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Bilirubin Rebound after Intensive Phototherapy in Neonatal Jaundice: In Tertiary Care Hospital

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I. Introduction

Jaundice is the yellowish discoloration of skin and sclera due to elevated serum concentration of bilirubin. Most adults are jaundiced when total serum bilirubin level exceeds 2 mg/dl. Neonates however not appear jaundiced until the total serum bilirubin concentration exceeds 5 to 7 mg/dl.[1] Neonatal jaundice occurs in nearly 60% of term and 80% of preterm infants during the first week of life.[2]

Although jaundice is present in most newborns and is usually physiological, it is imperative to carefully monitor newborns to identify those at risk of developing bilirubin induced neurologic dysfunction. Acute bilirubin encephalopathy is caused by the toxic effects of unconjugated bilirubin on the CNS. Symptoms include poor feeding, lethargy and high pitched cry in a jaundiced infant. If acute bilirubin encephalopathy is untreated, it may induce kernicterus and progress rapidly to advanced manifestations such as opisthotonus and seizure.[3]

Kernicterus is the chronic permanent clinical sequelae of bilirubin toxicity due to bilirubin staining of the brain in the region of basal ganglia, hippocampus, substantia nigra and brainstem nuclei; it is characterized by severe athetoid cerebral palsy, paralysis of upward gaze, hearing loss and intellectual impairment.[4]

Early detection and prevention of these complications has led to recommendations to screen all neonates for hyperbilirubinemia.[3-5]

Phototherapy is used worldwide for the treatment of neonatal jaundice.[6-7] The need for exchange transfusion has been significantly reduced since the introduction of phototherapy.[8] It is effective, noninvasive, convenient, easy to use and not expensive.[9-10] However the prolongation of phototherapy is not justified since it has many short-term and possible long-term side effects.[9-10] It leads to prolonged hospitalization and may negatively affect the mother infant bonding. At the same time, discontinuation of phototherapy too early may allow bilirubin to rise to unacceptable levels, which may require reinstitution of phototherapy.

Although bilirubin absorbs visible light with wavelengths of approximately 400 to 500 nm, the most effective lights for phototherapy are those with high-energy output near the maximum adsorption peak of bilirubin (450 to 460 nm). Special blue lamps with peak output at 425 to 475 nm are the most efficient for phototherapy. Cool white lamps with a principal peak at 550 to 600 nm and a range of 380 to 700 nm are usually adequate for treatment. Fiberoptic phototherapy (phototherapy blanket) have been shown to reduce bilirubin levels although less effectively for term infants, likely due to the limited skin exposure it can offer.[11]

Intensive phototherapy implies irradiance in the blue-green spectrum (wavelengths of approximately 430–490 nm) of at least 30 $\mu W/cm^2$/ nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's surface area as possible. This can be achieved by placing the infant on bili-blanket and using additional overhead phototherapy units with special blue lights and lowering the phototherapy units to within a distance of 15-20 cm.[4]

Sigificant bilirubin rebound (SBR) is defined as postphototherapy bilirubin level needing reinstitution of phototherapy.[11]

The 1994 Practice Parameter of the American Academy of Pediatrics (AAP), which was applicable at the time this study was being performed, but not applicable to neonates with hemolytic conditions, recommended that in most cases no further measurement of bilirubin is necessary following discontinuation of phototherapy, except possibly for cases in which phototherapy was instituted early and discontinued before the infant was 3–4 days old. In July 2004, AAP issued a revised clinical guideline, "Management of hyperbilirubinemia in the newborn infants 35 or more weeks of gestation". The recommendations suggested that discharge from hospital need not be delayed in order to observe an infant for rebound. The present recommendation is to follow up bilirubin measurement within 24 hours of discharge for those cases in which phototherapy was used for neonates with hemolytic diseases, initiated early, or discontinued before the infant is

3–4 days old. The Committee observed significant rebound among neonates who had been rehospitalised for hyperbilirubinaemia to be a rare occurrence and suggested a bilirubin measurement or clinical evaluation after 24 hours in these infants as a clinical option.[4]

Neonates with Coombs positive isoimmunisation, borderline prematurity, onset of phototherapy ≤72 hours, or a post-phototherapy rate of bilirubin rise greater than expected for age in hours, should be regarded as high risk for bilirubin rebound. On the other hand, babies readmitted for hyperbilirubinemia other than hemolytic etiology appear to be at low risk. No set of recommendations can be definitely conclusive. Post-phototherapy bilirubin follow up is essential and it should also incorporate a combined approach of individualisation, evaluation of risk factors, and application of common sense.[13]

Though various studies had been done for detection of bilirubin rebound worldwide, but only few studies had been so far conducted in India, specially in the eastern region.

The present study has been carried out to find out the incidence of rebound hyperbilirubinemia in babies treated with phototherapy and the relation with gestational age, birth weight, prematurity etc. in Neonatal Intensive Care Unit of Institute of Child Health, Kolkata during the period from June 2010 to May 2011.

II. Review Of Literature

Neonatal hyperbilirubinemia

The normal adult serum bilirubin is <1 mg/dl. Adult appears jaundiced when the serum bilirubin is >2 mg/dl, and newborn appears jaundiced when it is >7 mg/dl.[11] Neonatal jaundice occurs in nearly 60% of term and 80% of preterm infants during the first week of life.[2] Also 6.1% of well term newborns have a maximum serum bilirubin level >12.9 mg/dl. A serum bilirubin level >15 mg/dl is found in 3% of normal term babies.[11]

Source of bilirubin

Bilirubin is derived from the breakdown of heme-containing proteins in the reticuloendothelial system. The normal newborn produces 6 to 10 mg of bilirubin/kg/day, as opposed to the production of 3 to 4 mg/kg/day in the adult.[11]

1. The major heme-containing protein is red blood cell (RBC) hemoglobin. Hemoglobin released from senescent RBCs in the reticuloendothelial systems is the source of 75% of all bilirubin production. One gram of hemoglobin produces 34 mg of bilirubin. Accelerated release of hemoglobin from RBCs is the cause of hyperbilirubinemia in isoimmunization (e.g. Rh and ABO incompatibility), erythrocyte biochemical abnormalities (e.g. glucose-6- phosphate dehydrogenase and pyruvate kinase deficiencies), abnormal erythrocyte morphology (e.g. hereditary spherocytosis, sequestrated blood and polycythemia.[11]

2. The other 25% of bilirubin is called early-labelled 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 and peroxidase), and from free heme.[11]

Bilirubin metabolism

The heme ring from heme-containing proteins is oxidized in reticuloendothelial cells to biliverdin by the microsomal enzyme heme oxygenase. This reaction releases carbon monoxide (CO) and iron. Biliverdin is then reduced to bilirubin by the enzyme biliverdin reductase. Catabolism of 1 mol of hemoglobin produces 1 mol each of CO and bilirubin.[11]

1. **Transport**. Bilirubin is nonpolar, insoluble in water, and is transported to liver cells bound to serum albumin. Bilirubin bound to albumin does not usually enter the central nervous system and is thought to be nontoxic.

2. **Uptake**. Nonpolar, fat-soluble bilirubin cross the hepatocyte plasma membrane and is bound mainly to cytoplasmic ligandin (Y protein) for transport to the smooth endoplasmic reticulum.

3. **Conjugation**. Unconjugated bilirubin (UCB) is converted to water-soluble conjugated bilirubin (CB) in the smooth endoplasmic reticulum by uridine diphosphate glucoronyl-transferase 1A1 (UGT 1A1). The monoglucoronide may be further conjugated to bilirubin diglucoronide. Both mono- and diglucoronide forms of CB are able to be excreted into the bile canaliculi against a concentration gradient.

4. **Excretion**. CB in the biliary tree enters the gastrointestinal tract and is then eliminated from the body in the stool. CB is not normally resorbed from the bowel unless it is converted back to UCB by the intestinal enzyme β- glucoronidase.[11]
Resorption of bilirubin from gastrointestinal tract and delivery back to the liver for reconjugation is called enterohepatic circulation.[11]

Normal bilirubin metabolism and bilirubin metabolism during phototherapy is shown in Fig 1.

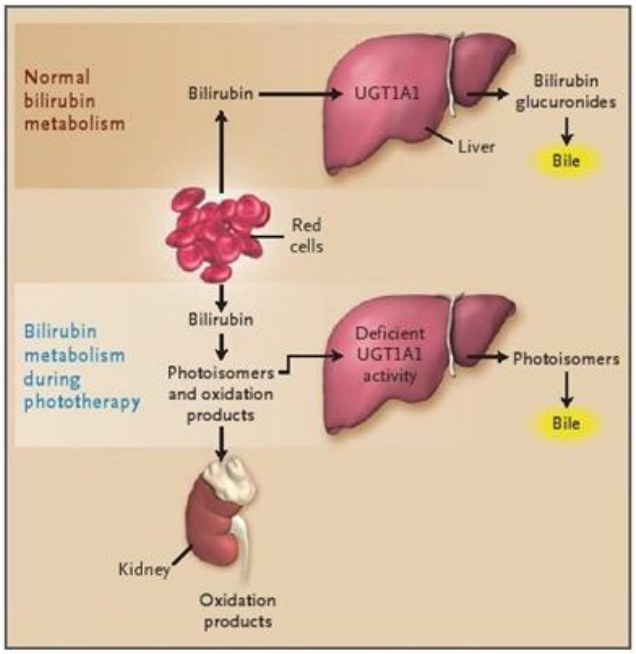


Fig. 1: Normal bilirubin metabolism and bilirubin metabolism during phototherapy[14]

Physiological jaundice

Visible jaundice usually appears between 24-72 hours of age. Total serum bilirubin level usually rises in full-term infants to a peak of 6 to 8 mg/dl by 3 days of age and then falls. A rise to 12 mg/dl is in the physiological range. In premature infants, the peak may be 10 to 12 mg/dl on the 5th day of life, possibly rising over 15 mg/dl without any specific abnormality of bilirubin metabolism. Levels <2 mg/dl may not be seen until 1 month of age in both full-term and premature infants. Safe bilirubin levels in prematures vary according to gestational age.[11]

This "normal jaundice" is attributed to the following mechanism:[11]

I. Increased bilirubin production due to

a. Increased RBC volume per kilogram and decreased RBC survival (90 days versus 120 days) in infants compared with adults.

b. Increased ineffective erythropoiesis and increased turnover of nonhemoglobin heme-protein.

