"PHENOBARBITONE AS AN ADJUVANT THERAPY TO PHOTOTHERAPY IN TREATMENT OF HYPERBILIRUBINEMIA IN NEWBORN BABIES - A RANDOMIZED OPEN LABELLED STUDY"

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MD

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LIST OF ABBREVIATIONS

AAP	-	American Academy of Pediatrics
MOD	-	Mode of delivery
BIND	-	Bilirubin Induced Neurological Dysfunction
DCT	-	Direct Coomb's Test
LSCS	-	Lower Segment Cesarean Section
NVD	-	Normal Vaginal Delivery
NICU	-	Neonatal Intensive Care Unit
PRIMI	-	Primi gravida
TSB	-	Total Serum Bilirubin
USB	-	Unconjugated serum bilirubin
DOL	-	Day of Life
HOL	-	Hour of Life

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INTRODUCTION

In neonates, hyperbilirubinemia is a common and, in most circumstances, harmless condition. Jaundiceis seen in around 60% of term infants and 80% of preterm infants within the first week of life. The deposition of unconjugated, non-polar, lipid soluble bilirubin pigment in the skin causes the yellow colour. This unconjugated bilirubin is a by-product of heme-protein catabolism in reticuloendothelial cells, resulting from a sequence of enzymatic events involving heme oxygenase and biliverdin reductase, as well as non-enzymatic reducing agents (1). As seen by recent cases of kernicterus in apparently healthy term and near-term neonates, neonatal hyperbilirubinemia remains a public health problem. Kernicterus can be avoided in these neonates if significant hyperbilirubinemia for their age is detected and treated quickly. Universal screening for severity of hyperbilirubinemia before hospital discharge may predict the neonatal population at risk for excessive hyperbilirubinemia within the first week after delivery (2). When the total serum bilirubin level is within the normal range, jaundice is considered physiologic.

It's difficult to define this normal range. Normal TSB has been found to range from 12.9 mg/dl to 17.5 mg/dl at the upper limit (95th percentile) (4). However, bilirubin levels within the physiological range in preterm new-borns are potentially dangerous if left untreated and must be treated with

phototherapy (3,4). In case of hyperbilirubinemia persisting beyond 10 days in full term and 21 days in preterm infants, it should be considered non-physiologic or pathological. (5) To reflect the alterations associated with acute bilirubin. encephalopathy, the phrase "bilirubin induced neurologic dysfunction" was developed. (7)

Acute bilirubin encephalopathy is a rare condition that can lead to kernicterus and is characterised by a tetrad of choreoathetoid cerebral palsy, high-frequency central neural hearing loss, vertical gaze palsy, and dental enamel hypoplasia (6). Kernicterus has been described in seemingly healthy term and late preterm gestation breastfed new-borns without proven haemolysis in the last several years (9). The foundation for successful hyperbilirubinemia care has been determining the amount of jaundice. However, the clinical evaluation of hyperbilirubinemia using the "Kramer Index" has been impacted by observer variability and skin colour. As a result, the gold standard for identifying and treating hyperbilirubinemia in infants is total serum bilirubinmeasurement. (11).

Bhutani et al produced an hour-specific bilirubin nomogram that showed that measuring TSB can helpidentify new-borns who are at risk of having higher percentile TSB which can lead to neonatal jaundice. (12) Uridine-di-phosphate glucuronyl transferase enzyme is activated by phenobarbitone. By this mechanism phenobarbitone is able to decrease the increase in serum bilirubin in infancy. Our study was done to assess the efficacy of

phenobarbitone on neonatal unconjugated hyperbilirubinemia. This study mainly focussed on neonatal jaundice which occurs in the first two weeks. Apart from perhaps boosting hepatic absorption of bilirubin, the main impact of phenobarbital is to increase hepatic glucuronoyl transferase (UGT) activity and bilirubin conjugation. (16) The effect of phenobarbital on non-pathologic, indirect hyperbilirubinemia has been studied in several research. There are many studies done on the effect of phenobarbital in decreasing the hyperbilirubinemia of non-haemolytic disease of new-born infants. All these studies have a common conclusion that phenobarbital decreases the rate of blood exchange transfusion(9,11). But some studies have reported that phenobarbital has no effect on the total serum bilirubin level in babies with nonhemolytic disease.(23) Our study purpose was to evaluate the effect of phenobarbital and phototherapy combination on the established hyperbilirubinemia of new-borns. We have compared the effect of a combined therapy of phenobarbitone and phototherapy with a monotherapy that is phototherapy alone in this study.

AIMS AND OBJECTIVES

To evaluate the effect of a combined therapy with Phenobarbitone and phototherapy versus a monotherapy of Phototherapy alone in treatment of established neonatal hyperbilirubinemia. We compared the following parameters in both groups:

1. Peak Total serum bilirubin and peak unconjugated serum bilirubin

2. Duration of phototherapy

3. Need of exchange transfusion

4. Days of hospitalization

RESEARCH HYPOTHESIS

Use of Phenobarbitone with phototherapy reduces the duration of phototherapy mainly by induction of enzyme glucuronyl transferase. Phenobarbitone can also prevent the rise in total serum bilirubin which can occur during the phototherapy leading to phototherapy failure. Phenobarbitone can thus cause a decrease in duration of phototherapy and duration of hospitalisation when given as an adjuvant therapy with phototherapy.

REVIEW OF LITERATURE

A yellow discoloration of the skin and mucosa and sclera, along with a high serum bilirubin concentration is termed as hyperbilirubinemia. Icterus can be visualised in new-borns if the serum bilirubin levels are higher than 5 to 7 mg/dl (17). Neonatal jaundice is seen in a high proportion in preterm new-borns. Physiological jaundice can be also seen in 70-80% of term babies. (18). Any blood bilirubin level greater than 17 mg/dl is pathologic, and the cause should be investigated. (24)

We can visually measure the intensity of jaundice by using Kramer's rule. Because of the maximum perfusion of the face, trunk, and limbs, jaundice progresses cephalocaudally. (23) In addition to that, the affinity of albumin and bilirubin for blood differs along with the difference in the distance from the heart. If head and neck is jaundiced it implies a total serum bilirubin level of 4 to 8 mg/dl, icterus in upper trunk indicates a serum bilirubin of 5 to 12 mg/dl, and the icteric lower trunk and thigh indicate a serum bilirubin of 8 to 16 mg/dl, and icteric palms and soles indicate that the total serum bilirubin is greater than 15 mg/dl. (28) This method is not completely accurate and can not be done in routine clinical practice as it always requires good daylight for examination and the interpretation in dark-skinned babies are difficult by this rule.

Severity Of Jaundice Evaluation

As we mentioned above, total serum bilirubin increases in the following order- head and neck: 4-8mg/dl, upper trunk: 5-12mg/dl, lower trunk and thigh: 8-16mg/dl, palm, and soles: >15mg/dl, this is known as the Kramer's index. The thickness of skin in various regions of the body is related to the Cephalocaudal course of jaundice, with skin being thinnest on the face and thick over the palms and soles. Because of conformational changes in the bilirubin-albumin complexes, the cephalocaudal colour variation could be attributable to a difference in blood flow or skin lipid content. (6) By examining cephalocaudal development in natural daylight, the severity of jaundice can be determined.

Kramer Index

Areas of Body	Range of bilirubin (mg)
Face	4-8
Upper trunk	5-12
Lower trunk and thighs	8-16
Arms and lower legs	11-18
Palms and soles	>15

Increased bilirubin synthesis, less effective binding and transportation, less efficient conjugation, and excretion, and increased enterohepatic circulation

are all factors that make new-borns at increased risk Of hyperbilirubinemia. RBC haemoglobin, which produces 34 mg bilirubinper gram of haemoglobin, and early bilirubin, a 25% bilirubin formed by inefficient erythropoiesis in bone marrow and other heme-containing proteins are two sources of bilirubin. (20) Bilirubin is formed when heme-containing proteins are broken down. The breakdown of erythrocyte haemoglobin produces 75% of all bilirubin in infants. Other proteins such as myoglobin, cytochromes, catalase, and peroxidases break down to produce the remaining 25% of bilirubin. (48) The lysis of senescent red blood cells (RBC) in the reticuloendothelial cell initiates bilirubin production (59). 35 milligrams of bilirubin are produced for every gram of haemoglobin. (58)

Hepatic Uptake and Transport:

Unconjugated bilirubin binds reversibly with albumin on its way to the liver after being released from the reticuloendothelial system. Conjugation takes place in the liver. The circulating bilirubin that is not coupled to albumin is referred to as "free bilirubin," and it is this biirubin that can induce neuronal damage in the brain (47). Metabolic disturbances. such as acidosis and hypoxia, hypothermia, and infections are some of the factors which leads to the splitting of bilirubin-albumin complex. (45) Salicylates, sulphonamides, sodium benzate, and indomethacin are drugs which reduce bilirubin-albumin binding. (46)

Physiological and pathoogical jaundice are two types of neonatal hyperbilirubinemia. Physiological jaundice is defined as noticeable jaundice after 24 hours, with peak bilirubin levels of 12 mg/dl seen 3–5 days after birth. Peak bilirubin levels in preature infants might reach 15 mg/dl on days 5 to 7 (28).

Pathological jaundice requires timely treatment. Pathological jaundice is the onset of jaundice within the first 24 hours of life, a rise in serum bilirubin > 0.2 mg/dl/hour, symptoms of any other underlying Disease. Phototherapy is required when jaundice appears within 24 hours of birth, persists for more than 3 weeks, and direct bilirubin is greater than 2 mg/dl. (34)

Babies with physiological hyperbilirubinemia do not need any treatment. They just need to be closely monitored to ensure that the condition does not worsen. Pathological hyperbilirubinemia warrants examination, therapy, and close monitoring. Identification of at-risk neonates, evaluation of the aetiology of pathological hyperbilrubinemia, determination of treatment thresholds, and follow-up of neonates with severe hyperbilirubinemia have to be done in neonatal jaundice.

Although bilirubin, as an antixidant, protects against free radical damage, it must be monitored and corrected in case it's above the threshold value, to prevent severe hyperbilirubinemia (defined as serum bilirubin > 20 mg/dl), which can lead to acute bilirubin encephalopathy. (34) In case if it's not treated in time, these

babies may develop chronic bilirubin encephalopathy. Features of chronic bilirubin encephalopathy include cerebral palsy mainly choreoathetoid type, sensorineural deafness, intellectual defects, enamel dysplasia, and upward gaze limitation. The cornerstone of management of neonatal jaundice is early identification of risk factors, immediate vigilant surveillance of these high-risk new-borns, and the commencement of timely intervention. Apart from starting phototherapy, maintenance of good calorie intake and hydration are also important. Condition causing reduction of enterohepatic circulation, sepsis, asphyxia, acidsis and temperature instability disrupts the bilirubin metabolism, prevents bilirubin-albumin binding, and eventually destroys the blood-brain barrier integrity.(38)

Phototherapy is a treatment method that uses blue-green light with a wavelength that correspnds to the peak absorption of bilirubin (450-460nm) (39). Phototherapy is particularly Effective with special blue lamps with wavelengths of 425-475 nm. There are mainly three types of photochemical reactions which occur when bilirubin absorbs light. These are photoisomeization (70%), structural isomerisation, and photo-oxidation. It is these reactions which converts bilirubin to a polar form, thereby allowing it to be excreted in urine and stool more easily. phototherapy if properly administered can decrease the total serum bilirubin at a rate of 1-2 mg/dl every 4-6 hours. This in turn prevent the consequences of hyperbilirubinemia (41) Estimation of transcutaneous bilirubin using a transcutaneous bilirubinometer be used to determnes the amount and severity of

jaundice. Transcutaneous bilirubinometer is non-invasive and simple way to measure the serum bilirubin. But measurement of TSB with transcutaneous bilirubinometer is unreliable when serum bilirubin levels are more than 15 mg/dl. It is the group that requires phototherapy but is not identified by this device. Hence the use of a bilirubinometer to monitor new-borns during phototherapy administration is not reliable. Although a transcutaneous bilirubinometer can be used as a screening tool, treatment decisions must be made based on serum bilirubin estimates.

Conjugated and unconjugated bilirubin are the 2 types of bilirubin. Unconjugated bilirubin is the main component that causes an increase in serum bilirubin in neonatal hyperbilirubinemia. Unless conjugated bilirubin's value surpasses 50% of the total serum bilirubin, the decision whether to start treatment or not is made based total serum bilirubin. (40) Even though phototherapy is effective in treatment of neonatal jaundice, it has other adverse effects such as disruption of maternal-infant interaction, disruption of thermal environment, hypocalcaemia, disruption of circadian rhythm and bronze baby syndrome. It can also cause long-term side effects such as retinal damage and retinopathy of prematurity, increased occurrence of patent ductus arteriosus, chromosomal damage, nevus, and skin cancer. (49)

Adjuvant therapies such as intravenous immunoglobulin, Phenobarbione, tin-metalloporphyrin, oral clofibrate, and oral agar have been used in the case of iso-immune and haemolytic illness, to delay the need for phototherapy. Exchange

transfusion removes partially haemolysed red cells. It can also remove unattached antibodies. (52) Exchange transfusion process is invasive and has many adverse effects. Hence exchange transfusion is used as a last resort and its reserved only for use in babies with phototherapy failure and impending or early stages of acute biliruin encephalopathy for reversing as well as preventing the progression to brain damage. (54) Fresh compatible, non-haemolyzed antibody and bilirubin-free red cells will replenish 87 percent of the patient's blood volume. (56). But exchange transfusion can cause rebound of serum bilirubin to 60% of pre-transfusion levels in 1 hour. (60)

Adverse Effects of Exchange Transfusion

1. Hypocalcaemia and hypomagnesemia caused by citrate ion binding to ionic calciu, may appear as ECG abnormalities and cardiac dysfunction. (38) If a recorded drop in serum calcium is observed, it is necessary to seek medical attention. In such cases, calcium supplements should be given intravenously if needed.

2. Hypoglycaemia is caused by a high dextrose content in transfused blood, which causes a reactive increase in endogenous insulin, thereby resulting in a drop in blood sugar.

3. Citrate in transfused blood causes acid-base imalance in the form of metabolic alkalosis. (32)

4. Hyperkalaemia caused by transfusion of stored blood can be avoided by receiving fresh blood, washing the RBC, and replacing it with fresh plasma. (31)

5. Graft versus host disease, manifests as a maculopapular rash, eosinopenia, lymphopenia, and thrombocytopenia. (34) Transfusing. irradiated blood can prevent this.

