/O YASHODHA	F	111995	19/2/15	23	1	Oxy	B	42 WKS	294	EmergencyLSCS	2	3.2	3.5	O	51.6	9.2/0.1	NO	no	DISCHARGED
76	B/O ADILAKSHMI	M	112540	20/2/15	25	1	No	B	41 WKS	287	EmergencyLSCS	2	2.96	3.8	A	50.8	13.04/0.02	no	NO	DISCHARGED
77	B/O VANITHA	F	113851	21/2/15	27	3	No	O	39 WKS	273	EmergencyLSCS	2	3.27	4.1	O	56.8	6.8/0.01	NO	NO	DISCHARGED
78	B/O RESHMI	F	113809	21/2/15	21	2	No	O	39 WKS	273	EmergencyLSCS	2	2.92	3.6	O	50.8	10.2/0.1	NO	NO	DISCHARGED
79	B/O CHOWDAMMA	M	113774	21/2/15	31	1	No	A	39 WKS	273	EmergencyLSCS	2	3.3	3.7	O	56.7	10.2/0.1	no	no	DISCHARGED
80	B/O MAMATHA	M	111991	19/2/15	22	2	Oxy	AB	39 WKS AND 4 DAYS	277	EmergencyLSCS	2	3	3.6	O	52.4	11.2/0.01	NO	NO	DISCHARGED
81	B/0 FARDANA TAJ	M	111987	19/2/15	20	1	Oxy	O	38 WKS AND 4 DAYS	270	EmergencyLSCS	2	3	3.2	O	50.3	11.0/0..1	NO	NO	DISCHARGED
82	B/O SHILPA	F	111993	19/2/15	23	1	Miso	B	40 WKS AND 2 DAYS	282	EmergencyLSCS	2	2.6	3	O	54.6	10.2/0.01	NO	NO	DISCHARGED
83	B/O MAMATHA	M	113835	22/2/15	25	2	Oxy	O	39 WKS AND 1 DAY	274	Normal	3	3.32	3.2	A	52.4	8.3/0.01	NO	NO	DISCHARGED
84	B/O SHAMALAMMA	F	113910	22/2/15	30	6	Oxy	O	39 WKS AND 2 DAYS	275	Normal	3	2.92	3	O	54.6	10.2/0.02	no	NO	DISCHARGED
85	B/O PRABHAVATHI	M	113947	23/2/15	21	1	Miso	B	38 WKS AND 1 DAY	267	Normal	3	2.56	2.5	O	54.5	16.8/0.1	YES	NO	DISCHARGED
86	B/O NAGAMANI	M	113791	21/2/15	24	1	Oxy	O	4O WKS AND 3 DAYS	283	Normal	3	2.86	3.4	A	50.4	9.8/0.01	NO	NO	DISCHARGED
87	B/O JAMUNA	M	114442	23/2/15	19	1	Oxy	A	39 WKS AND 6 DAYS	279	Normal	3	3.05	3.7	O	56.7	10.2/0.01	NO	NO	DISCHARGED
88	B/O VARALAKSHMI	F	113930	23/2/15	23	1	Oxy	O	38 WKS AND 6 DAYS	272	Normal	3	2.84	2.8	O	60.2	17.0/0.02	YES	NO	DISCHARGED
89	B/O SAVITHRAMMA	M	113932	23/2/15	22	1	Miso	O	40 WKS	280	Normal	3	3.04	2.9	AB	58.6	15.8/0.02	YES	NO	DISCHARGED
90	B/O VIDYA	M	128533	42066	26	2	No	A	41 WKS AND 2 DAYS	289	ElectiveLSCS	1	2.7	3.4	O	56.1	11.3/0.01	NO	NO	DISCHARGED
91	B/O KALAVATHI	F	128042	29/3/15	25	1	No	B	40 WKS AND 4 DAYS	284	EmergencyLSCS	2	3.2	3.2	B	61.2	8.4/0.02	NO	NO	DISCHARGED
92	B/O SUMA	M	128543	30/3/15	28	1	Oxy	AB	4O WKS AND 4 DAYS	284	ElectiveLSCS	1	2.76	3.8	A	54.5	12.3/0.01	NO	NO	DISCHARGED