II. Increased enterohepatic circulation caused by high levels of intestinal β- glucoronidase, proponderence of bilirubin monoglucoronide rather than diglucoronide, decreased intestinal bacteria and decreased gut motility with poor evacuation of bilirubin laden meconium.

III. Defective uptake of bilirubin from plasma caused by decreased ligandin and

binding of ligandin by other anions.

IV. Defective conjugation due to decreased UGT-1A1 activity.

V. Decreased hepatic excretion of bilirubin.

Pathological jaundice

Pathological jaundice may not be easy to distinguish from physiological jaundice. Total serum bilirubin (TSB) concentration have been defined as non- physiologic if concentration exceeds 5 mg/dl on first day of life in term neonate, 10 mg/dl on second day, or 12-13 mg/dl thereafter.[1] Any TSB elevation exceeding 17 mg/dl should be presumed pathologic and warrants investigation for a cause and possible intervention, such as phototherapy. Appearance of jaundice within 24 hours, peak TSB levels above the expected normal range (Fig. 2), presence of clinical jaundice beyond 3 weeks and conjugated bilirubin (dark urine staining the clothes & light colored stool) would be categorized under pathological jaundice.

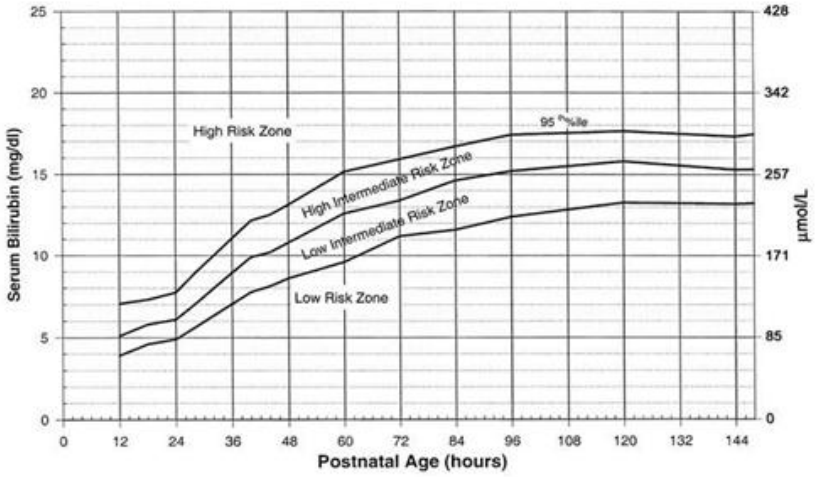


Fig.2: Normogram for designation of risk in 2840 well newborns at 36 or more weeks gestational age with birth weight of 2000 g or more or 35 or more weeks gestational age and birth weight of 2500 g or more base on the hour-specific serum bilirubin values. The serum bilirubin level was obtained before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level exceeding the 95th percentile (high risk zone).[4]

In addition to using the time based nomogram, the physician must be aware of the risk factors most often associated with the development of severe hyperbilirubinemia, as listed in Table 1.[4]

Table. 1: Risk factors for development of severe hyperbilirubinemia in infants of 35 or more weeks gestation (in approximate order of importance)

Major risk factors

Predischarge TSB or TcB level in the high-risk zone (Fig 2)
Jaundice observed in the first 24 h

Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated ETCOc

Gestational age 35–36 wk
Previous sibling received phototherapy
Cephalohematoma or significant bruising

Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive

East Asian race

Minor risk factors

Predischarge TSB or TcB level in the high intermediate-risk zone (Fig 2) Gestational age 37–38 wk

Jaundice observed before discharge
Previous sibling with jaundice

Macrosomic infant of a diabetic mother
Maternal age ≥25 years
Male gender

Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)

TSB or TcB level in the low-risk zone (Fig 2)
Gestational age ≥41 wk
Exclusive bottle feeding
Black race

Discharge from hospital after 72 h *Race as defined by mother's description.

TSB=Total serum bilirubin; TcB=Transcutaneous bilirubin; G6PD= Glucose-6- phpsphate dehydrogenase; ETCOc=End-tidal carbon monoxide

Bilirubin toxicity
Acute bilirubin encephalopathy
The clinical presentation of acute bilirubin encephalopathy can be divided into three phases:

1. *Early phase*: In the early phase of acute bilirubin encephalopathy, severely jaundiced infants become lethargic and hypotonic and suck poorly.[15]

2. *Intermediate phase*: It is characterized by moderate stupor, irritability and hypertonia. The infant may develop fever and high-pitched cry, which may alternate with drowsiness and hypotonia. The hypertonia is manifested by backward arching of the neck (retrocollis) and trunk (opisthotonus). There is anecdotal evidence that an exchange transfusion at this stage, in some cases, might reverse the central nervous system changes.[16]

3. *Advanced phase*: CNS damage is probably irreversible and is characterized by pronounced retrocollis-opisthotonus,shrill cry, no feeding, apnea, fever, deep stupor to coma, sometimes seizures and death.[15,17]

Kernicterus

Kernicterus is a pathologic diagnosis and refers to yellow staining of the brain by bilirubin together with evidence of neuronal injury. The use of term Kernicterus in the clinical setting is used to denote the chronic and permanent sequele of bilirubin toxicity.[18,19,20]

In the chronic form of bilirubin encephalopathy surviving infants may develop a severe form of athetoid cerebral palsy, auditory dysfunction, dental enamel dysplasia, paralysis of upward gaze and less often intellectual and other handicaps. Most infants who develop Kernicterus have manifested some or all of the signs listed above in the acute phase of bilirubin encephalopathy. However, occasionally there are infants who have developed very high bilirubin levels and subsequently the signs of kernicterus but have exhibited few, if any, antecedent clinical signs of acute bilirubin encephalopathy.[4,17,21]

The American Academy of Pediatrics: Subcommittte on Hyperbilirubinemia published a guideline for the management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation.[4]

The following are the key elements of the recommendations provided by this guideline. Clinicians should:
1. Promote and support successful breastfeeding.
2. Establish nursery protocols for the identification and evaluation of hyperbilirubinemia.
3. Measure the total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level on infants jaundiced in the first 24 hours.
4. Recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.
5. Interpret all bilirubin levels according to the infant's age in hours.
6. Recognize that infants at less than 38 weeks' gestation, particularly those who are breastfed, are at higher risk of developing hyperbilirubinemia and require closer surveillance and monitoring.
7. Perform a systematic assessment on all infants before discharge for the risk of severe hyperbilirubinemia.

8. Provide parents with written and verbal information about newborn jaundice.
9. Provide appropriate follow-up based on the time of discharge and the risk assessment.
10. Treat newborns, when indicated, with phototherapy or exchange transfusion.

Clinical assessment

Originally described by Kramer, dermal staining of bilirubin may be used as clinical guide to the level of jaundice. Dermal staining in newborns progress in a cephalo-caudal direction[22]. The newborn should be examined in good daylight. The skin should be blanched with digital pressure and the underlying color of skin and subcutaneous tissue should be noted. A rough guide for level of dermal staining with level of bilirubin is included in Table 2.

Table 2. Guide to dermal staining with level of bilirubin (Modified from Kramer's original article)[22]

Area of baby	**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

However, visual estimation of bilirubin levels from the degree of jaundice can led to errors,[23,24] particularly in darkly pigmented infants.

Laboratory evaluation

A TcB and/or TSB measurement should be performed on every infant who is jaundiced in the first 24 hours after birth.[25] The need for and timing of a repeat TcB or TSB measurement, will depend on the zone in which the TSB level falls (Fig 2),[4] the age of the infant and the evaluation of the hyperbilirubinemia.

Recommendations for TSB measurement after the age of 24 hours are provided in Table 3.[4]

Table 3: Laboratory Evaluation of the Jaundiced Infant of 35 or More Weeks' Gestation[4]

Indications	Assessments
Jaundice in first 24 h	Measure TcB and/or TSB
Jaundice appears excessive for infant's age	Measure TcB and/or TSB
Infant receiving phototherapy or TSB rising rapidly (ie, crossing percentiles [Fig 2]) and unexplained by history and physical examination	Blood type and Coombs' test, if not obtained with cord blood Complete blood count and smear Measure direct or conjugated bilirubin It is an option to perform reticulocyte count, G6PD, and ETCOc, if available Repeat TSB in 4–24 h depending on infant's age and TSB level
TSB concentration approaching exchange levels or not responding to phototherapy	Perform reticulocyte count, G6PD, albumin, ETCOc, if available
Elevated direct (or conjugated) bilirubin level	Do urinalysis and urine culture. Evaluate for sepsis if indicated by history and physical examination
Jaundice present at or beyond age 3 wk, or sick infant	Total and direct (or conjugated) bilirubin level If direct bilirubin elevated, evaluate for causes of cholestasis Check results of newborn thyroid and galactosemia screen, and evaluate infant for signs or symptoms of hypothyroidism

Phototherapy

Although bilirubin absorbs visible light with wavelengths of approximately 400 to 500 nm, the most effective lights for phototherapy are those with high-energy output near the maximum adsorption peak of bilirubin (450 to 460 nm) as shown in Fig.3. Special blue lamps with peak output at 425 to 475 nm are the most efficient for phototherapy.[6] Cool white lamps with a principal peak at 550 to 600 nm and a range of 380 to 700 nm are usually adequate for treatment. Fiberoptic phototherapy (phototherapy blanket) have been shown to reduce bilirubin levels although less effectively for term infants, likely due to the limited skin exposure it can offer.[11]