6. Thermo-dysregulation caused by cold blood transfusion. It can be avoided by adequately warming the blood by using a radiant warmer.

7. Thrombo-vascular events such as thrombosis, embolism, and vasospasm (30).

8. Long-term events, such as portal vein thrombosis, can result in extra hepatic portal vein blockage.

These limitations of current treatment necessiate the need of development of innovative adjunctive therapies that lessen the side effects of existing therapies while also reducing the necessity for invasive therapies.

Phototherapy can lead to insensible water loss. It also causes temperature instability. Patent ductus arterisus incidence rate is also observed to increase in babies exposed to phototherapy light. Exchange transfusion also have many adverse effects. Hence an alternate method to decrease the incidence of 'pathological' hyperbilirubinemia neonates is a need of the hour. This study is conducted keeping this in mind to find an alternate, efficient, cheap and non-invasive method to treat hyperbilirubinemia in new-borns. Phenobarbitone is

found to satisfy all the above criteria. Hence it can be used to treat neonatal jaundice without having any complications of invasive methods like exchange transfusion. As phenobarbitone cause sedation and other side effects it cannot be used universally, used only in high-risk babies.

Heme metabolism produces bilirubin. Bilirubin is mainly composed of haemoglobin, myoglobin, cytochrome, catalase, peroxiase, and free heme. Heme oxygenase oxidises the heme ring of heme-containing molecules to biliverdin in the reticuloendothelial system. (46) It is the biliverdin reductase which converts bilierdin to bilirubin. Bilirubin is a nonpolar, water insoluble substance. Bilirubin is transported to the liver after attachment with albumin. Bilirubin coupled to albumin dissociates from albumin and crosses the plasma membrane, where it binds to cytoplasmi ligandin and enters the endoplasmic reticulum. (18) Bilirubin gets converted to conjugate form by uridine diphosphate glucuronyl transferase, afterwards it is excreted into the bile canaliculi. (22)

By increasing the uridine-diphosphate glucuronyl transferase enzyme activity phenobarbione can reduce the unconjugated bilirubin found in the new-born period (46). Intestinal glucuronidase enzyme converts conjugated bilirubin to unconjugated bilirubin, which enters the enterohepatic circulation. Intestinal bacteria convert it to urobilin. Afterwards it is expelled in stool and urine as urobilin and stercobilin, respectively. (26)

Most of the bilirubin in circulation is unconjugaed and binds to albumin. Bilirubin that has been albumin-bound is unable to pass the blood-brain barrier. 1 gram of albumin binds to 8.5 mg/dl of biliubin in the blood, and the level of albumin in the blood correlates with gestational age and post-natal age. Adult values are achieved only by 5 months of age. (28) The factors that increase risk of bilirubin-induced neurological dysfunction are asphyxia, sepsis, hypothermia, acidosis, hypoalbuminemia, acidosis, low birth weight, preterm new-borns, haemolysis, and caloric depriation. (20)

Bilirubin deposition in the brain is increased by the following causes- Increased free bilirubin, reduced albumin quantity, reduced binding capacity and increased bilirubin acid precipitation mainly in the nerve cell membrane (57). Brain injury can be exacerbated by a disruption of the blood-brain barrier and aciosis. Unconjugated bilirubin builds up in the basal ganglia, pons, and cerebellum. Deposited bilirubin disrupts neurotransmission. It causes mitochondrial malfunction, impairs the intracellular membrane functin, and manipulates the enzymatic actions. It can also cause pigmentation and necrosis of brain tissue.

Kerniterus creates a yellow staining in the basal ganglia that are mainly noted on globus pallidus and subthalamic nucleus. (44) The auditory, oculomotor, and vestibular nuclei are increasingly vulnerable. (46) The cerebellum (Purkinje cells) and the hippocampus, mainly the CA2 sector, are also at an increased risk. Reduced feeding, lethargy, changeable aberrant tone

(hypotonia and/or hypertonia), high pitched cry, retrocollis and opisthotonos, fever, convulsions, sun setting sign and death are all symptoms of acute bilirubin encephalopathy. (48)

Chronic bilirubin encephalopathy (kernicterus) is a clinical tetrad. It includes the following-

1. Disorders of movement- athetosis and dystonia, spasticity and hypotonia,

2. Auditory dysfunction - Hearing loss, auditory desynchrony

3.Oculomotor dysfunction- gaze and lateral gaze impairments, strabimus

4. Deciduous teeth enamel hypoplasia

In the treatment of infant jaundice, phototherapy is the bedrock. When bilirubin absorbs phototherapy light, it undergoes three types of photochemical reactions. Photoisomeriation (70%), Structural isomerisation, and photo-oxidation are the three processes. Phototherapy acts on bilirubin bound to albumin in the capillaries and the interstitial space. (57) Photoisomerization transforms unconjugated 4z 15z bilirubin into the less toxic, polar form, that can be eliminated in the bile. (58) This is a reversible mechanism. This process leads to a fast gastrointestinal reabsorption. Structural isomerization is the intramolecular cyclization of bilirubin to lumiubin. It is this lumirubin that contributes 2% to 6% of serum bilirubin. Afterwards it is excreted in the bile and urine. (54) The less significant of all

three reactions involved in the conversion of bilirubin to tiny polar compounds is the photo-oxidation.

Factors that influence phototherapy efficacy are as follows- the spectrum and irradiance of phototherapy light, surface area of light exposure, and the duration of exposure to phototherapy light. The optimal light spectrum is 425 to 475 nm, which comes in the blue green spectrum. The amount of light emitted varies on the distance between the light source and the neonate. To boost irradiance, the phototherapy lights are situated 20 cm away from the baby. (56) Double-surface phototherapy, Triple surface phototherapy and the use of aluminium foils in the phototherapy unit margin increase the amount of surface area exposed to phototherapy.

Phototherapy can be started in many ways, including: 1. Compact fluorescent light tubes, that are particularly successful at lowering bilirubin levels.

2. Halogen lamps- Even though the size is small risk of burns is more, so not used.

3. Fibreoptic systems- It is effective in administering phototherapy and do not pose risk of retinal injury. It's safe and hence it is ideal to be used as Bili blanket at home.

4. Light emitting diodes (LEDs)- Optimum irradiance can be generated by LEDs. LEDs can cause total serum bilirubin level drop by about 1 to 2 mg/dl. (64).

In case serum bilirubin continues to rise despite phototherapy and reaches the level of threshold for exchange transfusion, the condition can be called as phototherapy failure. Adjunctive therapies have been developed to overcome the problem of phototherapy failure. Intravenous immunoglobulin is used in iso-imune haemolytic diseases to reduce haemolytic rate by inhibiting the Fc receptor. The main limiting problem is the cost of IvIG. Also, it's only beneficial in situations with immunological haemolysis.

Phenobarbione is another option for causing uridine diphosphate glucuronyl transferase enzyme induction. (60) Phenobarbitone has a long latency time of 48 to 72 hours for enzyme induction. The side effects like reduction in serum vitamin k levels and respiratory depression are not commonly observed. (28) Long-term treatment of phenobarbtone is beneficial in lowering serum bilirubin in neonates with crigglar-najjar syndrome type II, and it is one of the successful remedies. (50) The rise in serum bilirubin is also reduced by using oral agar and charcoal. They act as bilirubin binding agents. Increase in stool frequency, caused by oral agar leads to an increase in intraluminal bilirubin clearance. But these medications are not used in routine practice. (54)

Heme oxygenase inhibitors,such as metalloporhyrin’s also reduce bilirubin production (66). Clofibrate, an enzyme inducer i neonatal jaundice, has also been found to lower phototherapy failure rates and duration. (60). Clofibrate is also in the early phases of development.

Phototherapy is the most widely used treatment for neonatal hyperbilirubinemia. But phototherapy has several side effects which includes short term side effects and long term side effects. It decreases the mother-infant attachment in the initial days of life, hence decreases both breast milk secretion and breast-feeding duration. Huge insensile water loss, and dehydration are the side effects of phototherapy. Other problems encountered because of the fluorescent lamps used for phototherapy are hyperthermia as well as hypothermia in new-borns. (43) This occurs because of alteration of infant's microenvironment by the fluorescent lamps. Phototherapy can also cause a drop in total and ionised calcium levels (40) Increased urine calcium excretion is mainly the cause of this effect. Furthermore, light can disrupt calcium homeostasis by blocking melatonin secretion in the pineal gland, resulting in hypocalcaemia. (41) behaviours such Phototherapy may disrupt the Th-2/Th-1 transitin. (37) TNF-alpha, IL-1 beta, and IL8 levels can be increased by phototherapy, although IL-6 levels are decreased. (38) The main cause of Th-2/Th-1 switch diorder is a change in cytokine levels. (38) TH2/TH1 switch malfunction and dysfunction of lymphocytes are caused by phototherapy-induced chromosomal and DNA breakage.

When the retina is exposed to blue light, photon absorption increases thereby increasing the retina's sensitivity to light-induced cell death. This leads to retinal damage. Bilirubin functions as an antioxidant, hence it may help to prevent ROP. (28) With the increase in the adverse effects of phototherapy

and the risk of failure associated with phototherapy, a new form of therapy that can act as a supplementary, substitute, that prevents patients from being subjected to phototherapy for long duration is required.

Phenobarbital, commonly known as phenobarbitone, and marketed under the brand name Luminal, is a barbiturate medicine. Phenobarbitone, being cheap efficient and easily available is recommended by the World Health Organization (WHO) in developing countries for the treatment of certain kinds of epilepsy. It is used to treat seizures in young children. Route of administration can be oral, intravenous, or intramuscular. Intravenous phenobarbitone is used in case of Status epilepticus. Phenobarbital can also reduce the need for exchange transfusion in neonatal hyperbilirubinemia. (62) Phenobarbital is a cytochrome P450 inducer In case of patients with Crigler–Najjar syndrome type II or patients with Gilbert's syndrome, phenobarbital is occasionally taken in modest dosages to aid in the conjugation of bilirubin.

Phenobarbital is given to infants suspected of having new-born biliry atresia (49) Phenobarbital is used as a second-line treatment for neonates with neonatal abstinence syndrome, which is a disorder characterised by withdrawal symptoms caused by prenatal opiate exposure. (51)

The oral bioavailability of phenobarbial is approximately 90%. Peak plasma concentration is obtained eight to twelve hours after oral dosing. Phenobarbitone is one of the longest-acting barbiurates. Phenobarbitone has a long half-life of about 2-7 days. Phenobarbitone also has a low protein

binding rate (20 to 45 %). (61) The liver metabolises phenobarbital mainly through hydroxylation and glucuronidation. Phenobarbitone causes the induction of cytochrome P450 2B6 (CYP2B6) via the CAR/RXR nuclear receptor heterodier. (64) It is then eliminated by the kidneys.

By interacting with GABA receptor subunits, phenobarbital acts as an allosteri modulator, extending the duration of opening of the chloride ion channel. (67) Phenobarbital works by increasing the flow of chloride ions into the neuron, thereby lowering the excitability of the post-synaptic neuron. (68)

By increasing the activity of the uridine-diphosphate glucuronyl transferase enzyme, phenobarbitone reduces the biirubin increase found in the new-born period. (64) Phenobarbitone also can reduce the need for exchange transfusions and the length or duration of phototherapy by lowering the peak total serum bilirubin or the duration of hyperbilirubinemia. (61) Several studies have been done on the use of phenobarbitone to reduce the incidence and/or severity of jaundice in low birthweight or other 'at-risk' neonates. These were published since 1960s and 1970s, when phototherapy was not widely used, and the prevalence of kerniterus was high. These studies suggested that phenobarbitone medication, if started soon after birth, could reduce peak serum bilirubin levels.

Kernicterus in premature VLBW infants practically vanished with enhanced intensive care and more aggressive use of phototherapy devices, and phenobarbione use decreased significantly. Although phenobarbitone was

later widely studied for the prevention of intraventricular haemorrhage, it was not widely used for treatment of neonatal hyperbilirubinemia. Kumar, et al studies were done by giving phenobarbitone in a loading dose of 10 mg/kg. According to the study, phenobarbitone was more effective in controlling peak serum bilirubin level if loading dose was administered at start of phototherapy. Beneficial effect of phenobarbitone in reducing hyperbilirubiemia and in reducing treatments like phototherapy and exchange transfusion and in reducing treatment related complications and morbidities are of special relevance in a tertiary care resource-restricted setting where the availability of working phototherapy units and adequately trained staff for performing procedures like exchange transfusion are less. In a limited resources setting, phenobarbial in combination with phototherapy may be helpful to new-born infants, as it causes a faster decline in total serum bilirubin, thus decreasing the need for blood exchange transfusion than phototherapy alone.

Based on the findings of Waltman et al., it was explained that decrease in total serum bilirubin was observed in trials done by administering phenobarbitone. In established hyperbilirubinemia of the infant, phenobarbitone along with phototherapy lead to a quick drop in total serum bilirubin, which was statistially and clinically associated with a considerable decrease in blood exchange transfusion rate. (67) However, this was contradicted by two important studies by Wong et al. and Nazir et al., who evaluated the effect of

combination therapy with the effect of monotherapy on TSB. (30) (56) Both of these studies were done on very a smaller number of patients with non-haemolytic hyperbilirubinemia. This explains the disparity in the study. Other factor which lead to a disparity in result of the study was that sepsis was not considered at all in the study even though there were two deaths among the study participants because of neonatal septicaemia.(54) Babies with positive CRP and/or any sign of sepsis requiring antibiotics should not be chosen as study participant, as sepsis is a well-known cause of exaggerated hyperbilirubinemia.

Modalities For Determining Jaundice

Icterometer – A device that compares the colour of your skin to the colour codes on a plastic strip.

Transcutaneous Bilimeter - A device that uses computerised spectrophotometry to measure blood flow.

Normal Bilirubin Levels in New-born

The amount of TSB in cord blood varies between 1.4 and 1.9 mg/dl (14). Because foetal bilirubin is removed by the mother, cord TSB levels are relatively normal at birth. The infant must do the process of conjugation and excretion after birth. All infants suffer a spike in TSB after delivery due to maturational limitations in bilirubin conjugation and elimination. Many factors influence the total serum bilirubin values in new-borns, including

gestatonal age and breast feeding. Bilirubin levels in term babies rise gradually from birth, peaking at 5 to 7 mg/dl around days 3 to 5, and then falling by days 7 to 10 (15)

The clinical course of physiological jaundice was separated into two phases by Gartner and colleagues 13:

- Phase 1 - lasts for the first 5 days of life in term babies This phase is indicated by a rapid rise in TSB for 3-4 days, following which the level begins to fall.
- Phase 2 - Characteried by stable, but elevated total serum bilirubin levels lasting for 2 weeks.