93	B/O NAGALAKSHMI	M	128519	30/3/15	20	1	No	A	4O WKS AND 1 DAY	281	EmergencyLSCS	2	2.6	3.5	A	60.2	9.4/0.02	NO	NO	DISCHARGED
94	B/O NAGARATHNA	F	128918	31/3/15	24	1	No	O	39 WKS AND 1 DAY	274	EmergencyLSCS	2	2.91	2.6	B NEGATIVE	56.7	15.6/0.04	YES	NO	DISCHARGED
95	B/O NETHRA	M	128539	31/3/15	25	2	Oxy	AB	40 WKS AND 1 DAY	281	ElectiveLSCS	1	3	3.4	O	53.4	8.6/0.01	NO	NO	DISCHARGED

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96	B/O VANAJA	F	128888	31/3/15	25	2	Miso	O	39 WKS AND 6 DAYS	279	EmergencyLSCS	2	3.1	3	O	56.7	9.8/0.03	NO	NO	DISCHARGED
97	B/O PREMA	F	128578	31/3/15	20	1	No	O	39 WKS AND 3 DAYS	276	EmergencyLSCS	2	3	3.2	O	63.1	10.2/0.02	NO	NO	DISCHARGED
98	B/O KAVITHA	M	128534	31/3/15	25	2	No	A	39 WKS AND 5 DAYS	278	EmergencyLSCS	2	2.7	3.1	O	60.2	11.4/0.02	NO	NO	DISCHARGED
99	B/O NETHRAVATHI	F	128892	31/3/15	23	1	No	O	40 WKS AND 1 DAY	281	EmergencyLSCS	2	3.2	3	O	56.8	12.9/0.01	NO	NO	DISCHARGED
100	B/O PREMA	F	128934	42008	22	2	Oxy	A	40 WKS AND 3 DAYS	283	ElectiveLSCS	1	2.6	3.2	O	60.2	11.7/0.02	NO	NO	DISCHARGED
101	B/O SARASWATHI	F	128935	42008	23	1	Miso	O	37 WKS AND 3 DAYS	262	EmergencyLSCS	2	2.56	3.4	Notdone			NO	NO	DISCHARGED
102	B/O NISHATHI FATHIMA	M	124578	42039	25	3	Oxy	O	38 WKS AND 4 DAYS	270	Normal	3	2.72	3.2	Notdone			NO	NO	DISCHARGED
103	B/O THABASUM TAJ	M	988318	41822	25	4	Oxy	AB	38 WKS AND 3 DAYS	269	Normal	3	2.97	3.4	Notdone			NO	NO	DISCHARGED
104	B/O VIJAYA	F	988789	41884	28	2	Miso	O	39 WKS AND 2 DAYS	275	EmergencyLSCS	2	2.5	3.1	Notdone			NO	NO	DISCHARGED
105	B/O MADAHAVI	M	988953	41884	21	1	Oxy	B	40 WKS	280	Normal	3	2.5	3.8	Notdone			NO	NO	DISCHARGED
106	B/O PARVATHI	M	987619	41824	35	2	Oxy	B	38 WKS AND 6 DAYS	272	ElectiveLSCS	1	4.05	3.1	Notdone			NO	NO	DISCHARGED
107	B/O BHARATHI	M	948352	21/9/13	23	1	No	O	39 WKS AND 4 DAYS	277	EmergencyLSCS	2	2.69	3.9	Notdone			NO	NO	DISCHARGED
108	B/O VANI	M	98756	21/9/13	19	1	Oxy	AB	40 WKS AND 1 DAY	281	Normal	3	3.38	3.3	Notdone			NO	NO	DISCHARGED
109	B/O ARUNA	M	377225	28/8/13	24	2	Miso	A	38 WKS AND 4 DAYS	270	Normal	3	2.58	3.5	Notdone			NO	NO	DISCHARGED
110	B/O AYESHA	F	378954	14/9/13	22	2	Oxy	O	40 WKS	280	Normal	3	2.9	3.2	Notdone			NO	NO	DISCHARGED
111	B/O SUJATHA	M	379261	16/9/13	22	2	Miso	A	39 WKS AND 5 DAYS	278	Normal	3	2.7	3.3	Notdone			NO	NO	DISCHARGED