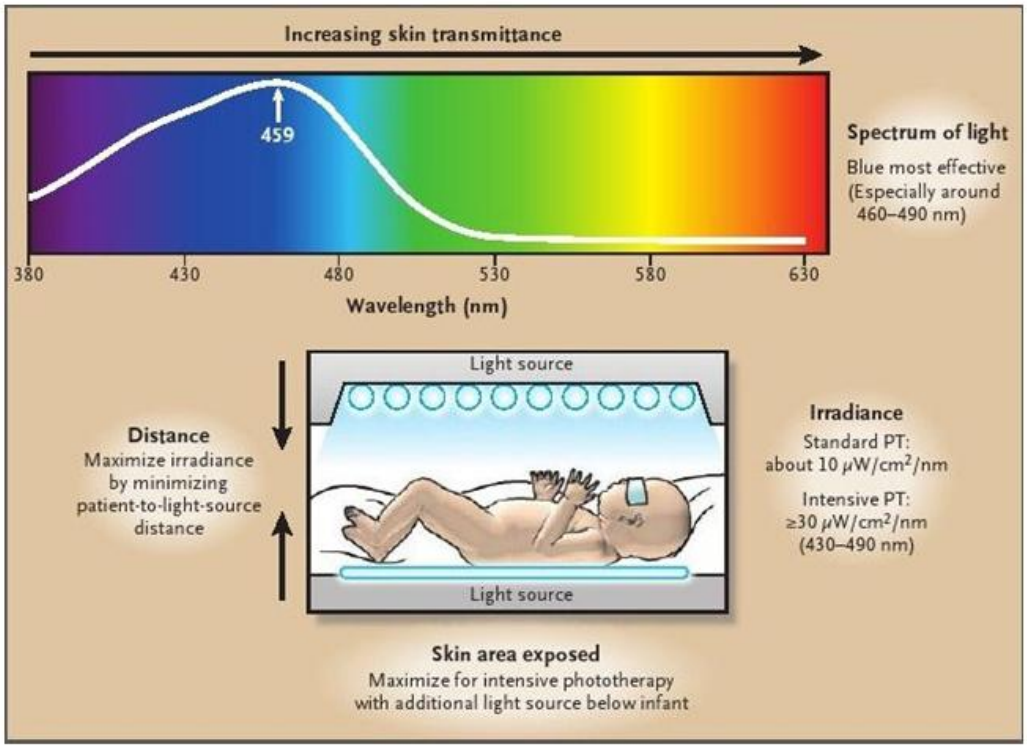


Fig.3: Important Factors in the Efficacy of Phototherapy[14]

Mechanism of phototherapy

When bilirubin adsorbs light, three types of photochemical reactions occurs.[11]

1. Photoisomerization occurs in the extravascular space of skin. The natural isomer of UCB (4Z, 15 Z) is instantaneously converted to a less-toxic polar isomer (4Z, 15 E) that diffuses into the blood and is excreted into the bile without conjugation. After approximately 12 hours of phototherapy, the photoisomers make up approximately 20% of total bilirubin. Photoisomerization occurs at low-dose phototherapy (6μW/cm^2/nm) with no significant benefit from doubling the irradiance.

2. Structural isomerization is the intramolecular cyclization of bilirubin to lumirubin. Lumirubin makes up 2% to 6% of serum concentration of bilirubin during phototherapy and is rapidly excreted in the bile and urine without conjugation. Unlike photoisomerization, the conversion of bilirubin to lumirubin is irreversible, and it can not be reabsorbed. It is the most important pathway for the lowering of serum bilirubin levels and is strongly related to the dose of phototherapy used in the range of 6 to 12 μW/cm^2/nm.

3. The slow process of **photo-oxidation** converts bilirubin to small polar products that are excreted in the urine. It is the least important reaction for lowering bilirubin levels.

Mechanism of phototherapy is shown in Fig.4

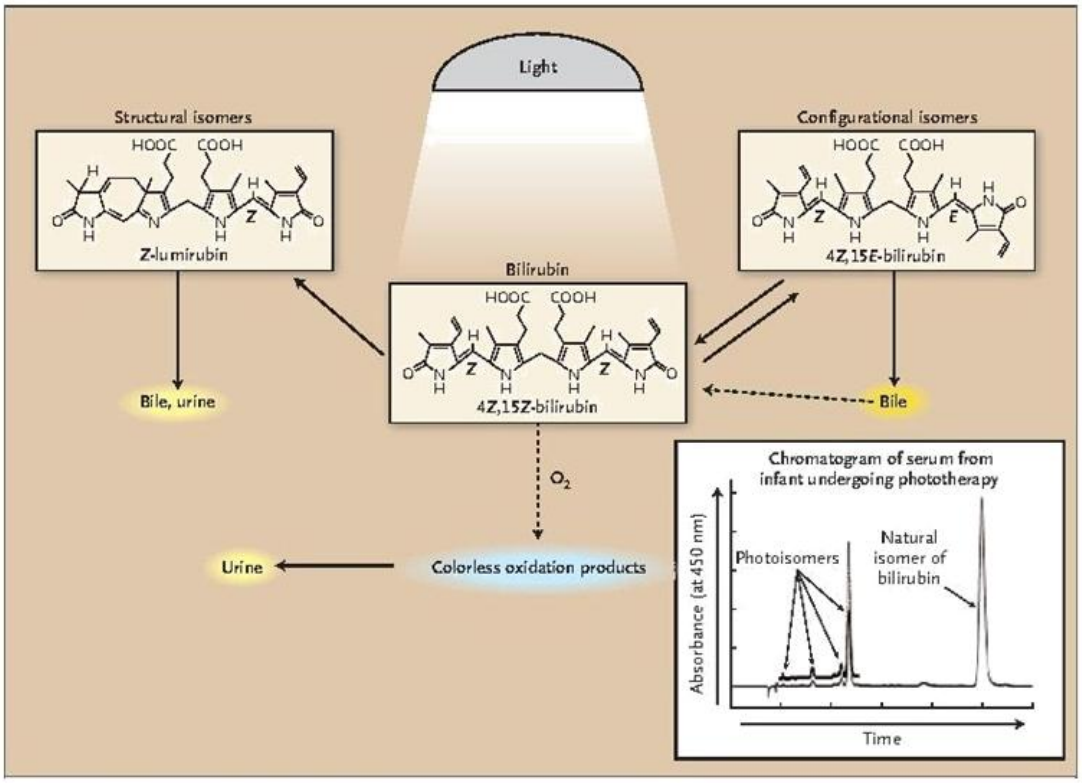


Fig.4: Mechanism of phototherapy[14]

Side effects of phototherapy

Reports of clinically significant toxicity from phototherapy are rare.[27,28] In infants with cholestasis, phototherapy can produce the bronze baby syndrome.[29,30] When phototherapy is stopped and cholestasis resolves, the coloration disappears. Rare purpuric and bullous eruptions have also been reported in infants with severe cholestatic jaundice who are receiving phototherapy' [31,32] probably as a result of sensitization by accumulating porphyrins. An erythematous rash can occur in infants treated with tin- mesoporphyrin who are subsequently exposed to sunlight or daylight fluorescent bulbs.[23] Congenital porphyria, a family history of porphyria, and concomitant use of photosensitizing drugs or other agents are absolute contraindications to phototherapy; severe blistering and agitation during phototherapy could be a sign of congenital porphyria.[24] Conventional phototherapy can produce an acute change in the infant's thermal environment, leading to an increase in peripheral blood flow and insensible water loss.[25,33] In term infants, left ventricular output and renal blood flow velocity (RBFV) decreases, whereas left pulmonary artery and cerebral blood flow velocity (CBFV) increases. In preterm, CBFV also increases and RBFV decreases. All velocities return to baseline after discontinuation of phototherapy.[34,35] A recent study suggested that intensive phototherapy might increase the number of atypical melanocytic nevi identified at school age,[36] although other research has not shown this association.[37] Intensive phototherapy does not cause hemolysis.[38] Swedish studies have suggested that phototherapy is associated with type 1 diabetes[39] and, possibly, asthma.[40] Because bilirubin is a powerful antioxidant,[41] lowering total serum bilirubin levels, particularly in an infant with very low birth weight, could have undesirable consequences,[42] but none have yet been clearly identified.

Intensive Phototherapy

Intensive phototherapy implies irradiance in the blue-green spectrum (wavelengths of approximately 430–490 nm) of at least 30 μW/cm^2/ nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's surface area as possible.[4]

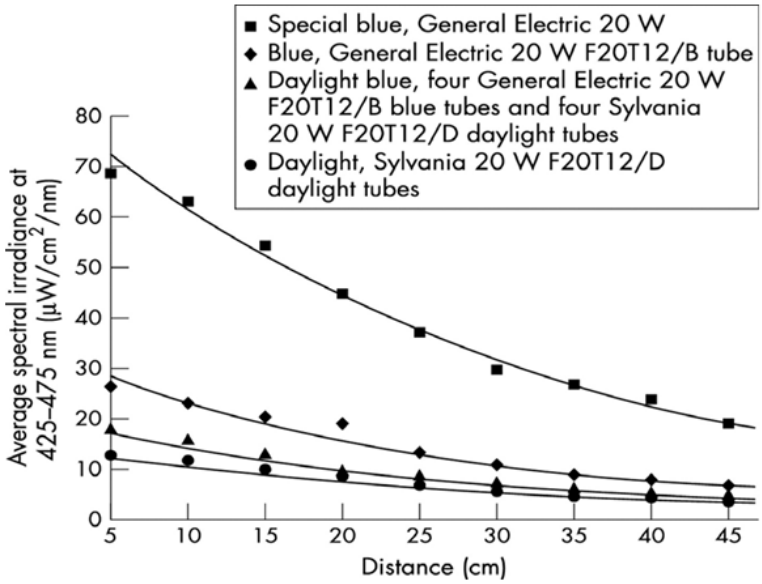


Fig 5. Effect of light source and distance from the light source to the infant on average spectral irradiance[4]

As can be seen in Fig 5, the distance of the light source from the infant has a dramatic effect on the spectral irradiance, and this effect is most significant when special blue tubes are used. To take advantage of this effect, the fluorescent tubes should be placed as close to the infant as possible. To do this, the infant should be in a bassinet, not an incubator, because the top of the incubator prevents the light from being brought sufficiently close to the infant. In a bassinet, it is possible to bring the fluorescent tubes within approximately 10 cm of the infant. Naked term infants do not become overheated under these lights. It is important to note, however, that the halogen spot phototherapy lamps cannot be positioned closer to the infant than recommended by the manufacturers without incurring the risk of a burn. When halogen lamps are used, manufacturer's recommendations should be followed. The reflectors, light source, and transparent light filters (if any) should be kept clean.[4]

When bilirubin levels are extremely high (more than 30 mg/dL [513 μmol/L]), and intensive phototherapy is used, a decline of as much as 10 mg/dL (171 μmol/L) can occur within a few hours,[43] and a decrease of at least 0.5 to 1 mg/dL per hour can be expected in the first 4 to 8 hours.[44] On average, for infants of more than 35 weeks' gestation readmitted for phototherapy, intensive phototherapy can produce a decrement of 30% to 40% in the initial bilirubin level by 24 hours after initiation of phototherapy.[45] The most significant decline will occur in the first 4 to 6 hours. With standard phototherapy systems, a decrease of 6% to 20% of the initial bilirubin level can be expected in the first 24 hours.[46]