Jaundice And Breast Feeding

Breastfed infants are three times more likely than bottle-fed infants to develop neonatal hyperbilirubinemia. Although there are two occurrences associated with breast milk and jaundice, breast feeding jaundice and breast milk jaundice, there is significant overlap between the two entities, and they may be indistinguishable in some new-borns (19). Breast-feeding jaundice usually appears between the ages of 2-4 days and peaks between the ages of 3-6 days. Breastfed new-borns get breast-feeding jaundice in about 10% of cases. (18) Breastfed new-borns consume fewer calories than bottle-fed infants, resulting in less faeces by weight and significantly reduced biliubin excretion in the first three days of life (16). Breastfeeding jaundice is treated by encouraging rather than restricting breastfeeding. New-borns who nursed more than 8 times a day had lower

bilirubin levels than infants who nursed less than 8 times a day, according to De Carvalho and colleagues (26) The AAP recommends boosting milk intake by increasing feeding since it results in greater caloric intake, weight gain, increased meconium passage, and decreased bilirubin levels. Breast milk jaundice is commonly observed between the ages of 4 and 7 and peaks between the ages of 5 and 15. (18) Breast milk jaundice is thought to be caused mostly by the chemicals in breast milk. (22) Increased intestinal absorption of bilirubin into the enterohepatic circulation . the most plausible route. Breast milk has a higher level of beta-glucuroniase activity, and this contributes to breastmilk jaundice. (29) Bile salt - induced lipase, found in human milk, promotes fat absorption, which is thought to be linked to an increase in intestial bilirubin absorption. Breast-milk jaundice is caused by a decrease in the synthesis of urobilinogen in breast-fed neonates. Breast-fed babies excrete urobilin later in their stools than formula-fed babies. (20)

Hyperbilirubinemia Without Conjugation

1) Increased bilirubin production or bilirubin burden on the liver

Immune-mediated haemolytic illness, Rh isoimmunization, and ABO or other blood group incompatibility

2) Defects in the red cell membrane

Spherocytosis, elliptocytosis, pyropoikilocytosis, and stomatocytosis are all hereditary conditions.

G6PD deficiency, pyruvate kinase deficiency, and other erythrocyte enzyme insufficincy are examples of red cell enzyme abnormalities.

3) Hemoglobinopathies

Alpha and beta thalassemia are two types of thalassemia

4) Unstable Haemoglobin

Heinz body haemolytic anaemia is a type of haemolytic anaemia that is present at birth.

5) Other factors

DIC, sepsis, Blood extravasation, hematomas, pulmonary, abdominal, brain, or other occult bleeding, polycythaemia, macrosomic infants of diabetic mothers

6) Abnormalities in circulation of the enterohepatic system

Breast milk jaundice, Pyloric stenosis, Ileus (little or major bowel blockage)

7) Reduced clearance

Prematurity, G6PD deficiency, and pyruvate kinase deficiency are all symptoms of pyruvate kinase insufficiency.

8) Inborn Errors of metabolism

Crigler Najjar syndromes 1 and 2, Galactosemia, Tyrosinemia, Hypothyroidism, Gilbert syndrome.

Haemolytic illness of new-borns is the most commonly diagnosed pathologic cause of hyperbilirubinemia. Rh and ABO incompatibility is the most common cause of RBC destruction in foetuses and new-borns. ABO incompatibility is evident in moms of the O blood type and infants of the A or B blood types.

Glucose-6-phosphate dehydrogenase deficiency is a major cause of neonatal hyperbilirubinemia among the hereditary diseases that cause haemolytic illness in infants. G6PD is an enzyme found in all cells of the body that protects cells, particularly RBCs, against oxidative damage. Cells become sensitive to oxidation in the absence of G6PD and resulting in cellular death. (26) Haemolysis and hyperbiliubinemia in G6PD deficiency can be induced by oxidative stressors such as sepsis and exposure to a variety of chemicals such as naphthalene and antisepsis agents used in the umbilical cord. G6PD deficiency is an X-linked condition that causes hyperbilirubinemia and kernicterus in new-borns.

Decreased Bilirubin Clearance

Conjugation of bilirubin inside the hepatocyte depends on a single form of the uridine diphosphoglucuronate glucuronosyltransferase (UGT) enzyme. (32) Three inherited defects of UGT deficiency are noted to cause neonatal hyperbilirubinemia: Crigler Najjar syndrome types 1 and 2, Gilbert syndrome.

Conjugated Hyperbilirubinemia

Conjugated bilirubin levels in the blood are a less common but substantial cause of hyperbilirubinemia in new-borns. The major symptom of new-born cholestasis is conjugated hyperbilirubinemia, which should be distinguished from unconjugated hyperbiliubinemia. Any infant who has been jaundiced for more than three weeks should have his or her total and direct bilirubin levels measured and be assessed for neonatal cholestasis.

KERNICTERUS

The name "kernicterus" was first used to describe the yellow staining of the brain. It's a term for the acute and long-term repercussions of hyperbilirubinemia. Further-more, the names "kernicterus" .and "bilirubin encphalopathy" have been interchanged. To represent the alterations associated with acute bilirubin encephalopathy, the term "bilirubin-indced neurologic dysfunction" was recently developed, coupled with a score system to assess the severity of symptoms.

Pathophysiology

The basal ganglia, particularly the globus pallidus and subthalamic nucleus, the hippocampus, substantia nigra, cranial nerve nuclei, particularly the oculomotor, vestibular, cochlear, and facial nerve nuclei, and other brain stem nuclei, as well as the anterior horn cells of the spinal cord, are the areas of the brain most affected by bilirubin staining. (33) The clinical signs of bilirubin encephalopathy can be explained by these sites of neuronal damage. Bilirubin transit across an intact blood-brain barrier is supported by several theories. Bilirubin binds to the

phospholipids of capillary endothelial cells, which then easily mirate into the brain, allowing entry through an intact blood-brain barrier. Anything that makes bilirubin's capacity to bind with albumin more difficult, such as greater bilirubin production, lower albumin levels, or competition for binding sites, can result in more free bilirubin and hence improve bilirubin transport into the brain. Bilirubin has a tendency to absorb hydrogen ions, generating hazardous bilirubin acid aggregates that can harm capillary endothelial cells and promote bilirubin uptake by the brain (17). Because bilirubin is increased in an acidic environment, this could explain why aciosis plays a role in bilirubin encephalopathy. Bilirubin has also been shown to pass the compromised blood-brain barrier. To generate neuronal damage, bilirubin must dissociate from albumin. Bilirubin encephalopathy is caused by hypersmolar solutions, hypercarbia, hypoxia, cerebral infection, and an increase in blood pressure. Injury to cellular membranes is expected to play a substantial influence. Free bilirubin reaches intracellular organelles such as mitochondria, endoplasmic reticulum, and nucleus in the same way that free biliubin enters the brain by binding to membrane phospholipids, according to Volpe (36). Susceptibility to injury in the brain varies depending on cell type, brain maturiy, and brain metabolism. A peak serum bilirubin level of greater than 20mg/dl has traditionally been used to predict a bad outcome in Rh haemolytic disorder new-borns. (33) Serum bilirubin levels of less than 25 mg/dl in otherwise healthy new-borns (without haemolytic illness) are unlikely to put the babies at risk of neurodevelopmental problems. Acute encephalopathy normally proceeds in three stages, each of which becomes

more severe. The initial phase lasts for a few days and is marked by a little stuor (lethargy, sleepiness, slight hypotonia, decreased movement and poor sucking). Infants who are not well-managed throughout this stage have a significantly worse prognosis.

Symptoms And Significance

Backward arching of the neck (retrocollis) and trunk (opisthotonos), rigid extension of all four extremities, tight-fisted posturing of the arms and crossing extension of the legs are all signs of enhanced tone. Following that, phase three is marked by severe lethargy or coma, increased tone, pronounced retrocollis and opisthotonos, a sharp cry, and no feeding. Kernicterus is manifested by a tetrad of extrapyramidal, auditory abnormalities, gaze palsies, and dental dysplasia. Chronic bilirubin encephalopathy is manifested by a tetrad of extrapyramidal, auditoryabnormalties, gaze palsies, and dental dysplasia. (19) These symptoms may not appear till the child is 6 months to a year old. Athetosis of all limbs is the most noticeable motor movement, albeit arms are more affected than legs. Chorea, ballismus, and tremor are examples of other movements. In kernicterus, the most common gaze anomaly is an upward look. High-frequency hearing loss is the most frequent auditory problem.

Neuronal Injury Caused by Bilirubin in Premature Infants

Premature infants are at greater risk for developing kernicterus than full-term infants. Although kernicterus is rare occurrence in the new-born critical care unit, analyses of recent kernicterus cases have revealed that late preterm gestation is a substantial risk factor for severe hyperbilirubinemia.

Bilirubin Screening on A Global Scale

It has been advocated to focus early post-discharge follow-up and serum bilirubin measures on those new-borns who most at risk are, while limiting or eliminating repeat bilirubin readings in those who are less at risk.

The purpose of the predictive bilirubin nomogam is to provide a practical, easily accessible guide for monitoring the severity of jaundice so that simple preventive measures such as feeding and care counselling, the use of formula or expressed breast milk supplements, or phototherapy can be implemented as soon as possible. The American Academy of Paediatrics' practise standard for the care of hyperbilirubinemia in healthy neonates, published in 1994, suggested that any baby found to be jaundiced by visual evaluation be given a serum bilirubin test during the first 24 hours following birth. (11)

It further stipulates that all neonates discharged within 48 hours of birth should be seen by a health care practitioner within 2-3 days. The decision to monitor serum bilirubin during follow-up is left to the discretion of the healthcare

provider based on his or her visual assessment of the severity of jaundice. If the TSB rises at a rate of 6 mg/dl or higher in 24 hours, when the TSB exceeds 18 mg/dl by the age of 49-72 hours, 20 mg/dl after 72 hours, or if the infant is unwell for any reason, phototherapy is suggested. (14)

The Impact of Hourly Bilirubin Value

The bilirubin levels can escalate to dangerous levels before being detected as excessive and addressed unless the visual estimation of severity of jaundice is precise and there is concern about its intensity, especially when connected to neonatal age in hours. The clinical practise of reporting biliubin based on the number of days since the patient was born was deceptive. Because bilirubin levels rise in "hours" of life rather than "days," the time of sample must be in "hours of life" rather than "days of life." It is more accurate to report bilirubin levels in hours rather than days. (28) This enables the level to be placed in a percentile tract for hour-specific bilirubin readings. The prognostic effect of hour specific bilirubin was initially reported by Bhutani et al (29). TSB levels were measured in all term and near-term babies during standard screening for this investigation. At the time of TSB measurement, the postnatal age (hours) was recorded. From hour specific pre and post discharge TSB values of neonates, a percentile-based bilirubin nomogram for the first week was created.

The zones of the nomogram are as follows:

> 95th centile - high-risk zone Upper intermediate (76th-95th centile) and lower intermediate (76th-95th centile) risk zones (40th-75th centile) The 40th percentile is considered to be a low-risk zone (26).

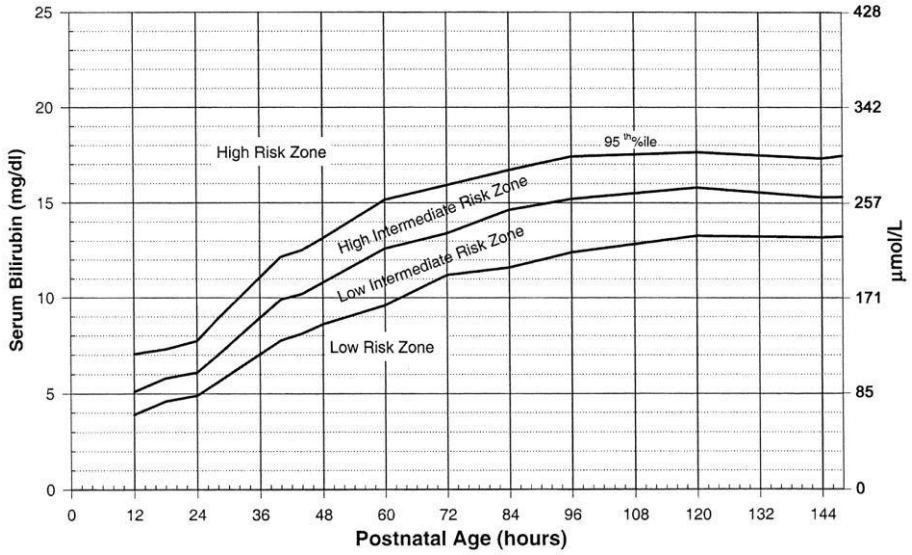

Photo 1: Bhutani's Nomogram

Based on their findings, the risk of subsequent hyperbilirubinemia was calculated as a 1:22 ratio for disease vs. no disease. The overall risk is zero in the low-risk zone, roughly half (1:45) in the lower intermedite zone, tripled (1:7) in the upper intermediate zone, and 14 times in the high-risk zone (2:3). The attraction of nomogram stems from its ease of use, accessibility, and low cost.

Hyperbilirubinemia and the probability of early discharge

The highest bilirubin level occurs when a baby is discharged from the hospital before he or she is 36 hours old. As a result, jaundice has become a major OPD issue, and we need to rethink our strategy guarantee that we don't overlook any

babies who have a high bilirubin level. All serum bilirubin evaluations and interpretations must be done in terms of the baby's age in hours, not days.

Breast feeding does not need to be routinely discontinued only for the goal of establishing a diagnosis of breastmilk or breastfeeding jaundice, according to Gartner (1994).

MATERIALS AND METHODS

STUDY DESIGN

Randomized Controlled Trial- Double Blinded

STUDY PERIOD

December 2019- July 2021

STUDY POPULATION

All new-born babies admitted for treatment of hyperbilirubinemia in Shri B.M Patil Medical College, Hospital and Research Centre, Vijayapura, both inborn and out born babies referred to here fulfilling the inclusion and exclusion criteria.