112	B/O NAZHAPASHA	F	379087	16/9/13	20	2	Oxy	O	4O WKS AND 2 DAYS	282	Normal	3	2.9	3.4	Notdone			NO	NO	DISCHARGED
113	B/O MANJULA	F	948067	18/9/13	22	1	No	O	38 WKS	266	ElectiveLSCS	1	2.67	3	Notdone			NO	NO	DISCHARGED
114	B/O AMARAVATHI	F	948234	13/9/13	24	2	Miso	O	40 WKS	280	Normal	3	2.5	3.4	Notdone			NO	NO	DISCHARGED
115	B/O BHARATHI	F	104416	42037	24	3	Oxy	A	40 WKS AND 6 DAY	286	EmergencyLSCS	2	2.9	4	Notdone			NO	NO	DISCHARGED
116	B/O NETHRAVATHI	F	129318	42008	26	2	No	A	38 WKS AND 3 DAYS	269	ElectiveLSCS	1	3.2	3.2	Notdone			NO	NO	DISCHARGED
117	B/O PREMA	F	128934	42008	22	2	No	O	40 WKS AND 2 DAYS	282	ElectiveLSCS	1	2.6	3.8	Notdone			NO	NO	DISCHARGED
118	VARALAKSHMI	M	108714	42310	24	2	No	B	38WKS AND 5 DAYS	271	EmergencyLSCS	2	3.6	3.2	Notdone			NO	NO	DISCHARGED
119	GEETHA	M	109970	13/2/15	28	2	Miso	O	39 WKS AND 4 DAYS	277	Normal	3	2.6	3	Notdone			NO	NO	DISCHARGED
120	VARALAKSHMI	F	109488	42340	20	2	Oxy	O	38 WKS AND 6 DAYS	272	Normal	3	2.7	3.4	Notdone			NO	NO	DISCHARGED

MASTER CHART

121	MAMATHA	F	109957	13/2/15	26	2	No	O	39 WKS AND 2DAYS	275	EmergencyLSCS	2	2.58	3.9	Notdone			NO	NO	DISCHARGED
122	DEEPA	M	109787	13/2/15	22	2	Oxy	O	38 WKS AND 6 DAYS	272	Normal	3	2.6	4	Notdone			NO	NO	DISCHARGED
123	ANITHA	M	110465	16/2/15	18	1	No	O	41 WKS AND 2 DAYS	289	EmergencyLSCS	2	2.78	3.8	Notdone			NO	NO	DISCHARGED
124	AKSHITHA	M	111005	16/2/15	20	1	No	O	40 WKS AND 4 DAYS	284	EmergencyLSCS	2	3.11	3.3	Notdone			NO	NO	DISCHARGED
125	ROOPA	F	110939	16/2/15	20	1	No	O	38 WKS AND 6 DAYS	272	EmergencyLSCS	2	3.6	3.4	Notdone			NO	NO	DISCHARGED
126	MUNIRATHNAMMA	M	110840	16/2/15	30	1	No	A	40 WKS AND 3 DAYS	283	EmergencyLSCS	2	2.6	3.8	Notdone			NO	NO	DISCHARGED
127	BHAGYAMMA	M	110978	16/2/15	30	2	No	B	38 WKS AND 3 DAYS	269	ElectiveLSCS	1	3.1	3.3	Notdone			NO	NO	DISCHARGED
128	GAYATHRI	F	110935	16/2/15	22	1	Oxy	A	40 WKS AND 2 DAYS	282	Normal	3	2.85	3.5	Notdone			NO	NO	DISCHARGED
129	NOORJHAN	M	111025	17/2/15	30	6	No	O	39 WKS	273	ElectiveLSCS	1	3.68	3.2	Notdone			NO	NO	DISCHARGED
130	SHILPA	F	111993	19/2/15	23	1	No	B	40 WKS AND 2 DAYS	282	EmergencyLSCS	2	2.6	3.3	Notdone			NO	NO	DISCHARGED