Rebounding Bilirubin Levels

Significant bilirubin rebound (SBR) is defined as postphototherapy bilirubin level needing reinstitution of phototherapy.[12]

In the absence of hemolytic disease in healthy term infants, the cessation of phototherapy results in a mild rebound in the level of TSB concentration. [1]

Hospital discharge does not need to be delayed for observation for rebound in such cases. However, in the presence of hemolytic disease or in sick or low-birth-weight infants, such reassurance may not be warranted. Because hemolysis or other processes responsible for increased bilirubin production may continue, the rebound in these cases depends not only on the effectiveness of phototherapy but also on the severity of the bilirubin production.[14]

The 1994 Practice Parameter of the American Academy of Pediatrics (AAP), which was applicable at the time this study was being performed, but not applicable to neonates with hemolytic conditions, recommended that in most cases no further measurement of bilirubin is necessary following discontinuation of phototherapy, except possibly for cases in which phototherapy was instituted early and discontinued before the infant was 3–4 days old. The subsequent (2004) recommendations suggest that discharge from hospital need not be delayed in order to observe an infant for rebound. The AAP Subcommittee on Hyperbilirubinemia now recommends a follow up bilirubin measurement within 24 hours of discharge for those cases in which phototherapy was used for neonates with hemolytic diseases, initiated early, or discontinued before the infant is 3–4 days old. The Committee regards significant rebound among neonates who had been rehospitalised for

hyperbilirubinaemia to be a rare occurrence and suggests a bilirubin measurement or clinical evaluation after 24 hours in these infants as a clinical option.[4]

Kaplan et al.[13] stated that post-phototherapy neonatal bilirubin rebound to clinically significant levels may occur, especially in cases of prematurity (37 weeks), direct Coombs test positivity, and those treated <72 hours. These risk factors should be taken into account when planning post-phototherapy follow up. A total of 30 (13.3%) neonates developed significant rebound. Twenty two of these (73%) were retreated with phototherapy. Multiple logistic regression analysis showed significant risk for aetiological risk factors including positive direct Coombs test (odds ratio 2.44, 95% CI 1.25 to 4.74) and gestational age,<37 weeks (odds ratio 3.21, 95% CI 1.29 to 7.96). A greater number of neonates rebounded among those in whom phototherapy was commenced <72 hours (26/152, 17%) compared with >72 hours (4/74, 5.4%) (odds ratio 3.61, 95% CI 1.21 to 10.77).

Yetman et al showed that infants completing phototherapy for hyperbilirubinemia who are otherwise healthy do not require follow-up solely to identify a rebound bilirubin level. In their study, review was completed for 264 consecutive newborns receiving phototherapy for hyperbilirubinemia to determine whether a "rebound" increase in total serum bilirubin (TSB) level occurs after termination of phototherapy. The difference between mean TSB levels at discontinuation of phototherapy and at rebound was calculated by paired-t test. TSB levels at rebound were significantly lower than at discontinuation of phototherapy for infants weighing > 1800 g (positive and negative Coombs' test results). There were no statistically significant differences among infants in the smaller weight categories, regardless of Coombs' test results[47].

Al Saedi et al stated that the rebound of bilirubin level after termination of phototherapy in otherwise healthy term infants is minimal; thus measurement of serum bilirubin is not required after termination of phototherapy and adds unnecessary expense, prolongs hospitalization, or both. They followed neonates for 8.3 (5.3) hours post-phototherapy and documented decrease in mean post- phototherapy bilirubin concentrations, although upper limits of the rebound were not provided[48].

Tan et al studied 3802 infants who received phototherapy for nonhemolytic jaundice. Of 2879 full-term infants receiving standard white light phototherapy, only 24 (0.66%) required a second dose of phototherapy following rebound compared with 4 (2.8%) of 141 term infants receiving intensive phototherapy with special blue lights (p<.001).[49]

Erdeve and colleagues found that bilirubin concentrations did not increase significantly in 375 neonates followed for up to 12 hours after discontinuation of phototherapy, although 5.1% of these neonates did have repeat phototherapy. However, neither the upper limit of the rebound range nor the criteria for repeat phototherapy in that study were stated.[50]

In the study by Lazar et al, none of 58 infants weighing more than 1500 g had a total serum bilirubin level rebound that required additional phototherapy. They followed serum bilirubin levels to their natural peak in term neonates with non- hemolytic hyperbilirubinaemia. The upper range of rebound bilirubin reached a peak of 267 mmol/l. However, the data from this series cannot be extrapolated to neonates with haemolytic conditions.[51]

Brown and colleagues found minimal increases in serum bilirubin concentrations in <2000 g birth weight infants treated with prophylactic phototherapy, but in babies >2000 g birth weight, treated only if they actually developed hyperbilirubinaemia, TSB values continued to decline once phototherapy was discontinued.[52]

Maisels et al showed that 13 (8.2%) of 158 infants treated with phototherapy before discharge from the nursery and only 1 (0.7%) of 144 infants who first received phototherapy on readmission received repeated phototherapy (P=.002). According to this study, it is not necessary to keep infants in the hospital to check for rebound. However, for infants who require phototherapy during their birth hospitalization and for those with significant hemolytic disease, they recommend obtaining a follow-up bilirubin level 24 hours after discharge. This is probably not necessary in those who are readmitted for phototherapy but, because rare instances of significant rebound have occurred in these infants, additional clinical follow-up is appropriate, particularly if phototherapy is discontinued at higher total serum bilirubin levels than used in this study.[53]

Del Vecchio et al studied 48 neonates, of whom one 36 week gestation infant was retreated with phototherapy for a rebound bilirubin level of 17.0 mg/dl.[54]

Bansal et al stated that significant rebound rise of bilirubin is observed in 10% neonates needing intensive phototherapy and the risk factors are gestation less than 35 weeks, birth weight <2000 gm and onset of phototherapy within 60 h of age. Among 245 neonates with hyperbilirubinemia, post-phototherapy bilirubin estimation was done in 232 neonates. A total of 17 (7.3%) neonates developed significant bilirubin rise (SBR). In neonates with SBR, bilirubin increased by 2.3 mg/dL after stopping phototherapy. Risk factors for SBR included birth at <35 weeks of gestation, birthweight <2000 gm and onset of jaundice at <60 hrs of age.[12]

Bhutani et al stated that an hour-specific total serum bilirubin before hospital discharge can predict which newborn is at high, intermediate or low risk for developing clinically significant hyperbilirubinemia . Predischarge, 6.1% of the study population had TSB values in the high-risk zone at 18 to 72 hours; of these, 39.5% remained in that zone. Predischarge, 32.1% of the population had TSB values in the intermediate-risk zone. In a clinically significant minority of these newborns, the postdischarge TSB moved into the high-risk zone. The predischarge TSB in 61.8% of the newborn was in the low-risk zone and there was no measurable risk for significant hyperbilirubinemia.[55]

Reham et al suggested that newborn completing phototherapy for hyperbilirubinemia before the age of 2 weeks, who are cured, do not require a follow up test in the second day to check for rebound hyperbilirubinemia. In this study, total serum bilirubin level at the second day was found to be lower or equal to the level of discontinuation. No significant differences among infants regarding weight categories.[56]

Erdal et al reviewed 854 newborn receiving phototherapy for neonatal hyperbilirubinemia. TSB levels at rebound were significantly lower than at discontinuation of phototherapy for infants weighing >2500g. There were no statistically significant differences among infants in the smaller weight categories, regardless of Coombs' test results. Infants completing phototherapy for hyperbilirubinemia who are otherwise healthy do not require follow-up solely to identify a rebound bilirubin level.[57]

Manutham et al studied 202 term neonates, of which 10 neonates (4.9%) developed significantly rebound hyperbilurubinemia. All of them were treated with phototherapy again. An initial age of phototherapy (less than 48 hrs.) was the only significant risk factor contributing to rebound hyperbilirubinemia (odds ratio 6.3, 95% CI: 1.6-25.2). As per this study, rebound hyperbilirubinemia after complete phototherapy session was not common in term neonates. However, newborns having an early onset of jaundice within 48 hrs. requiring immediate phototherapy had more chance to develop rebound phenomenon.[58]

In the study by Lee et al, 7 (4.5%) of 154 babies required a second course of phototherapy. When compared with those babies not requiring treatment again, they had a higher mean serum bilirubin (234.3 vs 204.1, $p<0.001$) and were more likely to be younger than five days of life (3/7 vs 16/147, $p=0.041$) when phototherapy was first stopped. Other factors like sex, cephalohematoma, glucose-6-phosphate dehydrogenase deficiency, blood groups, Coombs' test, onset of jaundice, and hemoglobin level were not found to be significant.[59]

III. Aims And Objectives

To determine whether clinically significant rebound in serum bilirubin level occurs within 24 hours after termination of phototherapy in infants with either hemolytic or non-hemolytic hyperbilirubinemia.

IV. Materials And Methods

Study area

This study was performed in the Neonatal Intensive Care unit (NICU) at the Institute of Child Health , Kolkata
The study was approved by the Ethical Committee of Institute.

Parents of all children received a written explanation of the study.

Study population

All icteric infants requiring phototherapy were included in the study.

Exclusion criteria

Infants who failed phototherapy treatment and required exchange transfusion.

Study period

From June 2010 to May 2011

Sample size

Approximately 60.

Sample design

All icteric infants regardless of the birth weight, gestational age and the cause of jaundice or who had been discharged from the nursery and were readmitted for phototherapy were included in the study group.

Study design

Prospective observational study

Study tools
Clinical methods and materials and Laboratory methods performing bilirubin assay.

TSB measurement

For TSB measurement, blood was collected by venous puncture. TSB assays were performed in the clinical laboratory at the Institute of Child health using the automated analyzer. This analyzer measures TSB using a modified diazo reaction. The machine was calibrated daily according to the manufacture's recommendations. The assays used by this machine were previously studied in comparison with the gold standard bilirubin measurement of HPLC and were found to correlate well.

To identify the underlying etiology, Direct Coombs test, ABO and Rhesus blood group, glucose-6-phosphate dehydrogenase (G6PD) level, thyroid profile, reticulocyte count, C reactive protein and peripheral blood smear examination were done.