132 cases of hyperbilirubinemia were studied in the span of 19 months.

Method of collection of Data)

This is a hospital based randomized open label study conducted on neonates born in the maternity department of Shri. B. M. Patil Medical College and Research Hospital. Babies born in this hospital were screened for jaundice.

132 babies were enrolled in the study.

61 of them received phenobarbitone 10mg /kg /dose single IM injection as an adjuvant therapy. 61 will received only phototherapy. After 12 hours, 24 hours and 48 hours, serum bilirubin was again assessed for both groups by collecting the venous blood sample of baby.

INCLUSION CRITERIA

All babies who completed 37 weeks of gestation and born with a birth weight > 2.5 kg and with total serum bilirubin values meeting the threshold for phototherapy according to age specific nomogram by American Academy of Paediatrics[2] for phototherapy.

EXCLUSION CRITERIA

1. Premature babies
2. Low birth weight babies
3. new-borns with sepsis, asphyxia, shock
4. Babies born with congenital anomalies
5. small for gestation/ intrauterine growth restriction
6. Inborn errors of metabolism
7. Neonates with neonatal cholestasis, renal or liver disorders

8. neonates with coagulation disturbances

9. neonates with acid base disturbance, electrolyte disturbance

10. neonates with features of intrauterine infection

GROUPS ASSIGNED

1. Case group- Phenobarbitone with phototherapy

2. Control group- Phototherapy

DRUGS USED

A single intramuscular injection of phenobarbitone at a dose of 10 mg/kg/dose.

METHODOLOGY

On clinical examination, neonates who were found to be icteric were given a serum bilirubin test, and those whose blood bilirubin levels exceeded the AAP nomogram cut-off value for phototherapy or exchange transfusion were evaluated for exclusion factors. They were enrolled in the after receiving written and informed permission if exclusion factors were not present. Using a randomization system, these new-borns were assigned to one of two groups. Neonates of the case group (Phenobarbitone group) were given single intra-muscular injection 10 mg/kg on anterolateral thigh before the start of phototherapy. Neonates of the control group were given only phototherapy. Babies of both the group were given phototherapy at 20 cm under phototherapy unit with 6 fluorescent lamps of blue light spectrum continuously with interruption of phototherapy only during breast feeding. Babies were continuously monitored clinically and evaluated for development of side effects of either therapy in both groups. Serum bilirubin was monitored at the start of phototherapy and every 12 hours. Phototherapy was stopped when serum bilirubin fell 2mg/dl below age specific threshold according to AAP nomogram.

When bilirubin levels exceeded the AAP nomogram threshold for exchange transfusion, neonates whose bilirubin levels continued to rise despite intensive phototherapy were given an exchange transfusion. The blood group,

maternal blood group, coombs evaluation, and daily weight monitoring of neonates were all done before they started phototherapy. Serum bilirubin levels were examined for 12 hours after phototherapy ended, and if no rebound spike occurred, the neonates were discharged 24 hours later. Babies discharged were followed up 1 week after discharge for weight gain, features of cholestasis, feeding and bowel pattern and clinical evaluation were performed. The sex, birth weight, hour/day of life, maternal and new-born blood groups, bilirubin levels at the commencement of treatment, and peak bilirubin levels were all documented. The length of phototherapy and the number of times it failed, if any, were noted. Data on monitoring and follow-up were gathered. Babies were treated according to standard practise and were monitored for the development of any complications on a regular basis. The data was examined for statistical significance. Discrete variables were analysed by chi-square test and continuous variables by z test. P value < 0.05 was considered as statistically significant.

RESULTS

This study was conducted in the Neonatal Intensive Care Unit (NICU), Department of Paediatrics, Shri B.M. Patil Medical College Hospital. All babies admitted for treatment of neonatal jaundice which included both inborn babies and out born babies referred to our hospital for neonatal hyperbilirubinemia treatment were included in this study provided they fulfilled the inclusion criteria of our study. Study was conducted over a 19-month period, from December 2019 to July 2021.

During this study period 228 neonates got treatment for neonatal hyperbilirubinemia in our hospital. They were given treatment in the form of phototherapy light. Out of these 228 babies, 132 babies fulfilled the inclusion criteria of our study, and these 132 new-borns were enrolled into the study. Out of these 132 new-borns, 61 babies we randomized into a case group which we termed as combined therapy group or phenobarbitone group or a phenobarbitone with phototherapy group. Remaining 61 babies were randomized to a control group which we termed as monotherapy group or phototherapy alone group. Babies in the the case group or phenobarbitone with phototherapy group were given a single dose of intramuscular injection of phenobarbitone at a dose of 10mg/kg at start of phototherapy. Babies in this case group were continued on phototherapy as usual after the phenobarbitone single dose injection.

Serum bilirubin of babies in both the groups, case group and control group were then checked every 12 hours. Babies in both groups were monitored for development of any complication related to either phenobarbitone or phototherapy or both. Serum bilirubin of babies in combined therapy group and monotherapy group were tested at 12 hours, 24 hours, and 48 hours of phototherapy. Babies in either group, case group and control group were discharged when their serum bilirubin levels came within normal limits.

Statistical methods used

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables.

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript "c" are the degrees of freedom. "O" is observed value and E is expected value. C= (number of rows-1) *(number of columns-1)

The difference of the means of analysis variables between two independent groups was tested by unpaired t test.

The t statistic to test whether the means are different can be calculated as follows:

$$t = \frac{(\overline{x_1} - \overline{x_2}) - (\mu_1 - \mu_2)}{\sqrt{\frac{{s_1}^2}{n_1} + \frac{{s_2}^2}{n_2}}}$$

where $\bar{x}_1$ = mean of sample 1

$\bar{x}_2$ = mean of sample 2

n_1 = number of subjects in sample 1

n_2 = number of subjects in sample 2

${s_1}^2$ = variance of sample 1 = $\frac{\Sigma(x_1 - \bar{x}_1)^2}{n_1}$

${s_2}^2$ = variance of sample 2 = $\frac{\Sigma(x_2 - \bar{x}_2)^2}{n_2}$

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analysed using SPSS software v.23(IBM Statistics, Chicago, USA) and Microsoft office 2007.

Group	Number of neonates
Phenobarbitone with phototherapy	61
phototherapy	61

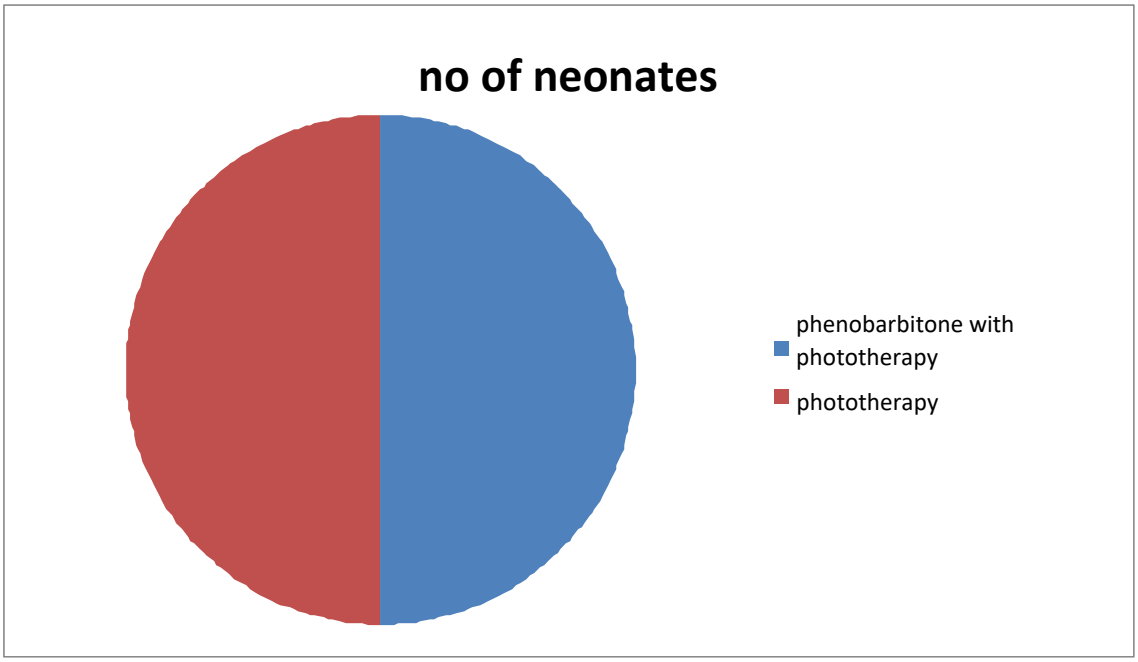

Fig 1: Number of neonates in both groups

SEX DISTRIBUTION AMONG NEONATES

33 male babies and 28 female babies were present in the control group or phototherapy only group. 38 male babies and 33 female babies were present in the case group or combined therapy group to whom the phenobarbitone injection was given.

Sex	Cases		Controls		p value
	N	%	N	%	
Male	38	62.3%	33	54.1%	0.359
Female	23	37.7%	28	45.9%	
Total	61	100.0%	61	100.0%	

Table: Distribution of Sex between Study Groups

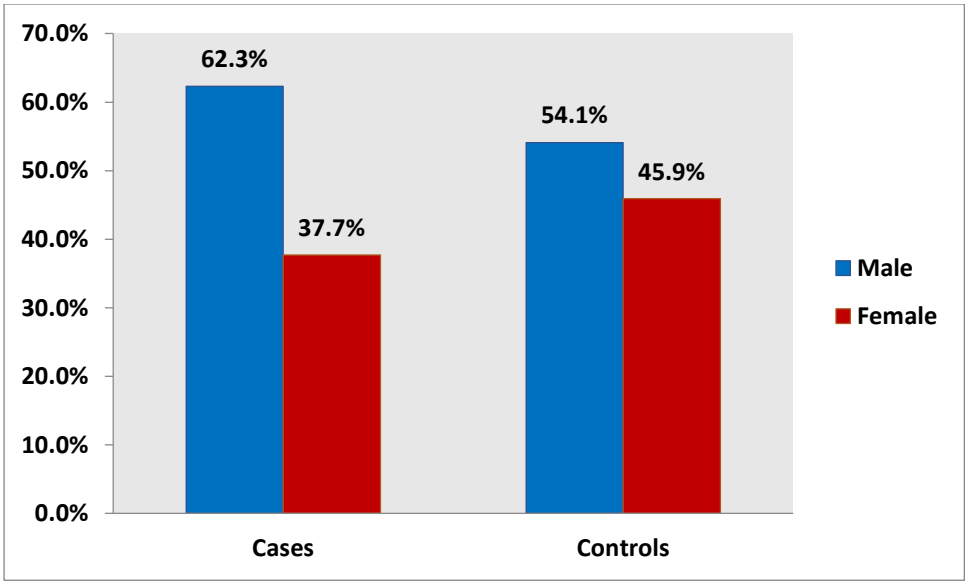

Figure: Distribution of Sex between Study Groups

Although the number of male babies were more in both case group and control group it was statistically insignificant with p value> 0.05. The increase in number of males presenting jaundice elucidates that male babies are at more risk of neonatal jaundice which needs to be studied further.

DISTRIBUTION OF BABIES INTO BABIES BORN TO PRIMI-GRAVIDA AND MULTI GRAVIDA MOTHERS

In phototherapy group there were 41 babies born to primi mothers and 20 babies born to multi gravida mothers. In phenobarbitone group there were 44 babies born to primi gravida mothers and 17 babies born to multi gravida mothers.

Gravida	Cases		Controls		p value
	N	%	N	%	
Primi	44	72.1%	41	67.2%	0.555
Multi	17	27.9%	20	32.8%	
Total	61	100.0%	61	100.0%	

Table: Distribution of Mothers into Primigravida and multi gravida between Study Groups

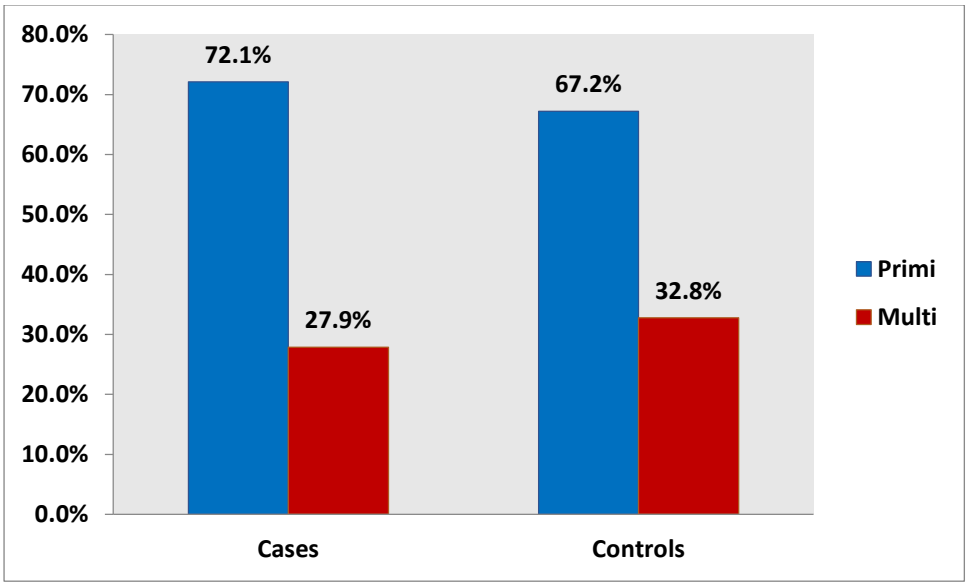

Figure: Distribution of babies into babies born to primi and multi gravida mothers in both Study Groups

Even though there were more number babies in both control and case group born to primi mothers more affected with neonatal hyperbilirubinemia than babies born to multi gravida mothers the distribution of babies into primi and multi mothers came statistically insignificant with p value> 0.05. The increase in number of babies presenting with jaundice in primi mothers indicates the that first born babies are having more risk of neonatal hyperbilirubinemia.

DISTRIBUTION OF BABIES BASED ON MODE OF DELIVERY BETWEEN STUDY GROUPS

In phototherapy group there were 30 babies born via LSCS and 31 babies born via NVD. In phenobarbitone group there were 37 babies born via LSCS and 24 babies born via NVD.

Mode of delivery	Cases		Controls		p value
	N	%	N	%	
LSCS	37	60.7%	30	49.2%	0.203
NVD	24	39.3%	31	50.8%	
Total	61	100.0%	61	100.0%	

Table: Distribution of Babies based on Mode of delivery between Study Groups

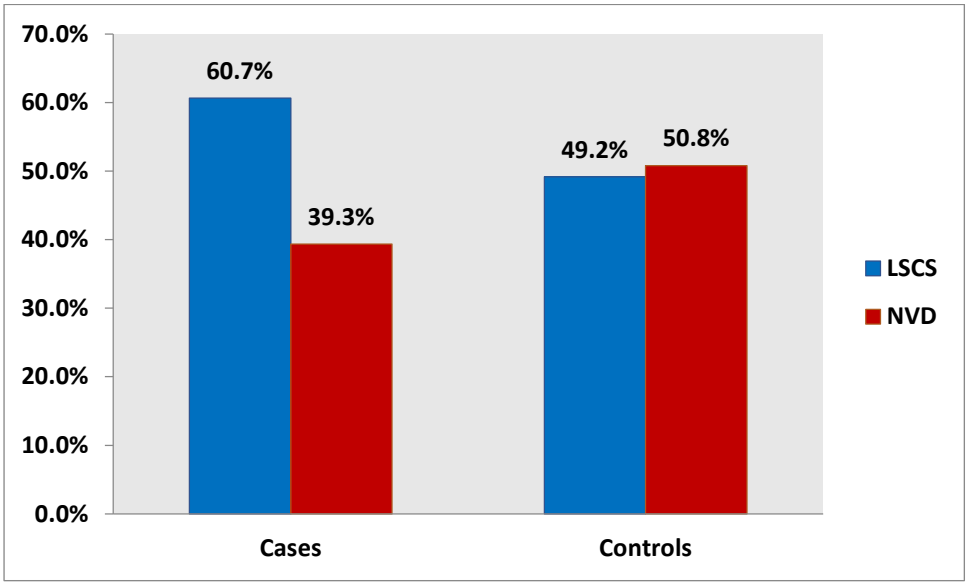

Figure: Distribution of Babies based on Mode of delivery between Study Groups

There were a greater number of babies born via LSCS affected by neonatal jaundice in Phenobarbitone group compared to babies born via NVD. but the distribution of babies based on mode of delivery was found to be statistically insignificant with p value> 0.05. The increase in number of babies presenting with jaundice in LSCS may be due to the increase in caesarean section in the current era compared to normal vaginal deliveries.

AGE OF BABIES (DAY OF LIFE) BETWEEN STUDY GROUPS

In this study, all babies who developed significant neonatal hyperbilirubinemia had a mean age of 3 days of life. There was no significant difference in number of babies who were started on phototherapy according to day of life at start of phototherapy.

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
Day of Life	3.2	0.8	3.1	0.6	0.459

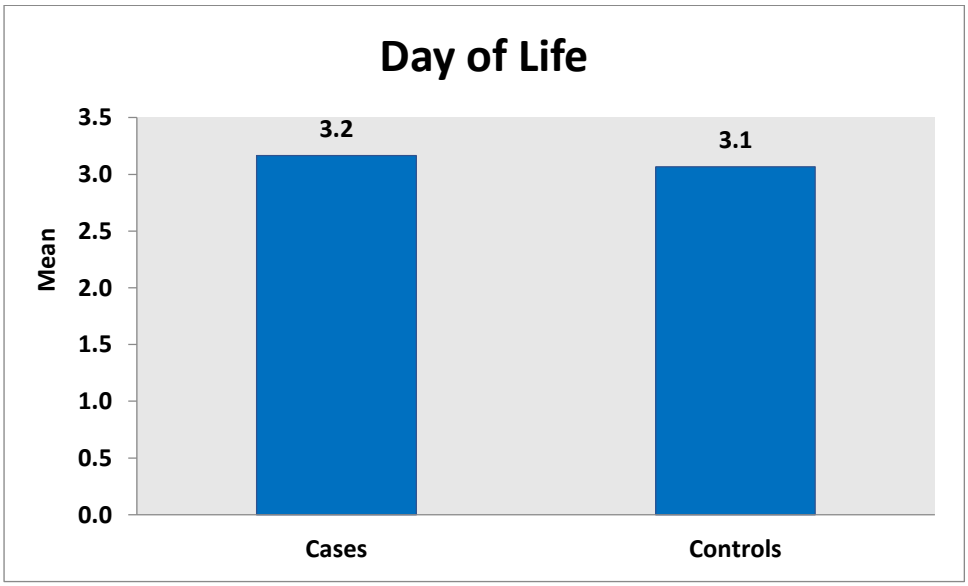

Table: Day of Life between Study Groups

AGE OF BABIES (HOUR OF LIFE) BETWEEN STUDY GROUPS AT START OF PHOTOTHERAPY

In this study, the number of babies who developed significant hyperbilirubinemia had a mean hour of life 72 hours. There was no significant difference in number of babies who were started on phototherapy according to hours of life at start of phototherapy.

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
Hour of Life	72.8	11.7	75.1	7.8	0.202

Table: Hour of Life between Study Groups

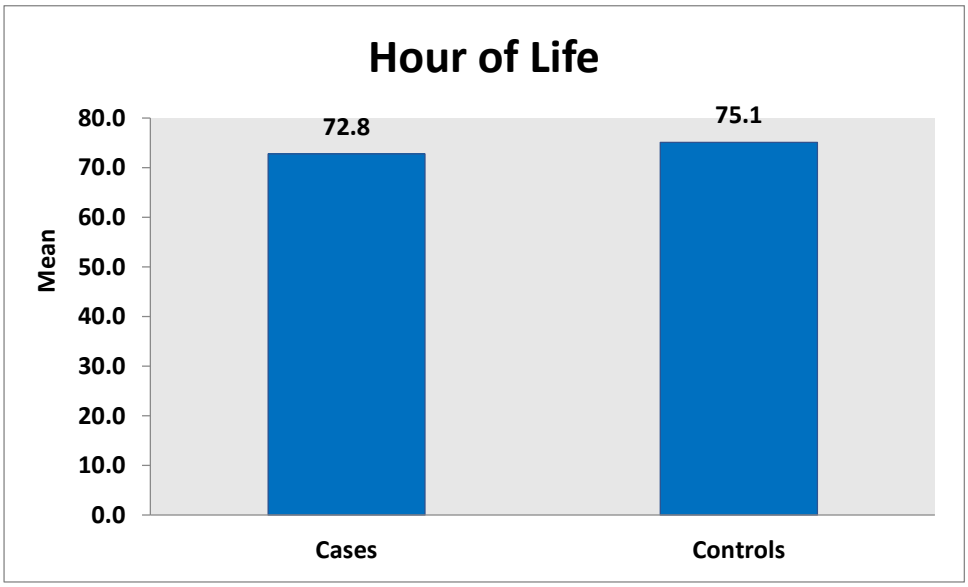

Figure: Hour of Life between Study Groups

DISTRIBUTION OF GESTATIONAL AGE BETWEEN STUDY GROUPS

All babies enrolled in this study were term neonates, greater than 37 weeks of gestation. Babies who had neonatal hyperbilirubinemia and who were started on phenobarbitone, and phototherapy had a mean gestational age of 38 weeks.

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
GA in Weeks	38.4	1.0	38.2	0.9	0.399

Table: Distribution of Gestational Age between Study Groups

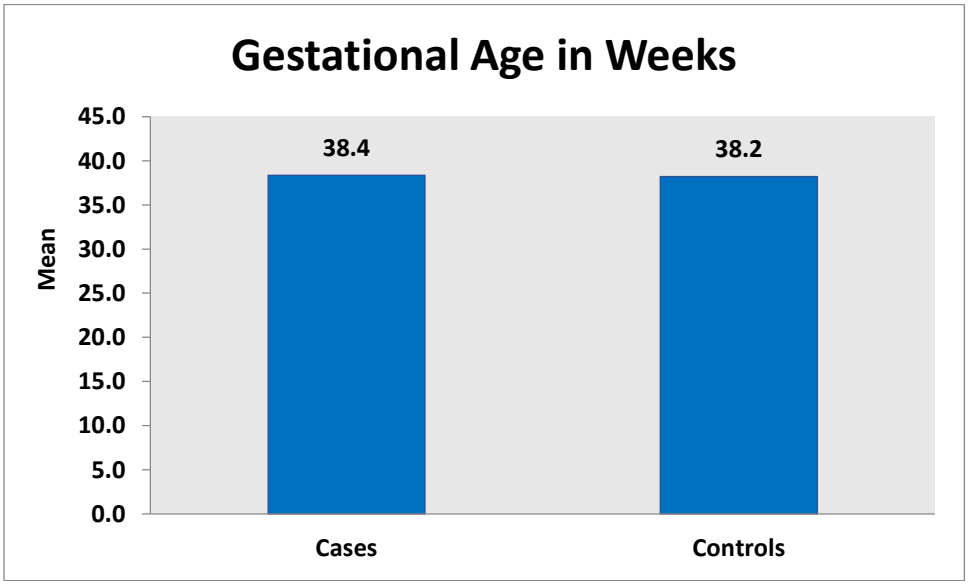

Figure: Distribution of Gestational Age between Study Groups

HOUR AT WHICH HYPERBILIRUBINEMIA WAS DIAGNOSED IN NEWBORNS IN STUDY GROUPS

Neonates in both study groups, case group and control group were tested to have neonatal hyperbilirubinemia at a mean age of 72 hours of life.

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
Hour of Jaundice	72.8	11.8	75.1	7.8	0.218

Table: Hour of Jaundice between Study Groups

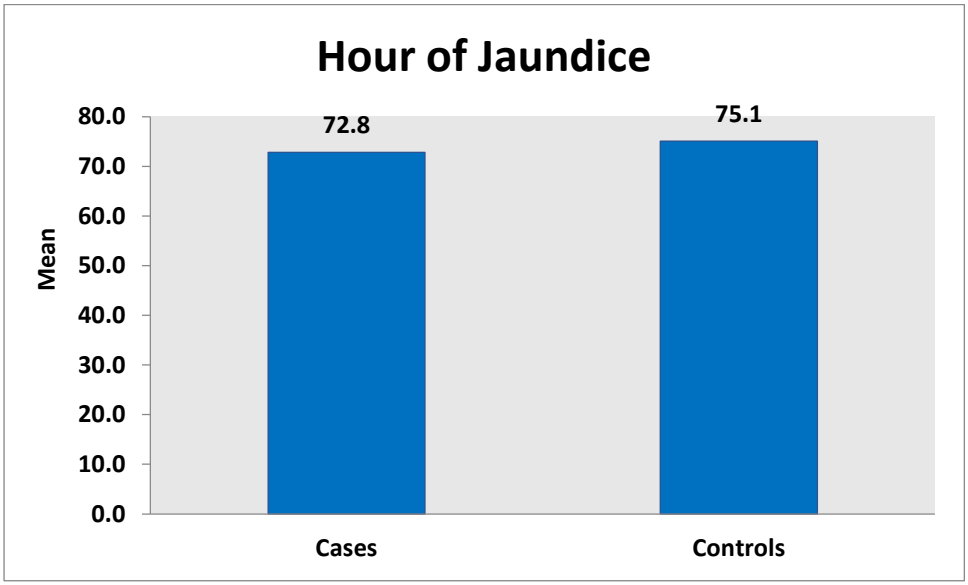

Figure: Hour of Jaundice between Study Groups

DISTRIBUTION OF BIRTH WEIGHT BETWEEN STUDY GROUPS

In this study, all babies enrolled had a normal birthweight of 2.5kg. Mean Birth weight was found to be 2.8 kg. There is no significant difference between birth weights of babies in both groups.

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
Birth Weight	2.8	0.2	2.7	0.2	0.340

Table: Distribution of Birth Weight between Study Groups

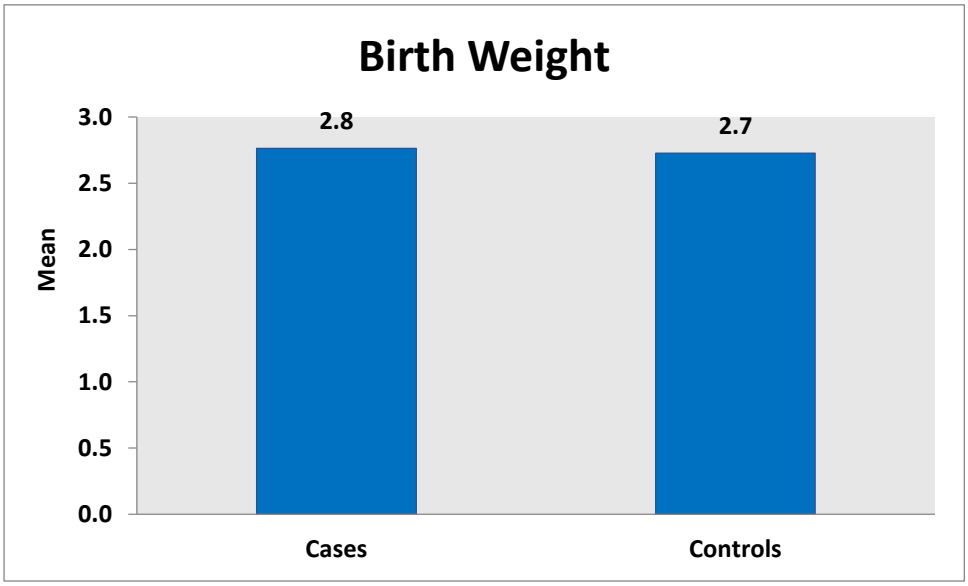

Figure: Distribution of Birth Weight between Study Groups

DURATION OF PHOTOTHERAPY BETWEEN STUDY GROUPS

In the cases group or the phenobarbitone group the mean value of duration of phototherapy was found to be 22.2hours and it was 24.2 hours in the control group in which babies were given a monotherapy that is only phototherapy. This data is depicted in the table below.

Parameters	**Cases**		**Controls**		**p value**
	Mean	**SD**	**Mean**	**SD**	
Duration of Phototherapy (hours)	22.2	2.6	24.2	2.4	0.039*

Note: p value* significant at 5% level of significance ($p<0.05$)

Table: Duration of Phototherapy between Study Groups

These results were analysed using Z test. The p value of the test which we got was 0.039, <0.05 which is statistically significant. Hence, we can say that there is a statistically significant reduction in the length or duration of phototherapy in babies who were enrolled in the case group or phenobarbitone group compared to babies who were enrolled in the control group or phototherapy alone group.