Risk level determination

We used the bilirubin normogram (Fig 2) developed by Bhutani et al to divide bilirubin levels into 2 groups, clinically significant jaundice, and nonclinically significant jaundice. The bilirubin normogram plots age in hours vs, bilirubin. As the level of bilirubin normally varies with age, this normogram helps to determine whether the level of bilirubin at a particular hour of life puts an infant at risk for developing clinically significant hyperbilirubinemia. If a bilirubin value is above the 95th percentile for age curve, the normogram predicts that the infant is in the "high-risk zone" for developing clinically significant hyperbilirubinemia. Similarly, bilirubin values between 75th and 95th percentile curves predict the infant is in the "high-intermediate risk zone".

Data analysis
Categorical variables are expressed as Number of patients and compared across groups using Chi Square test for Independence of Attributes. Continuous variables have been expressed as mean ± standard deviation compared across the 2 groups using unpaired t test (student's t test).
The statistical software SPSS version 16 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

V. Results And Analysis

Sixty jaundiced neonates were enrolled in the study. Of the total 60 neonates, 30 were male and 30 were female. Demographic datas like gestational age, postnatal age, birth weight etc. are listed in Table 4.

Table 4
Demographic characteristics of population

		Gestational age (wks)	Postnatal age (hrs)	Birth wt.(gm)	Prephototherapy bilirubin (mg/dl)	Postphototherapy bilirubin (mg/dl)	Bilirubin after stopping of phototherapy for 24 hrs (mg/dl)	Reticulocyte Count (%)
Pre term (n=12)	Mean	34.25	63.17	2039.17	15.39	9.81	8.71	2.56
	SD	2.14	17.69	378.69	1.82	1.91	3.76	1.20
	Median	35.00	60.00	2025.00	15.60	9.80	7.40	2.00
	Minimum	30.00	46.00	1450.00	12.20	7.40	5.00	1.70
	Maximum	36.00	96.00	2500.00	18.60	13.00	14.80	5.60
Term (n=48)	Mean	38.73	78.88	2862.29	18.92	12.57	9.31	2.01
	SD	1.05	17.32	247.33	2.78	2.06	2.30	0.31
	Median	39.00	72.00	2800.00	18.90	12.90	9.40	2.00
	Minimum	37.00	48.00	2500.00	11.60	6.60	4.60	1.50

	Maximum	42.00	120.00	3900.00	24.60	16.80	20.40	3.10
Total (n=60)	Mean	37.83	75.73	2697.67	18.22	12.02	9.19	2.12
	SD	2.23	18.37	430.94	2.97	2.30	2.63	0.63
	Median	38.00	72.00	2795.00	18.70	12.50	9.10	2.00
	Minimum	30.00	46.00	1450.00	11.60	6.60	4.60	1.50
	Maximum	42.00	120.00	3900.00	24.60	16.80	20.40	5.60

Table 4 shows that 48 (80%) were term baby and 12 (20%) were preterm baby.

Of the total 12 preterm neonates, mean gestational age was 34.25 weeks with SD of 2.1;, mean postnatal age was 63.17 hours with SD of 17.69; mean birth weight was 2039.17 gms with SD of 378.69; mean prephototherapy bilirubin was 15.39 mg/dl with SD of 1.82; mean postphototherapy bilirubin was 9.81 mg/dl with SD of 1.91; mean bilirubin after stopping of phototherapy for 24 hours was 8.71 mg/dl with SD of 3.76 and mean reticulocyte count was 2.56% with SD of 1.20.

Remaining 48 term neonates had mean gestational age of 38.73 weeks with SD of 1.05; mean postnatal age 78.88 hours with SD of 17.3;, mean birth weight 2862.29 gms with SD of 247.33; mean prephototherapy bilirubin 18.92 mg/dl with SD of 2.78; mean postphototherapy bilirubin 12.57 mg/dl with SD of 2.06; mean bilirubin after stopping of phototherapy for 24 hours 9.31 mg/dl with SD of 2.30 and mean reticulocyte count 2.01% with SD of 0.31.

These total 60 neonates had mean gestational age 37.83 weeks with SD of 2.23; mean postnatal age 75.73 hours with SD of 18.37; mean birth weight 2697.67 gms with SD of 430.94; mean prephototherapy bilirubin 18.22 mg/dl with SD of 2.97; mean postphototherapy bilirubin 12.02 mg/dl with SD of 2.30; mean bilirubin after stopping of phototherapy for 24 hours 9.19 mg/dl with SD of 2.63 and mean reticulocyte count 2.12% with SD of 0.63.

Table 5
Sex Distribution

Sex	**No. of Births**	**% of Births**
Male	30	50.0
Female	30	50.0
Total	**60**	**100.0**

Chart 1

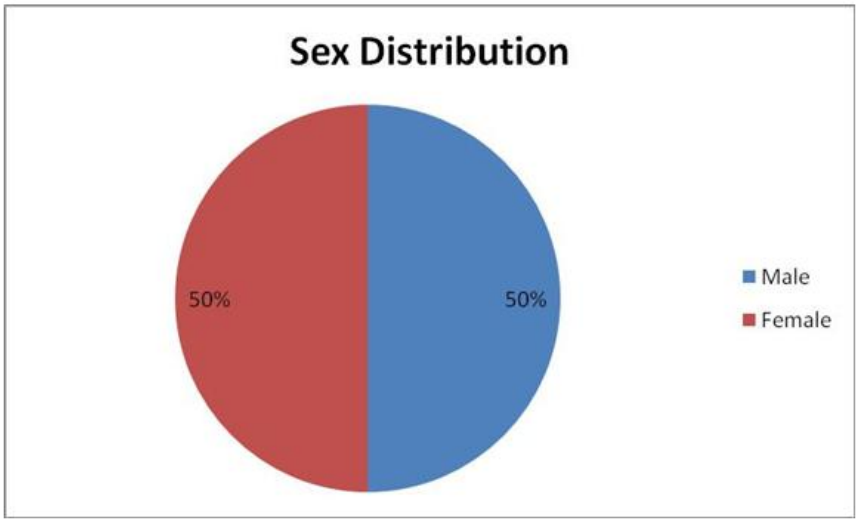
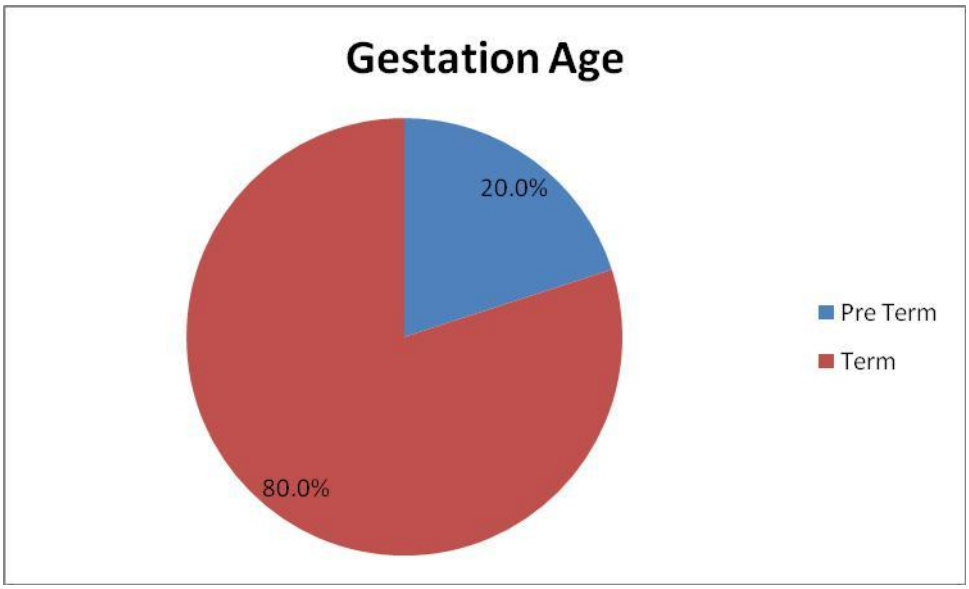


Table 5 and Chart 1 indicates that among 60 neonates, 30 were male (50%) and 30 were female (50%).

Table 6
Gestational age

Gestation Age	No of Births	% of Births
Preterm (<37 wks)	12	20.0
Term (≥37 wks)	48	80.0
Total	**60**	**100.0**

Chart 2

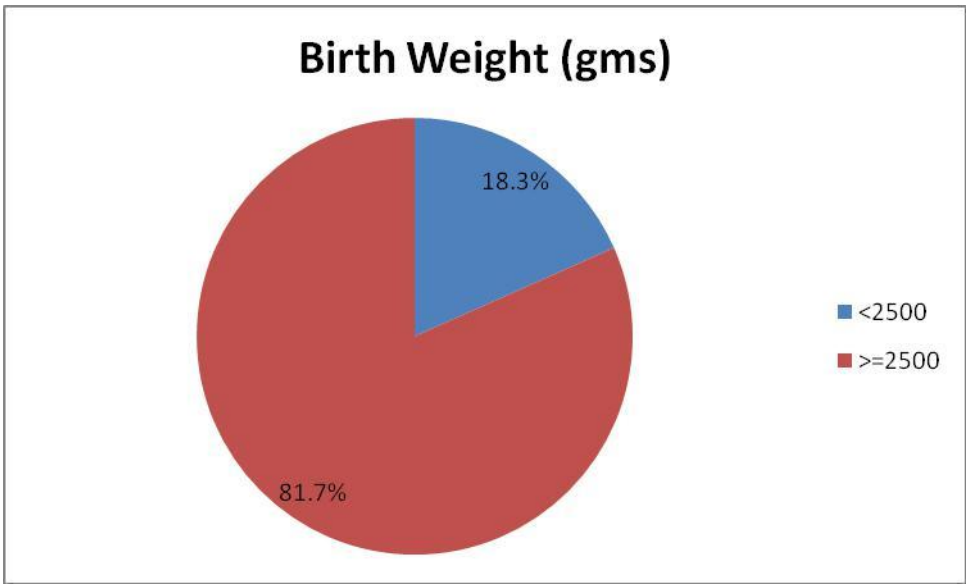


It is obvious from Table 6 and Chart 2 that 12 neonates were preterm (20%) and 48 were term (80%).