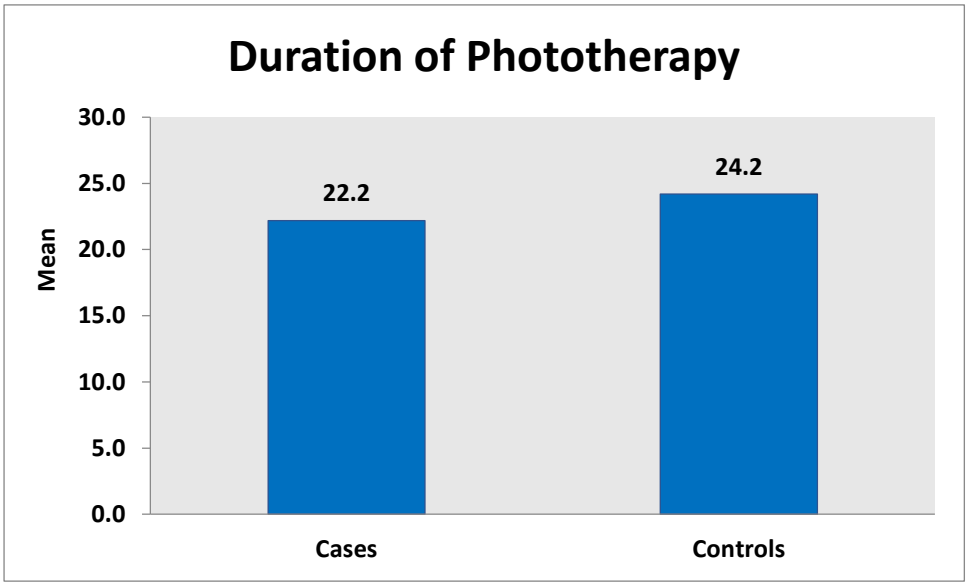

Figure: Duration of Phototherapy between Study Groups

In babies in the combined group who were given an adjuvant dose of inj.phenobarbitone at the start of phototherapy, the mean duration of phototherapy was found to be decreased to less than 24 hours. Mean duration of phototherapy of babies enrolled in the monotherapy group or control group in which phototherapy alone was given as the treatment for neonatal hyperbilirubinemia was found to be greater than 24 hours. Also, one baby in phototherapy only group showed a drastic increase in total serum bilirubin above the threshold value even after the start of phototherapy and baby had to be treated with an exchange transfusion.

On interpreting the data we collected from both groups, case and control group babies, a significant decrease in duration of phototherapy was noted in the case group or combined therapy group in which babies enrolled had received inj.phenobarbitone in addition to phototherapy treatment as per the protocol.

Babies who required phototherapy for only less than 24 hours were more in the case group in which babies enrolled received both phenobarbitone and phototherapy. Above table and graph clearly explains this significant difference in duration of phototherapy between babies of both the groups.

Statistically significant decrease in duration of phototherapy with statistically significant number of babies requiring only less than 24-hour duration of phototherapy was obtained in the study.

BLOOD GROUP INCOMPATIBILITY IN BOTH STUDY GROUPS

All babies enrolled in the study were checked for blood group incompatibility. Both maternal and baby blood group were tested in all enrolled babies and percentage of babies with ABO incompatibility and Rh incompatibility were calculated. In phenobarbitone group, there were 19.7% of babies with ABO incompatibility and 9.8% of babies with Rh incompatibility. In phototherapy group, there were 3.3% babies with ABO incompatibility and 1.6% babies with Rh incompatibility.

Incompatibility	**Cases**		**Controls**		**p value**
	N	**%**	**N**	**%**	
ABO Incompatibility	12	19.7%	2	3.3%	0.005*
RH Incompatibility	6	9.8%	1	1.6%	0.049*

Note: p value* significant at 5% level of significance ($p<0.05$)

Table: Distribution of Incompatibility between Study Groups

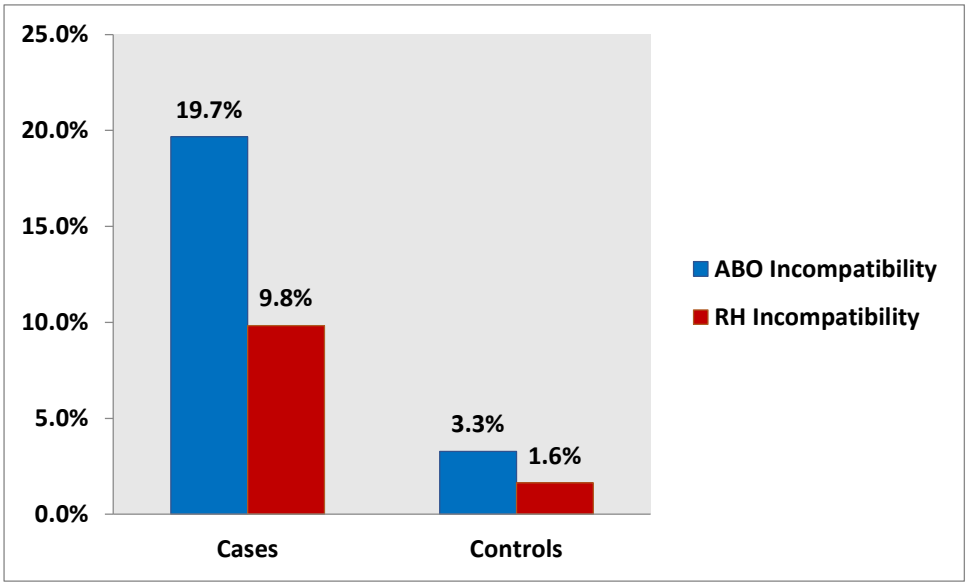

Figure: Distribution of Incompatibility between Study Groups

Babies in case group or Phenobarbitone group had an increased number of babies with blood group incompatibility. It was statistically significant with a p value <0.05. The significant difference can be due to the ABO incompatibility and Rh incompatibility, both of them can independently lead to neonatal jaundice as both of them are proved high risk factors in development of neonatal hyperbilirubinemia.

PEAK SERUM BILIRUBIN IN STUDY GROUPS

Peak bilirubin value in both case group and control group was compared. Total serum bilirubin did not show any increase in any group after the start of phototherapy except in one baby of control group for which exchange transfusion was done. Peak bilirubin was in proportionate with the total serum bilirubin at start of phototherapy. Data of peak serum bilirubin is depicted in the table below.

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
PEAK TSB	15.9	2.8	14.7	2.6	0.017*
12 hours TSB	11.5	2.5	11.9	2.4	0.369
24 hours TSB	8.5	1.9	9.9	1.8	<0.001*

Note: p value* significant at 5% level of significance (p<0.05)

Table: Distribution of TSB between Study Groups

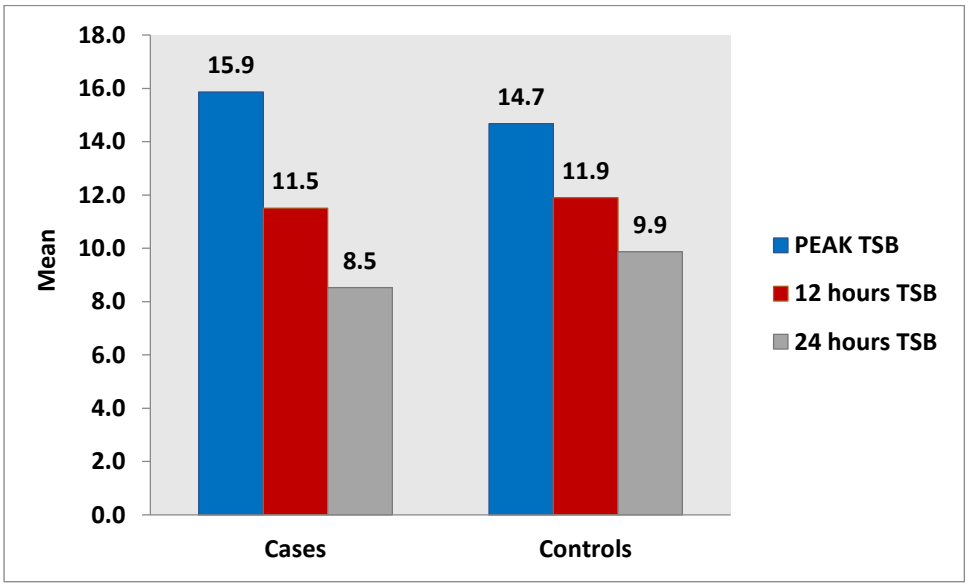

Figure: Distribution of TSB between Study Groups

Analysis of result was done by Z test. The results were noted to be statistically significant (p value 0.017 ($p<0.05$). The mean peak bilirubin was higher in phenobarbitone group (15.9) compared to 14.7 in phototherapy only group. However, the mean bilirubin at 12 hours were significantly low in cases (11.5) compared to 11.9 in controls. Peak Total Serum Bilirubin at 24 hours of life was also lower in cases (8.5) compared to a mean value of 9.9 in the control group.

UNCONJUGATED SERUM BILIRUBIN IN STUDY GROUPS

In both control group and case group, the unconjugated serum bilirubin value was proportional to the total serum bilirubin at the start time of phototherapy. Mean unconjugated serum bilirubin value of both groups are given in the following table.

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
Peak USB	15.0	2.5	14.1	2.4	0.047*
12 hours USB	10.8	2.2	11.3	2.2	0.275
24 hours USB	7.7	1.7	9.1	1.7	<0.001*

Note: p value* significant at 5% level of significance (p<0.05)

Table: Distribution of Unconjugated serum bilirubin between Study Groups

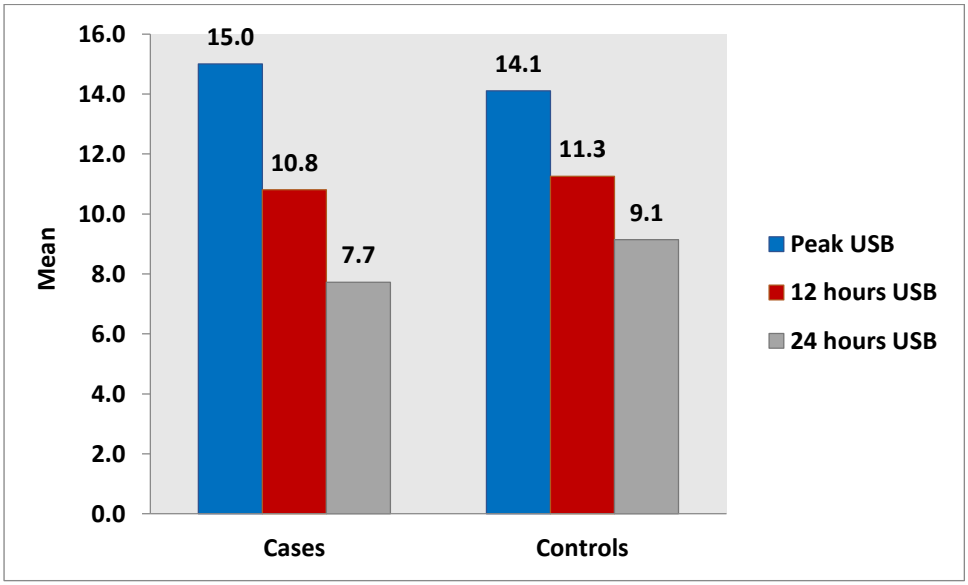

Figure: Distribution of USB between Study Groups

Z test was used for the analysis of the data on unconjugated serum bilirubin and it was found to be statistically significant (p value 0.017 ($p<0.05$). The mean peak unconjugated serum bilirubin was higher in phenobarbitone group (15.9) compared to 14.7 in phototherapy only group. However, the mean bilirubin at 12 hours were significantly low in cases (11.5) compared to 11.9 in controls. Peak total Serum Bilirubin at 24 hours of life was also lower in cases (8.5) compared to a mean value of 9.9 in the control group.

DURATION OF HOSPITAL STAY IN STUDY GROUPS

Analysis on the duration of hospital stay was done in both control group and case group. Duration of hospital stay was in proportion with the maximum value of total serum bilirubin at admission. Also, the hospital stay duration was significantly lower in phenobarbitone group compared to phototherapy only group.

Duration of Hospital Stay	Cases		Controls		p value
	N	%	N	%	
1days	46	75.4%	27	44.3%	<0.001*
2days	15	24.6%	34	55.7%	
Total	61	100.0%	61	100.0%	

Note: p value* significant at 5% level of significance (p<0.05)

Table: Duration of Hospital Stay between Study Groups

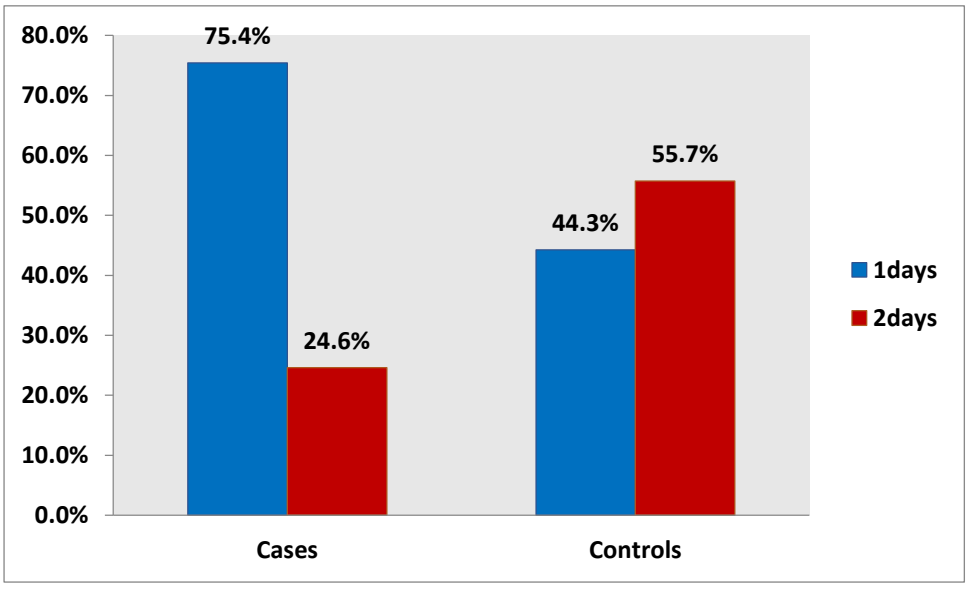

Figure: Duration of Hospital Stay between Study Groups

In the phenobarbitone group, 75% of the new-borns required only 24 hours of hospitalisation. On the other-hand 55% of new-borns in phototherapy only group needed 48 hours of hospitalisation. By decreasing the duration of hospital stay we can also minimize the expenditure involved to a significant extend.