Table 7
Birth Weight

Birth Weight (gms)	No of Births	% of Births
<2500	11	18.3
≥2500	49	81.7
Total	**60**	**100.0**

Chart 3

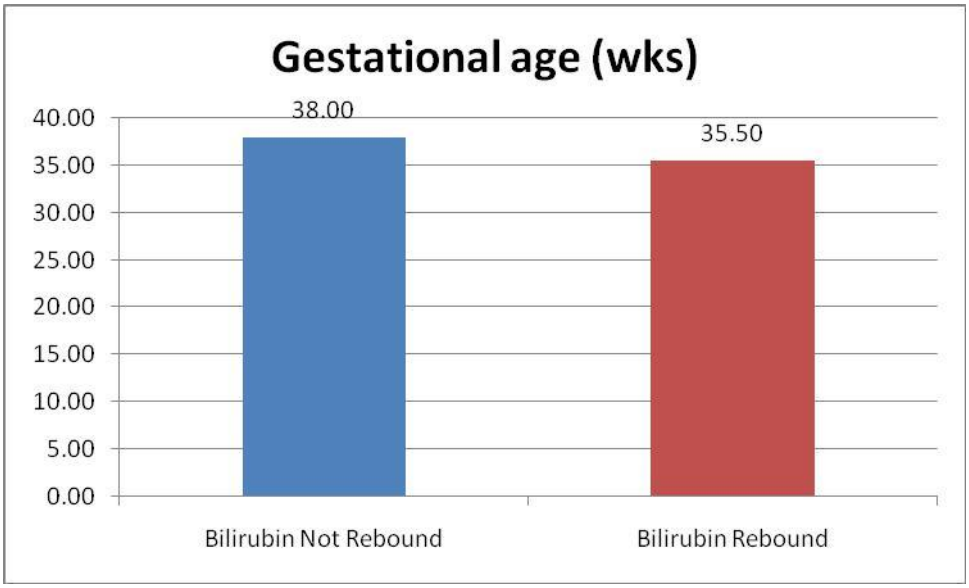


Among 60 neonates, 49 (81.7%) had birth weight of 2500 gm or more. 11 (18.3%) were below 2500 gm, out of which 1 neonate was below 1500 gm (very low birth weight) [Table 7 and Chart 3].

Table 8
Gestational Age

	Bilirubin			
	No Rebound	**Rebound**		
	Mean ± Std. Deviation	**Mean ± Std. Deviation**	**p Value**	**Significance**
Gestational age (wks)	38 ± 2.15	35.5 ± 2.38	0.029	**Significant**

Chart 4

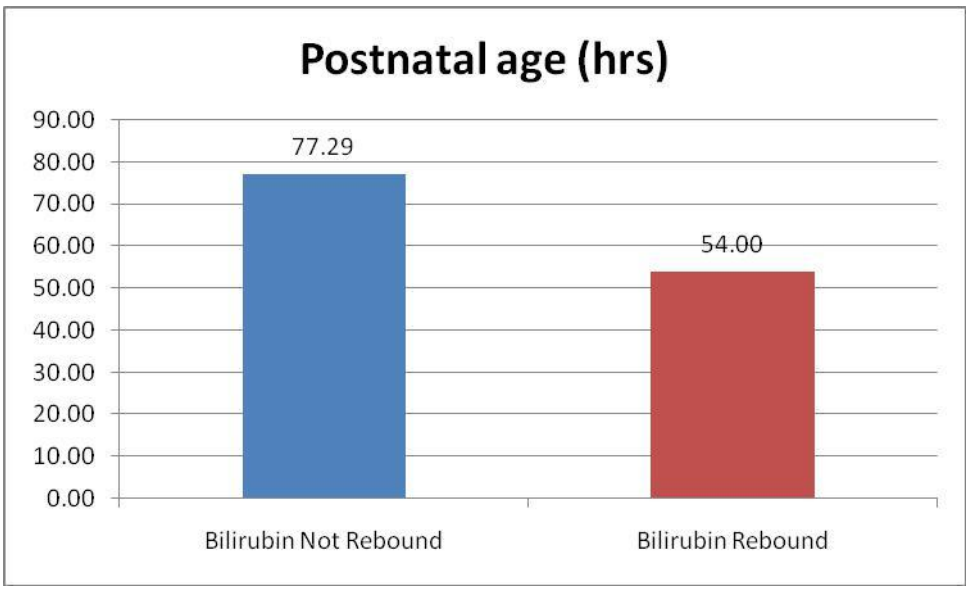


Inference:
Among 4 neonates with significant bilirubin rebound (SBR), mean gestational age was 35.5 weeks with standard deviation (SD) of 2.38 which is statistically significant (p value 0.029) [Table 8 and Chart 4].

Table 9
Postnatal Age

	Bilirubin			
	No Rebound	**Rebound**		
	Mean ± Std. Deviation	**Mean ± Std. Deviation**	**p Value**	**Significance**
Postnatal age (hrs)	77.29 ± 17.96	54 ± 6.93	0.013	**Significant**

Chart 5

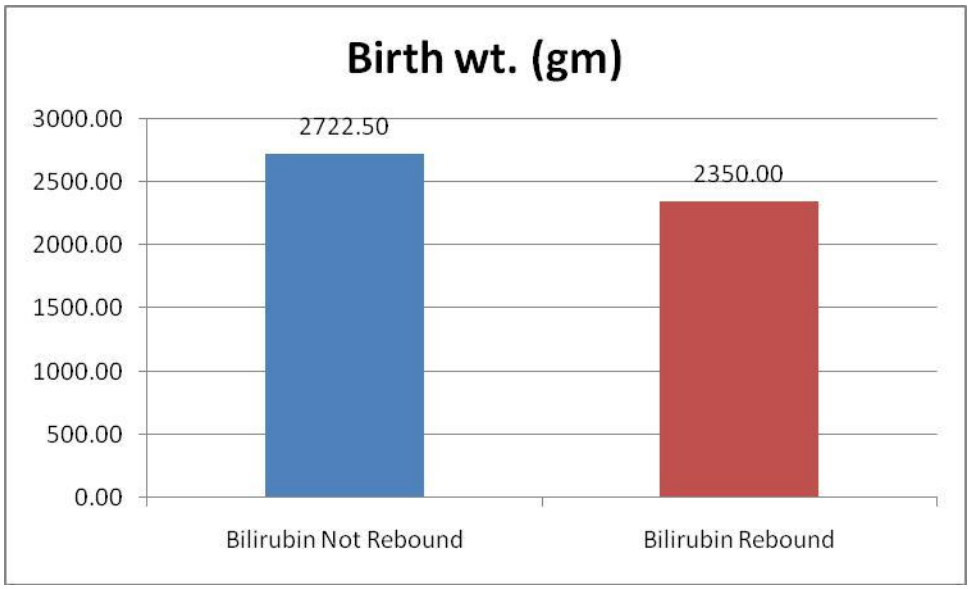


Inference:
Postnatal age in hours was statistically significant among neonates with SBR (p value 0.013). Mean postnatal age was 54 hours with SD of 6.93 [Table 9 and Chart 5].

Table 10
Birth weight

	Bilirubin			
	No Rebound	**Rebound**		
	Mean ± Std. Deviation	**Mean ± Std. Deviation**	**p Value**	**Significance**
Birth wt. (gm)	2722.5 ± 371.82	2350 ± 972.11	0.095	Not Significant

Chart 6

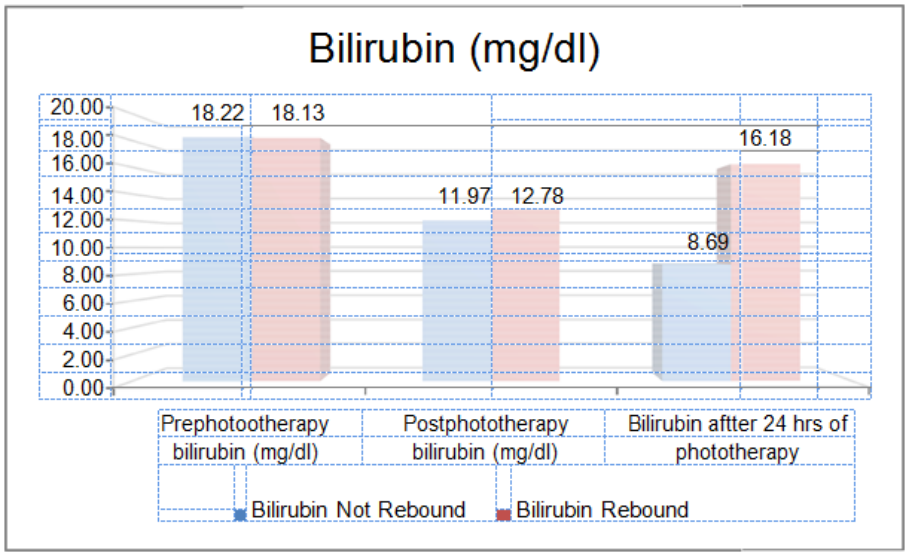


Inference:
Birth weight was not statistically significant (p value 0.095) [Table 10 and Chart 6].

Table 11
Bilirubin levels

	Bilirubin			
	No Rebound	**Rebound**		
	Mean ± Std. Deviation	**Mean ± Std. Deviation**	**p Value**	**Significance**
Prephototherapy bilirubin (mg/dl)	18.22 ± 2.9	18.13 ± 4.32	0.950	Not Significant
Postphototherapy bilirubin (mg/dl)	11.97 ± 2.28	12.78 ± 2.89	0.502	Not Significant
Bilirubin after 24 hrs. of stopping of phototherapy (mg/dl)	8.69 ± 1.78	16.18 ± 2.82	<0.001	**Significant**

Chart 7

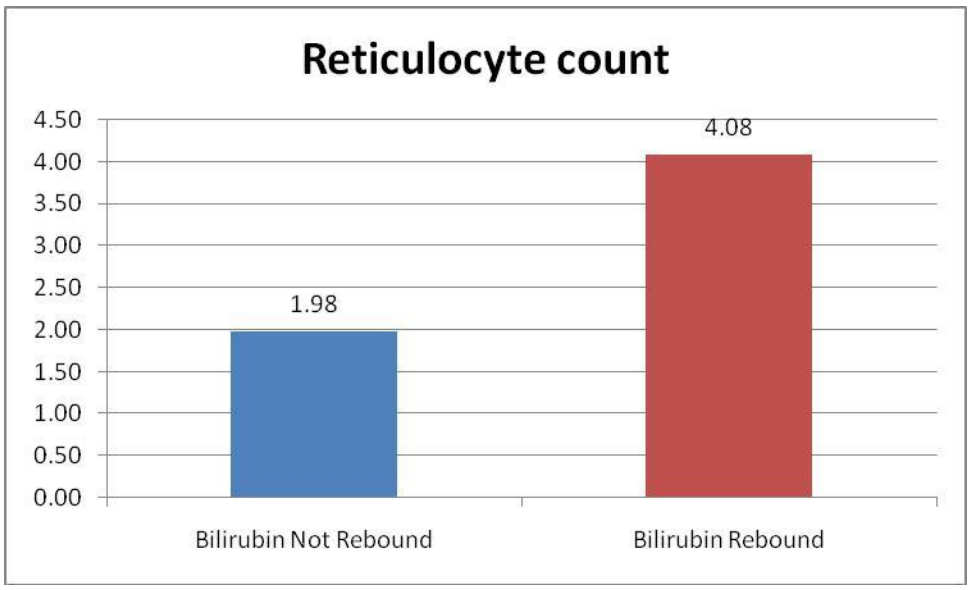


Inference:
Bilirubin after 24 hours of cessation of phototherapy was staatistically significant (p value <0.001) [Table 111 and Chart 7].