DISCUSSION

In 70% -80 % of term new-borns, neonatal hyperbilirubinemia occurs within the first 5 days of life. Most often it is seen between 25 hours to 144 hours of life in a neonate. Out of these 20 % to 30% babies requires phototherapy. The condition so called neonatal hyperbilirubinemia is treated by phototherapy in most parts of the world. Use of phototherapy significantly reduced bilirubin induced brain damage in babies with high levels of serum bilirubin during the early hours of life. But phototherapy has its adverse effects. There can be failure of phototherapy in some babies which may lead to requirement of more invasive procedures like exchange transfusion especially in situations like haemolytic jaundice. Hence some adjunctive treatment which can efficiently reduce the duration of phototherapy and hence, the duration of hospital stay is the need of the hour.

The results of our study showed that phenobarbitone is able to lower serum bilirubin values in new-born babies to a significant level. In this study there is a statistically significant difference in duration of phototherapy and duration of hospital stay between babies of two groups.

In a trial study done Levin, it was shown that there was a small but significant reduction of total serum bilirubin phenobarbitone in icteric babies who were treated with phenobarbitone. Decrease in total serum bilirubin was observed after 24 hours of administration of phenobarbitone intramuscular injection. (58) But as there were no significant differences in the mean peak serum bilirubin levels of

babies who were given phenobarbitone and who were not given phenobarbitone at 48 and 72 hours after the administration of phenobarbitone, authors concluded that phenobarbitone was not effective in the treatment of established neonatal jaundice. In our study we confirmed that phenobarbitone is useful in the decreasing the peak serum bilirubin levels in new-born babies with significant hyperbilirubinemia. We found that there was a reduction in bilirubin levels in the phenobarbitone treated group compared to the monotherapy group in which babies were given only phototherapy for the treatment of neonatal hyperbilirubinemia. The need for exchange transfusion was also found to be less in the phenobarbitone treated group of babies. A reduction in duration of phototherapy and a decrease in duration of hospitalisation was also observed in the phenobarbitone group. All these data indicate that phenobarbitone has its efficacy in treatment of neonatal hyperbilirubinemia when used as an adjuvant therapy to phototherapy. Our findings agree with the findings of Yeng and Field (1969) but does not match with the study done by Ramboer et al, McMullin and Cunningham et al. (19).

There was no increase in mortality rate in infants treated with phenobarbitone and no serious adverse effects were noted apart from mild drowsiness for initial 5-6 hours.

CONCLUSION

Here in this study, a very commonly encountered problem that is neonatal hyperbilirubinemia and its various treatment modalities and their efficacy and adverse effects were studied. In common practice phototherapy is the approved treatment followed now for the treatment of neonatal jaundice in majority of the hospitals. Often the duration of this phototherapy gets prolonged and affects the breast feeding and maternal and baby bonding. Also, phototherapy when give for prolonged duration has its own short term and long-term adverse effects in babies. Hence trial of adjunctive drugs for reducing the peak serum bilirubin which can decrease the phototherapy duration is going on. Phenobarbitone is one among such drugs Phenobarbitone was able to reduce the duration of phototherapy and the duration of hospital stay in this study. There were no major adverse effects during the use of phenobarbitone. Phenobarbione was effective in lowering bilirubin at single low dose of 10 mg/kg/dose intramuscular injection at start of phototherapy. Phenobarbitone in combination with phototherapy is a good treatment modality for neonatal hyperbilirubinemia as it results in a faster decline in total serum bilirubin and decrease the need for blood exchange transfusion when compared to the results of monotherapy done with phototherapy alone. This is an important development in treatment of neonatal jaundice which can be implemented in treatment of new-born hyperbilirubinemia.

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ANNEXURE- I

PARENTS / GUARDIAN CONSENT STATEMENT:

We confirm that Dr. Ranjima M is doing a study on **"**EFFICACY OF PHENOBARBITONE IN PROPHYLAXIS AND ADJUVANT THERAPY IN HYPERBILIRUBINEMIA IN NEWBORN". A hospital based randomized open label study. Dr Ranjima M has explained to us the purpose of research and the study procedure. We are willing to give as much as information required for the study and consent for investigations and the possible discomforts as well as benefits. We have been explained all the above in detail in our own language and we understand the same. Therefore, we agree to give consent for baby's participate as a subject in this research project.

_____ _____

(Parents / Guardian) Date

_____ _____

(Witness to signature) Date

ANNEXURE-2

PROFORMA

Name

IP No.

DOB Age in Days

Birth Weight Current Weight

Sex

Address

Obstetric Score

Mother's Blood Group Baby's Blood Group

APGAR Score

1 min:

5 min:

High Risk Factors:

Maternal – Primiparity / Teenage Pregnancy / Diabetes / Rh incompatibility / ABO incompatibility / Use of Oxytocin, bupivacaine.

Mode of Delivery: FTND / LSCS

Perinatal – Birth trauma/Birth Asphxyia / Delayed cord clamping / Congenital

Infections – CMV/Syphilis / Sepsis

Neonatal – Male sex / Prematurity / LBW / SGA / Polycythemia / Hypoglycemia

/ dehydration / weight loss

Others – Previous sibling received phototherapy or exchange transfusion.

General Physical Examination:

Birth weight: ..... kg

HR:	RR:	HC:
CFT:	TEMP:	LENGTH:

Systemic Examination:

CVS:

Respiratory System:

Gastro – Intestinal System:

CNS:

Baby Delivered on: ..... /..... / 20.....

Found Icteric on DOL: ..... On ..... /..... / 20.....

Whether Phototherapy Given:

Duration of Phototherapy

Whether SSPT / DSPT Given

Whether injection Phenobarbitone given:

Dose of injection Phenobarbitone given:

Date and Time of injection Phenobarbitone

Bilirubin values

Date			
TSB			
USB			

Mental Status: Normal / Sleepy / Lethargic / Apnea /Seizure

Muscle Tone: Normal / Mild to moderate Hypotonia / Hypertonia / Retrocolis / Ophisthotonus

Cry Patterns: Normal / High pitched cry / Weak or absent Cry

ANNEXUXE-3

ETHICAL CLEARANCE CERTIFICATE

IEC/NO-131/2019
22-11-2019

B.L.D.E. (DEEMED TO BE UNIVERSITY)

(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)

The Constituent College

SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The ethical committee of this college met on 13-11-2019 at 3-15 pm to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: Pehnobarbitone for prophylaxis and as an adjuvant therapy in hyperbilirubinemia in the newborn – A randomized open label study

Name of PG student: Dr Ranjima M, Department of Paediatrics

Name of Guide/Co-investigator: Dr R H Gobbur, Professor Department of Paediatrics

DR RAGHVENDRA KULKARNI
CHAIRMAN

Institutional Ethical Committee
B'LDEU's Shri B.M. Patil
Medical College,BIJ...UR-586103

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

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ANNEXURE-4

MASTERCHART

Sl. No.	Name	Day of Life	Hour of Life	Sex	Gravida Primi/Multi	Term - Preterm	GA in Weeks	Hour Of Jaundice	Birth Weight	NVD/LS CS	ABO Incompatibility	RH Incompatibility	Duration of Phototherapy (HRS)	PEAK TSB	Peak USB	Hour of INJ. P	12 hours TSB	12 hours USB	24 hours TSB	24 hours USB	Duration of Hospital Stay
1	B/O Baby Harish	3	72	F	P	T	38	72	2.6	LS	P	NIL	24	18.5	17	74	12.5	12	10.5	10	1
2	B/O Fathima Rafeeq	2	48	m	G2P1	T	39	48	2.8	LS	P	NIL	20	12	11.5	48	11	10	9.2	8.4	1
3	B/O Keerthi chandu	2	48	f	G2P1	T	40	56	3	NVD	P	NIL	22	12.4	11.5	56	9.1	8.2	5.1	4.7	1
4	B/O Chandrakala	2	58	m	p	T	39	58	2.8	NVD	P	NIL	24	14	12.8	60	11	10.3	9.1	8	1
5	B/O Pavithra	2	64	m	p	T	38	64	2.7	nvd	p	NIL	24	16	15	64	12	11	7.1	6	1
6	B/O Sunita sangappa	2	66	f	p	T	39	66	2.8	nvd	nil	p	24	15	14	68	11.4	12.1	7.2	6.3	1
7	B/O Nirmala	2	48	f	p	T	38	36	3	ls	nil	p	22	12	11	36	10.2	9.1	8.1	8	1
8	B/O Divya prakash	2	48	m	p	T	39	48	3.1	ls	nil	p	24	16.2	15.6	48	13.7	12.6	8.1	7.4	1
9	B/O Renuka yallappa	4	76	f	p	T	40	76	2.8	nvd	nil	NIL	24	16.3	15.4	78	12.4	10.8	9.4	8.1	1
10	B/O Priyanka	3	74	f	p	T	37	74	2.5	nvd	nil	NIL	22	19.6	18.1	76	15	13.2	9.1	8.2	2
11	B/O Suprita	3	72	m	p	T	40	76	3.19	ls	nil	NIL	26	22	16.6	72	10.4	8.7	9.3	7.9	2
12	B/O Venkamma	4	80	m	G3P2	T	39	80	2.5	ls	nil	NIL	28	16	15.7	80	14.8	14.5	13	12	2
13	B/O Shobha somanath	4	82	m	G2P1	T	40	40	2.5	LS	P	NIL	12	15	13.1	82	8.3	8	NIL	NIL	1
14	B/0 Rajeshwari	3	76	f	G3P2	T	39	76	2.6	LS	nil	NIL	22	15.7	13	76	13.2	12.1	11	8	1
15	B/O Maheshwari Kulkarni	3	74	m	p	T	37	74	2.5	LS	NIL	NIL	24	16	15.6	74	14.1	10.8	8	6.8	1
16	B/O Savitri Patil	4	76	m	G2P1	T	38	76	3	NVD	NIL	NIL	26	23.2	22.6	76	17.8	14.5	12	11	2
17	B/O Kashibai	3	72	f	p	T	39	72	2.9	NVD	NIL	NIL	24	17.3	14.2	72	12	10.7	9.2	7.9	2
18	B/O Santhoshi Prakash	3	74	m	p	T	38	74	3	NVD	nil	NIL	22	16.9	15.9	74	14.4	12.8	10	8	1
19	B/O Simran Kabeer	4	76	m	p	T	38	76	3.4	NVD	NIL	NIL	24	15.1	14.9	76	14.1	13	10.2	8.1	1
20	B/O Najreen Banu	3	72	f	p	T	38	72	2.8	NVD	NIL	NIL	12	12.6	12	72	7.7	6.6	NIL	NIL	1
21	B/O Harshitha koli	4	84	m	p	T	40	84	3.6	NVD	NIL	NIL	12	17.7	14.6	84	7.3	6.3	NIL	NIL	1
22	B/O Rajashri Mallikarjun	4	86	f	p	T	39	86	2.5	ls	nil	NIL	24	21	17.1	86	15.2	13.9	9.2	7.9	1
23	B/O Shajidhabi Yusuf	6	96	m	G2P2	T	39	96	2.7	LS	P	NIL	26	21.9	18.5	96	13.5	12.4	11.7	10	2
24	B/O Jyothi Kashinath	4	86	f	p	T	38	86	2.5	LS	NIL	NIL	24	18.9	13.1	86	12	11	7	6.1	1
25	B/O Ashwini	2	36	m	G2P2	T	38	82	2.5	LS	NIL	P	12	10.5	9.4	36	5.7	4.8	NIL	NIL	1
26	B/O Savitha	3	72	m	p	T	37	72	2.7	NVD	NIL	NIL	28	18	17	72	15.4	14.6	12.1	11	2
27	B/O Priyanka	4	82	m	G2P1	T	38	82	2.8	LS	NIL	NIL	24	17.1	16	82	12	11	9	8.6	1
28	B/O Savitri Anilkumar	4	84	m	p	T	40	84	2.9	LS	NIL	NIL	24	14	14	86	10.2	10	6.6	6	1
29	B/O Prabhavati Gajanand	2	56	m	P	T	40	56	2.5	LS	NIL	P	12	15	15	56	10.2	9.6	NIL	NIL	1
30	B/O Rajani Ambdar	3	74	m	G2P1	T	37	74	3.2	LS	NIL	NIL	24	13	12.4	74	9.2	9	8	7.1	1
31	B/O Ratna Bai	3	74	m	primi	T	38	74	2.8	LS	P	NIL	12	14.4	14	74	8.1	8	NIL	NIL	1
32	B/O Jayashree	3	72	m	P	T	39	72	3	NVD	NIL	NIL	22	18.7	18.6	74	11.2	11	6.8	6	1
33	B/O Ratnamma Dundappa	4	82	m	p	T	37	82	2.7	nvd	nil	NIL	24	17.7	17.7	82	12.1	12	9.2	9	1
34	B/O Nirmala Darmanna	4	84	f	G2	T	37	84	2.7	nvd	nil	NIL	26	16.7	16.7	84	12.1	12	10.2	9.6	2
35	B/O Jayashree	3	74	m	p	T	38	74	2.7	nvd	nil	NIL	14	14.4	14.4	74	10.2	9.6	nil	nil	1
36	B/O Shaila siddu	3	72	m	p	T	39	72	2.6	nvd	nil	NIL	24	17.2	17	72	11.1	11	10	8.2	1
37	B/O Shridevi Bagali	4	92	m	p	T	39	92	2.5	lscs	p	NIL	12	10.8	10.5	92	7.2	7	nil	nil	1
38	B/O Rajeshwari Harish	3	74	f	p	T	37	74	2.6	lscs	p	NIL	14	14.6	14.6	74	10.2	9.6	nil	nil	1
39	B/O Rashmi Prashant	3	72	f	p	T	39	72	2.5	lscs	p	NIL	24	15.4	15.4	72	9.2	9.2	7.2	6.1	1
40	B/O Sunitha Rajkumar	3	76	m	G2	T	38	76	2.5	lscs	nil	NIL	24	14.2	14.2	76	9.7	9	6.2	5.8	1
41	B/O Surekha Apparab	3	74	f	p	T	37	74	2.7	ls	nil	NIL	24	15.5	15.5	74	11.4	11	6.8	6	1
42	B/O Bhimbai Ramu	3	72	f	p	T	40	72	2.5	ls	nil	NIL	24	14.4	14.4	72	9.6	9.4	5.5	5	1
43	B/O Shashikala Arjun	4	76	m	p	T	39	76	3	ls	nil	NIL	26	24.8	23.1	76	16.1	15.4	10.2	9.4	2
44	B/O Aishwarya Ramesh	4	84	f	p	T	38	84	2.5	LS	NIL	NIL	24	18.4	18.4	84	10.5	10.5	5.3	5	1
45	B/O Laxmi	3	72	m	p	T	38	72	2.8	nvd	nil	NIL	26	16.6	16	72	12.8	12	9	8.1	2
46	B/O Rjashree Anand	3	72	f	p	T	37	72	3	ls	nil	NIL	24	14.8	14.8	72	10.3	10	8.1	7	1
47	B/O Vaishali Prakash	3	76	f	p	T	39	76	2.6	nvd	nil	NIL	24	15.8	15.8	76	10.8	10.8	6.1	6	1
48	B/O Jyothi Ramkrishna	2	56	f	G3P2	T	38	56	2.6	NVD	NIL	NIL	24	14.3	14.3	56	10.3	10.3	7.2	7.2	1
49	B/O Rekha	3	74	m	G2	T	37	74	2.9	ls	nil	NIL	24	15.2	15	74	12.1	11.8	9.1	9	2
50	B/O Prema Shivanand	2	58	m	p	T	38	58	3	ls	nil	NIL	12	12.3	11.2	60	6.1	6.1	nil	nil	1
51	B/O Fizabanu Irani	3	74	f	p	T	39	74	2.6	ls	p	NIL	24	14	14	75	12.7	12.5	7	7	1
52	B/O Parvati Manjunath	4	88	m	G2	T	38	88	2.5	NVD	NIL	P	24	13.2	13.2	90	10.1	9.9	6.1	5.6	1
53	B/O Sunitha Rajkumar	3	76	f	G2	T	37	76	2.8	NVD	NIL	NIL	24	14.8	14.4	76	12.6	12.4	8.2	8	2
54	B/O Amrutha Sanjay	4	82	m	p	T	39	82	2.9	ls	nil	NIL	24	15.8	15.8	82	13	12.6	7.4	7	1
55	B/O Mamtaz Rafiq	4	84	m	p	T	40	84	2.6	ls	nil	NIL	24	16.3	16.3	84	13.4	12.2	9.4	9	2
56	B/O Shilpa	2	58	m	p	T	37	58	2.5	ls	nil	NIL	24	13.8	13.8	58	11.5	11.5	6.7	6	1
57	B/O Bharathi Patil	2	62	m	G2	T	38	62	2.6	LS	NIL	NIL	24	12	12	62	8.9	8.7	7.1	6.4	1
58	B/O Kavitha	4	86	f	p	T	38	86	3.1	ls	nil	NIL	26	15	15	86	13.2	13.2	9	8.7	2
59	B/O Jayashree	3	72	m	p	T	37	72	2.7	ls	nil	NIL	24	14.6	14.2	72	12.1	11.8	7.4	7	1
60	B/O Pooja Ankalagi	4	84	m	p	T	38	84	2.8	ls	nil	NIL	24	16.4	16.2	84	15.5	15.1	12	11	2
61	B/O Rajeshwari Naikodi	3	74	m	p	T	39	74	2.9	nvd	nil	NIL	24	16.5	15.9	74	12	10	8.2	7.6	1