Table 12
Reticulocyte count

	Bilirubin			
	No Rebound	**Rebound**		
	Mean ± Std. Deviation	**Mean ± Std. Deviation**	**p Value**	**Significance**
Reticulocyte count	1.98 ± 0.24	4.08 ± 1.07	<0.001	**Significant**

Chart 8

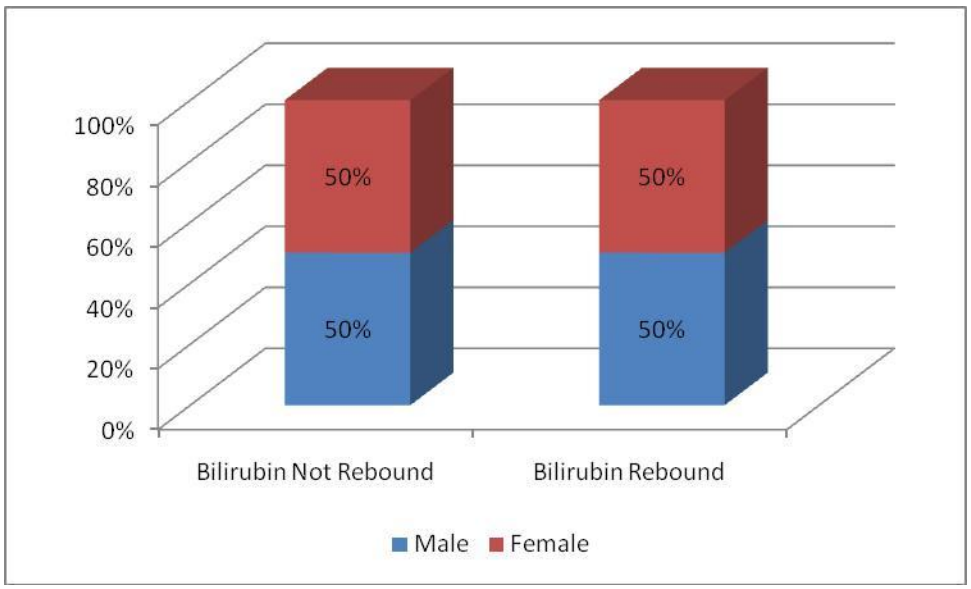


Inference:
Reticulocyte count was statistically significant with p value of <0.001. Mean reticulocyte count among neonate with SBR was 4.08, with SD of 1.07 [Table 12 and Chart 8].

Table 13
Sex distribution

Sex	Bilirubin			p Value	Significance
	No Rebound	Rebound	Total		
F	28 (50.0%)	2 (50.0%)	30 (50.0%)	1.000	Not Significant
M	28 (50.0%)	2 (50.0%)	30 (50.0%)		
Total	56 (100.0%)	4 (100.0%)	60 (100.0%)		

Chart 9



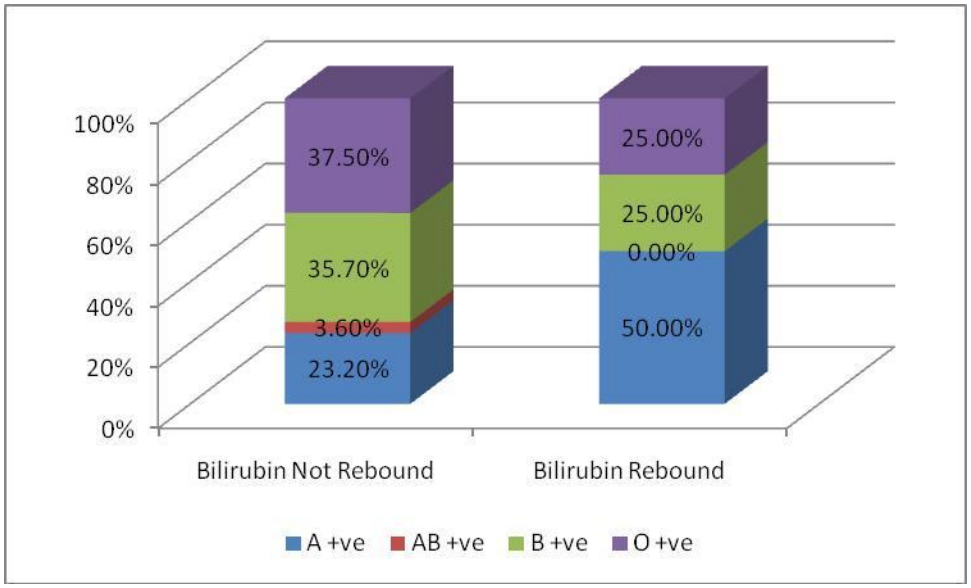
Inference:
Sex distribution was statistically insignificant (p value 1.0) [Table 13 and Chart 9].

Table 14
Mother's blood group

Mother's blood group	Bilirubin			p Value	Significance
	No Rebound	Rebound	Total		
A +ve	13 (23.2%)	2 (50.0%)	15 (25.0%)		
AB +ve	2 (3.6%)	0 (0.0%)	2 (3.3%)		Not

				0.683	Significant
B +ve	20 (35.7%)	1 (25.0%)	21 (35.0%)		
O +ve	21 (37.5%)	1 (25.0%)	22 (36.7%)		
Total	56 (100.0%)	4 (100.0%)	60 (100.0%)		

Chart 10



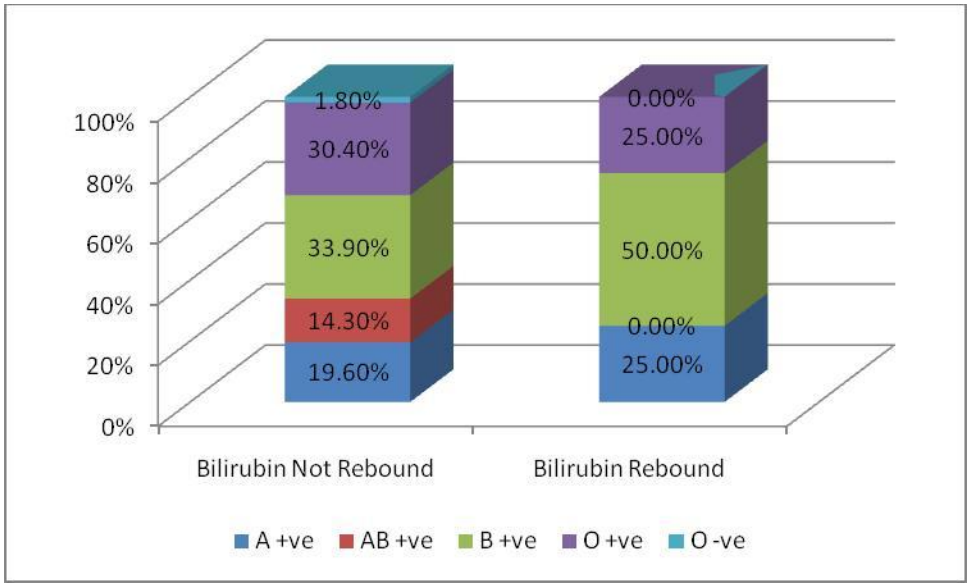
Inference:
Blood group of mothers were statistically not significant (p value 0.683) [Table 14 and Chart 10].

Table 15
Baby's blood group

Baby's blood group	**Bilirubin**			**p Value**	**Significance**
	No Rebound	**Rebound**	**Total**		
A +ve	11 (19.6%)	1 (25.0%)	12 (20.0%)	0.909	Not Significant
AB +ve	8 (14.3%)	0 (0.0%)	8 (13.3%)		
B +ve	19 (33.9%)	2 (50.0%)	21 (35.0%)		
O +ve	17 (30.4%)	1 (25.0%)	18 (30.0%)		

O -ve	1 (1.8%)	0 (0.0%0	1 (1.7%0		
Total	56 (100.0%)	4 (100.0%)	60 (100.0%)		

Chart 11



Inference:
Blood group of baby's were statistically insignificant (p value 0.909) [Table 15 and chart 11].

Table 16
Characteristics of 4 neonates requiring reinstitution of phototherapy

Gestational age (wks)	Birth wt. (gm)	Postnatal age (hrs)	Diagnosis	Pre-phototherapy bilirubin (mg/dl)	Post-phototherapy bilirubin (mg/dl)	Bilirubin after 24 hrs of cessation of phototherapy (mg/dl)	Reticulocyte count(%)
34	1750	48	G6PD deficiency	16.2	10.4	14.7	5.6
35	2000	60	Cephalohematoma	16.1	12.9	14.8	3.8
39	4800	48	Polycythemia (Infant of Diabetic mother)	24.6	16.8	20.4	3.1
34	1850	60	ABO incompatibility	15.6	11.0	14.8	3.8

Direct Coombs' tests (DCT) were done for all neonates which was negative. So there was no statistical significance of DCT in this study.

According to this study result in the Indian population, a total of 4 (6.67%) neonates developed bilirubin rebound among 60 neonates. Gestation at birth was less than 37 weeks in 3 neonates (mean 35.5 weeks; SD 2.38), p value of 0.029 which was statistically significant.

Other factors like postnatal age in hours (mean 54 hours; SD 6.93, p value

0.013), bilirubin after 24 hours of stopping of phototherapy (mean 16.18 mg/dl; SD 2.82, p value <0.001) and reticulocyte count (mean 4.08%; SD 1.07, p value <0.001) were found to be statistically significant.

In this study, birth weight was also found to be statistically insignificant (p value 0.95) for bilirubin rebound.

All of these 4 neonates presented to us with bilirubin level in "High-risk" zone for age (above 95th centile) in Normogram (Fig 2).

VI. Discussion

Sixty jaundiced neonates admitted in Neonatal Intensive Care Unit at Institute of Child Health, Kolkata undergoing phototherapy were included in the study regardless of birth weight, gestational age, cause of jaundice during the period from June 2010 to May 2011. The present study has been carried out to find out whether bilirubin rebound occurs in babies treated with phototherapy in hemolytic or non-hemolytic hyperbilirubinemia and it's relation with gestational age, postnatal age, birth weight, hemolysis etc.

Neonatal hyperbilirubinemia is a common problem encountered in the newborn nursery. Some 60% of normal newborns become clinically jaundiced sometime during the first week of life. Unconjugated (indirect) hyperbilirubinemia occurs as a result of excessive bilirubin formation and because the neonatal liver cannot clear bilirubin rapidly enough from the blood. Although most newborns with jaundice are otherwise healthy, they need to be monitored because unconjugated bilirubin is potentially toxic to the central nervous system. Sufficiently elevated levels of bilirubin can lead to bilirubin encephalopathy and subsequently kernicterus, with devastating, permanent neurodevelopmental handicaps.[60]

Kernicterus is now of greater concern for neonatologists and pediatricians because the earlier discharge from the hospital of mothers and neonates prevents an adequate monitoring of jaundice and thus keeping the possibility of hyperbilirubinemia above critical level.

Most infants are now discharged before age 48 hours, and peak bilirubin levels will almost always occur between 3 to 7 days of age. Thus additional monitoring and surveillance are essential to ensure that extreme hyperbilirubinemia does not occur.

Significant bilirubin rebound (SBR) is postphototherapy bilirubin level needing reinstitution of phototherapy.[12] A rebound in the total serum bilirubin level of

1 to 2 mg/dl and occasionally more — can occur after phototherapy is discontinued. Infants at increased risk of a clinically significant rebound are those born at less than 37 weeks of gestation, those with hemolytic disease, and those treated with phototherapy during the birth hospitalization. It is usually unnecessary to keep an infant in the hospital to check for rebound,but for infants who require phototherapy during their perinatal life and for those with well- defined hemolytic disease, a follow-up bilirubin level should be obtained 24 hours after discharge.

The revised American Academy of Pediatrics guidelines (2004) for prevention and management of hyperbilirubinemia emphasize the importance of an objective assessment of bilirubin status for all neonates prior to discharge and measurement of TSB after 24 hours of discharge to check for rebound is considered to be an option depending on the cause of hyperbilirubinemia.[4]

Previous reports in international literature have indicated that SBR is rare and therefore it is unnecessary to keep an infant in the hospital after phototherapy has been discontinued to check for SBR. Factors reported to influence incidence of SBR include prematurity, hemolysis, severity and onset of hyperbilirubinemia, and presence of other risk factors like G6PD deficiency.

According to the present study in the Indian population (eastern region), 4 (6.67%) neonates developed bilirubin rebound among total 60 neonates.

Bansal et al[12] found rebound hyperbilirubinemia in 7.3% neonates, but Kaplan et al[13] revealed 13.3% neonates with SBR.

Gestation at birth was less than 37 weeks in 3 neonates (mean 35.5 weeks; SD 2.38; p value of 0.029) which is statistically significant.

These finding correlates with the study by Bansal et al[12] and Kaplan et al[13].
Postnatal age in hours (mean 54 hours; SD 6.93, p value 0.013) was also found to be statistically significant. This result was also supported by the study Bansal et al[12], Kaplan et al[13] and Erdeve et al[50].
Manutham et al[58] suggested that newborns having an early onset of jaundice within 48 hours requiring immediate phototherapy had more chance to develop rebound phenomenon.

Bilirubin level after cessation of phototherapy for 24 hours (mean 16.18 mg/dl; SD 2.82, p value <0.001) was found to be statistically significant in this study which correlates with the study by Lee et al[59].

Statistical significance was also detected in the present study in reticulocyte count (mean 4.08%; SD 1.07, p value <0.001).

But birth weight was found to be statistically insignificant (p value 0.095) in the present study. Mean birth weight of rebounded neonates was 2350 gm with SD of 972.11.

Bansal et al[12] found statistical significance in low birth weight babies, but no significant was found in the study by Reham et al[56].

Direct Coombs' test was also found to be insignificant in present study. This finding was supported by the study by Lee et al[59]. But this was found to be statistically significant in the study by Kaplan et al[13].

All of these 4 neonates presented with bilirubin level in High-risk zone for age (above 95th centile) in Normogram (Fig 2).

In a study, Bansal et al identified gestation at birth<35 weeks, birth weight<2000 gm and onset of jaundice at <60 hours of postnatal age as a risk factors for significant bilirubin rebound. As per their study, 7.3% neonates developed significant bilirubin rebound. They recommend that a rebound bilirubin level must be obtained in high-risk neonates 18-24 h after stopping phototherapy. According to this study, discharge may be delayed for this purpose if follow-up is not ensured.[12]

In the present study, identified the risk factors are gestational age <37 weeks, postnatal age <60 hours, and hemolysis as evident by raised reticulocyte count.

In a novel study done by Kaplan and colleagues, significant bilirubin rise occurred in 13.3% neonates. They identified the risk factors like gestational age <37 weeks, starting of phototherapy within 72 hours of age and hemolysis or Direct Coomb's test positivity. As per this study, these risk factors should be taken into account when planning post-phototherapy follow up.[13]

But a study done in Hon Kong by Lee and colleague showed the significant factors which include TSB levels at discontinuation of phototherapy and stopping of phototherapy before Day 5. They didn't found other factors (like sex, cephalhematoma, glucose 6 phosphate dehydrogenase deficiency, blood groups, Coombs' test, onset of jaundice, and hemoglobin level) to be significant.[59]

A previous study by Lazar and colleague, has examined TSB level at discontinuation of phototherapy in newborns of Israeli infants. No infant in that study required reinstitution of phototherapy. However, the data from this series cannot be extrapolated to neonates with hemolytic conditions.[51]

Another study done in Saudi Arabia by Al Saedi et al[48] on only healthy term infants and they found that rebound of bilirubin after termination of phototherapy is minimal.

Maisels and Kring determined the incidence for rebound hyperbilirubinemia after stopping phototherapy; in addition, they compared rebound in the group of infants who received phototherapy during their birth hospitalization with rebound in those who were treated after discharge and readmission to the hospital. They concluded that it is not necessary to keep infants in the hospital to check for rebound serum bilirubin levels in infants treated with phototherapy. They recommended repeat serum bilirubin check 24 hours after discharge only if phototherapy was stopped at higher levels.[53]

In a study done in USA by Yetman[47] revealed that TSB levels at rebound were significantly lower than at discontinuation of phototherapy for infants weighing >1800 gms (positive and negative Coombs' test results).

There were no statistically significant differences among infants in the smaller weight categories, regardless of Coombs' test results. According to them, infants completing phototherapy for hyperbilirubinemia who are otherwise healthy do not require follow-up solely to identify a rebound bilirubin level.

In the present study in eastern region of Indian population, it was observed that the significant bilirubin rebound can occur in neonates with certain risk factors

(like prematurity, postnatal age <60 hours, and hemolysis). Etiological factors like G6PD deficiency, ABO incompatibility, polycythemia and cephalhematoma were also identified.

The present study had limitations. The sample size is small and carried out in fixed limited period. So further extensive study including large sample size is required to observe bilirubin rebound.

To conclude bilirubin measurement should be done after 24 hours of stopping of phototherapy in neonates with bilirubin levels at "high-risk" zone, born at less than 37 weeks gestation or onset of phototherapy within 60 hours of age and neonate having features of hemolysis. Neonate with these factors should be regarded as high risk for rebound hyperbilirubinemia. On the other hand, babies with hyperbilirubinemia due to non-hemolytic etiology, appear to be at low risk.

Early discharge should be delayed in babies with those risk factors.

VII. Summary And Conclusion

Neonatal jaundice, or hyperbilirubinemia is a common problem encountered in the newborn nursery. Complications of hyperbilirubinemia, such as acute bilirubin encephalopathy and/or kernicterus, is preventable. So early detection and prevention of these complications has led to recommendations to screen all neonates for hyperbilirubinemia.

Intensive phototherapy in neonatal hyperbilirubinemia rapidly declines serum total bilirubin below the threshold for treatment. A bilirubin level is usually checked 12 to 24 hours after phototherapy is stopped. A rebound in the total serum bilirubin level of 1 to 2 mg/dl and occasionally more — can occur after phototherapy is discontinued.

The present study was carried out in the NICU at the Institute of Child Health, Kolkata to determine whether clinically significant rebound in serum bilirubin level occurs within 24 hours after termination of phototherapy in infants with either hemolytic or non-hemolytic hyperbilirubinemia.

A total of 60 neonates were enrolled regardless of the birth weight, gestational age and the cause of jaundice or who had been discharged from the nursery and were readmitted for phototherapy were included in the study group. Infants who failed phototherapy treatment and required exchange transfusion were excluded from the study.

According to the present, 4 (6.67%) neonates developed bilirubin rebound out of total 60 neonates. Gestation at birth was less than 37 weeks in 3 neonates (mean 35.5 weeks; SD 2.38), p value of 0.029 which was statistically significant.

Other factors include postnatal age in hours (mean 54 hours; SD 6.93, p value

0.013), bilirubin after 24 hours of stopping of phototherapy (mean 16.18 mg/dl; SD 2.82, p value <0.001) and reticulocyte count (mean 4.08%; SD 1.07, p value <0.001) indicating statistical significance.

Various studies found birth weight as a significant factor. But in this study, birth weight was found to be statistically insignificant (p value 0.95). This may be due to smalle sample size.

Direct Coombs' test was also found to be insignificant.

The 4 neonates with SBR presented to us with bilirubin level in High-risk zone for age (above 95th centile) in Normogram (Fig 2).

To conclude, the result of the present study recommended that a rebound bilirubin level should be obtained in high-risk neonates (bilirubin at "High-risk zone", born at less than 35 weeks gestation or onset of phototherapy within 60 hours of age or those with hemolysis) 18-24 hours after stopping phototherapy. Discharge of these babies needs to be delayed for this purpose if follow-up is not ensured.

Though rebound phenomenon occurs only in small percentage of babies with hyperbilirubinemia, this should be checked to prevent the dreadful neurological consequences like kernicterus which is completely preventable.

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