Sl. No.	Name	Day of Life	Hour of Life	Sex	Gravida Primi/Multi	Term - Preterm	GA in Weeks	Hour Of Jaundice	Birth Weight	NVD/LS CS	ABO Incompatibility	RH Incompatibility	Duration of Phototherapy (HRS)	PEAK TSB	Peak USB	12 hours TSB	12 hours USB	24 hours TSB	24 hours USB	Duration of Hospital Stay
1	B/O HUSNENBAI	4	86	M	P	T	39	88	2.8	NVD	NIL	NIL	24	22	20	16	15	10	9	2
2	B/O Devamma	3	76	f	p	T	38	76	2.7	nvd	NIL	NIL	12	12	10.6	9.5	7.6	NIL	NIL	1
3	B/O Mallamma	4	88	f	p	T	38	88	2.8	LSCS	NIL	NIL	12	18	16.6	14	13.1	NIL	NIL	1
4	B/O DHANESHWARI	3	73	F	P	T	39	73	3	NVD	NIL	NIL	24	17.4	16.4	14.8	13.5	10.1	9.2	1
5	B/O yallawwa	3	72	f	p	T	39	74	2.8	LSCS	NIL	NIL	24	14.1	13.7	11.4	11	9.2	9	1
6	B/O Savita	3	76	f	G2P1	T	38	76	2.5	LSCS	p	NIL	28	18	17	15.1	14.8	13.4	12.9	2
7	B/O Dundawwa	3	74	m	p	T	38	74	2.8	LSCS	NIL	NIL	26	15	14.5	13	12.2	11.1	10.8	2
8	B/O Lakshmi Yallappa	3	76	m	p	T	39	76	2.6	nvd	NIL	NIL	26	13	12	11.5	10.4	9.2	8.9	2
9	B/O Rekha	3	74	f	p	T	40	74	2.8	lscs	NIL	NIL	24	12.6	12.4	10.4	9.8	8.4	8	1
10	B/O Sumangala malkappa	2	56	f	p	T	37	56	2.6	nvd	p	NIL	24	12.6	11.9	10.6	9.8	8.2	8	1
11	B/O Sudharani	3	78	m	G2P1	T	38	78	3	nvd	NIL	NIL	24	15	14.4	12.6	12	7.1	6.1	1
12	B/O Nilofer	3	74	m	G2P1	T	39	74	2.7	lscs	NIL	NIL	24	18.2	17.9	14.8	14	8.3	8	1
13	B/O Sunitha	3	78	m	p	T	39	78	2.6	nvd	NIL	NIL	28	17.7	16.5	13.5	12.6	11.4	10.9	2
14	B/O sunita Banni	4	86	m	p	T	38	86	2.8	nvd	NIL	p	24	15.2	15	13	11	9	8.4	1
15	B/O sunita Rakesh	2	56	f	G2P1	T	39	56	2.5	nvd	NIL	NIL	24	12.9	10.4	10.3	8.7	6.5	5.7	1
16	B/O Jyothi	3	72	f	p	T	37	72	2.6	nvd	NIL	NIL	28	19.3	18.3	12.2	11.6	9.5	9	2
17	B/O Shridevi Biradar	2	64	f	p	T	39	64	2.7	nvd	NIL	NIL	24	11	10.2	8.6	8.4	6	5.9	1
18	B/O Itanbai	4	86	m	p	T	37	86	2.5	nvd	NIL	NIL	26	13.7	12.8	12	11.3	10.6	8.7	2
19	B/O Nasreen Wasim	3	76	f	p	T	38	76	2.9	nvd	NIL	NIL	26	18.8	17.4	17.2	15.6	12.5	11.2	2
20	B/O Pushpa Sangappa	3	74	m	G3P2	T	39	74	3	lscs	NIL	NIL	28	17.3	16.3	16	14.9	12.6	11.6	2
21	B/O Roopa Hiremath	4	72	m	p	T	39	72	2.5	LSCS	NIL	NIL	24	17	15	13	12.9	11.9	10.5	2
22	B/O Jyothi	4	88	f	g2p1	T	39	88	2.6	nvd	NIL	NIL	28	18	17.8	14.7	13.6	10.7	9.4	1
23	B/O Kavya	3	74	m	p	T	38	74	2.6	LSCS	NIL	NIL	26	15.4	15.4	13.7	12.8	10.8	10.4	2
24	B/O jayashree	3	72	m	p	T	37	72	2.5	nvd	NIL	NIL	28	23	22	15.2	14.8	13.9	12.8	2
25	B/O Sujatha Anil	3	74	m	p	T	38	74	2.8	lscs	NIL	NIL	24	13.6	13.2	10	9.3	8.6	8.2	1
26	B/O Sangeetha Prashant	3	76	f	g2p1	T	38	76	2.5	LSCS	NIL	NIL	12	13.2	13	7.8	7.5	NIL	NIL	1
27	B/O Laxmi	3	74	f	G2P1	T	37	74	2.6	ftnd	NIL	NIL	24	11.4	11.4	10.2	9.1	8.2	7.1	1
28	B/O Ankita	4	86	f	p	T	39	86	3	lscs	NIL	NIL	26	14.6	14.6	12	11.6	10	9.2	2
29	B/O Shobha Ravi	2	64	m	p	T	38	64	2.7	lscs	NIL	NIL	12	13.8	13	9.7	9	NIL	NIL	1
30	B/O Aishwarya	4	88	m	p	T	39	88	2.6	nvd	NIL	NIL	12	13	12.6	7.6	7.4	NIL	NIL	1
31	B/O Bharati Mallappa	3	76	m	g2p1	T	40	76	2.5	nvd	NIL	NIL	26	12.6	12	10.6	10.2	9.4	8.6	2
32	B/O Suman Prakash	3	74	m	p	T	38	74	2.8	LSCS	NIL	NIL	24	15.7	15.7	13.6	13.4	12	11.6	2
33	B/0 Nethra yemanna	3	78	m	p	T	37	78	2.6	lscs	NIL	NIL	24	11.6	11.4	9.1	8.6	6.2	5.6	1
34	B/O Radha Mohan	4	82	m	g3p2	T	37	82	2.7	lscs	NIL	NIL	26	15	15	14.5	14	10	9.1	2
35	B/O Rekha Prashant	3	74	f	p	T	37	74	2.6	nvd	NIL	NIL	12	12.1	12	8.2	8.2	NIL	NIL	1
36	B/O Renuka Chennappa	2	64	m	p	T	38	64	3	nvd	NIL	NIL	26	13.2	13	10.4	10	9.1	8	2
37	B/O Tippanna kundargi	3	76	f	p	T	37	76	2.8	nvd	NIL	NIL	12	14	13.6	8	7.6	NIL	NIL	1
38	B/O Savita Patil	3	74	m	G2P1	T	40	74	3.1	LSCS	NIL	NIL	26	15	14.9	10.2	10	8.2	7.1	2
39	B/O Kavita Santosh	3	78	m	G2P1	T	39	78	2.6	nvd	NIL	NIL	24	14	13.6	12.8	12	10.4	9.2	2
40	B/O Vijaylaxmi Badiger	3	78	f	p	T	37	78	3	LSCS	NIL	NIL	24	15	14.6	13.2	11.8	10	9.4	2
41	B/O Laxmi Havalagi	3	72	f	p	T	37	72	2.7	lscs	NIL	NIL	24	15	15	12	11.4	6.8	6	1
42	B/0 Chinnamma Somu	2	64	m	G2P1	T	38	64	3.1	NVD	NIL	NIL	28	15	14.8	13.6	13	11.2	11	2
43	B/0 Kavitha	3	74	f	p	T	37	72	2.7	nvd	NIL	NIL	28	14	13.7	12.4	11.8	10.4	10	2
44	B/O Laxmi Somu	4	88	m	g2p1	T	38	88	2.6	LSCS	NIL	NIL	24	15.9	15.8	13.9	13	10.2	8.9	2
45	B/O Siddamma shrishail	3	74	f	p	T	39	74	2.5	LSCS	NIL	NIL	24	14.1	14.1	12.1	12.1	8	7.4	1
46	B/O Ashwini Devadas	4	86	f	G3P2	T	37	84	2.9	nvd	NIL	NIL	26	15	14	11.4	10.7	9.7	8.8	2
47	B/O Kajal Santhosh	2	62	m	p	T	39	62	3	LSCS	NIL	NIL	26	14	13.8	12.8	12.2	11	10.2	2
48	B/O Asha Basavaraj	3	74	f	p	T	38	74	2.5	LSCS	NIL	NIL	28	12.1	12	10	9.7	8.8	8.4	2
49	B/O Kasthuribai kambali	3	72	m	G2P1	T	39	72	2.6	LSCS	NIL	NIL	26	13	12.9	11	10.6	9.7	9.2	2
50	B/O Supriya	4	87	m	p	T	40	87	3	p	NIL	NIL	26	11.7	11.4	10.1	10.1	9.8	9.1	2
51	B/O Jayashree Sharanbasu	4	84	m	p	T	39	84	3	p	NIL	NIL	12	11.3	11	7.6	7.4	NIL	NIL	1
52	B/O Kaveri Ramanagouda	3	76	m	p	T	37	76	2.6	LSCS	NIL	NIL	12	11.3	11	7.8	7.6	NIL	NIL	1
53	B/O Laxmi Shrishail	3	72	f	G2P1	T	38	72	2.8	LSCS	NIL	NIL	24	13.4	13.4	11.2	11	9.6	9	1
54	B/O Firza	2	62	f	p	T	39	62	3	LSCS	NIL	NIL	26	15.1	14.8	13.2	12.7	11.3	9.5	2
55	B/O Mallamma Raju	4	87	f	p	T	39	87	2.6	p	NIL	NIL	24	17.1	16.2	13	12.5	11.2	11	2
56	B/O Nusrat	2	62	f	G2P1	T	37	62	2.5	p	NIL	NIL	24	17	16.4	15.6	14.4	12	11.3	2
57	B/O Shruthi Hosamani	2	64	m	p	T	37	64	2.5	LSCS	NIL	NIL	12	11	10.8	9.1	8.8	NIL	NIL	1
58	B/O Basamma	3	76	m	p	T	39	76	2.5	LSCS	NIL	NIL	12	11	10.5	9.5	8.7	NIL	NIL	1
59	B/O Shivaganga	3	72	f	G2P1	T	37	72	2.7	p	NIL	NIL	28	15.1	14.6	14	13.6	11.2	9.8	2
60	B/O Sunita	3	78	m	G2P1	T	39	78	2.9	p	NIL	NIL	26	13.6	12.8	12.2	11.9	9.8	9.6	2
61	B/O Pooja	3	76	m	p	T	39	76	2.8	LSCS	NIL	NIL	26	14.2	13.6	12.4	12	10.4	10.2	2

ANNEXURE-5

Newborn baby with hyperbilirubinemia