Original Research Article

A PROSPECTIVE OBSERVATIONAL STUDY ON THE APPRAISAL OF CONVENTIONAL CAUSE AND EFFICACY OF CONTINUOUS PHOTOTHERAPY IN PATIENTS WITH NEONATAL JAUNDICE

ABSTRACT:

BACKGROUND:

Neonatal jaundice is generally harmless, but high concentrations of unconjugated bilirubin may rarely cause kernicterus. Hyperbilirubinemia is the most common cause of neonatal readmission to the hospital, in the majority of cases, risk factors can be identified before discharge. Jaundice can also be a sign of serious liver disease such as biliary atresia, the prognosis for which is better if it is treated before age 6 weeks. We conducted this study to estimate the incidence of neonatal hyperbilirubinemia and to determine underlying causes. Early recognition of jaundice is vital for treatment of any underlying condition and for the appropriate use of phototherapy, which can safely control bilirubin concentration in most cases.

METHODOLOGY:

The study was conducted in Avis Ankura hospital for women and children. It is a well recognized, authorized hospital where gynaecological and neonatal care is provided. A total of 162 neonates were considered. Informed consent was obtained from all the subject's care takers. Subjects enrolled in the study were admitted in NICUs'. This study appraises the conventional cause of NNJ, evaluates the efficacy of continuous phototherapy and detects the phototherapy induced adverse reactions by using Naranjo's causality assessment scale.

RESULTS:

This study identifies commonest cause of neonatal hyperbilirubinemia and efficacy of continuous phototherapy. Out of 162 patients 94 patients (58%) were found to be males and 68 patients (42%) were found to be females. Low birth weight neonates (43.20%) were found to be more prone to neonatal jaundices. In this study, it was found that duration of phototherapy was longer in extremely low birth weight neonates (34 hours) in relation to birth weight and average duration of phototherapy. Based on the conventional cause, physiological cause (56.79%) was observed to be highest among other causes

of neonatal jaundice. The short term adverse reactions due to phototherapy, were identified using Naranjo's Causality Assessment Scale. The TSB levels were increased before phototherapy (pre-treatment) and decreased after phototherapies (post-treatment) which were assessed by using American Academy of Paediatrics guidelines.

CONCLUSION:

From this study, it was concluded that males were more prone to develop neonatal jaundice when compared with females. Physiological jaundice contributes maximum number of cases among the total cases. The use of phototherapy was inversely related to gestational age and birth weight. Every effort should be made to identify at-risk new born during admission and even before their discharge. This assessment should include measurement of serum bilirubin levels in infants who appear jaundiced or who have risk factors before they are discharged, preferably in the first few days of life. Appropriate follow-up needs to be arranged before the infants are discharged, including repeat serum bilirubin based on predictive hour specific serum bilirubin nomograms used when the infants are discharged.

KEYWORDS: Neonatal Jaundice (NNJ), Phototherapy, Total Serum Bilirubin (TSB), Naranjo's Causality Assessment Scale(NCAS).

INTRODUCTION:

Jaundice is one of the most common conditions that require medical attention in new-born babies . The concept of neonatal icterus is a common finding in new-born that is generally benign and self-limited . Neonatal jaundice (NNJ) refers to yellow colouration of the skin and the sclera (whites of the eyes) of new-born babies that result from accumulation of bilirubin in the skin and mucous membranes. This is associated with a raised level of bilirubin in the circulat ion, a condition known as hyperbilirubinemia(HB).

Newborn babies red blood cells (RBCs) have a shorter lifespan than those of adults. The concentration of RBCs in the circulation is also higher in Newborn babies (NBs) than it is in adults, so bilirubin levels are higher than they are later in life. The metabolism, circulation and excretion of bilirubin are also slower than in adults. Thus a degree of HB occurring as a result of this normal physiological mechanism is common in NB babies and usually harmless. It is difficult to tell which babies are at risk of developing high levels of bilirubin that could become dangerous, or who have a serious problem as the explanation for their jaundice .

TYPES OF JAUNDICE BASED ON CAUSES:

1. **PHYSIOLOGICAL JAUNDICE:**

Physiological jaundice refers to the common, generally harmless, jaundice seen in many new- born babies in the first weeks of life and for which there is no underlying cause . It is the most abundant type of NB HB, having no serious consequences. Jaundice attributable to physiological immaturity of

neonates to handle increased bilirubin production is termed as ‘physiological jaundice’. TSB level usually rises in term infants to a peak level by 3 days of age and then falls. Physiological jaundice includes:

a) Breast feeding jaundice:

It is known as breastfeeding jaundice (BFJ) or "breast-non feeding jaundice. Infants who are breastfed receive only small volumes of colostrum in the first days of life, which leads to dehydration and increased uptake of conjugated bilirubin from the intestines, both of which worsen HB. This type of BFJ may result from caloric deprivation and/or insufficient frequency of feeding. Insufficient caloric intake resulting from maternal and/or infant breastfeeding difficulties may increase serum UCB concentrations. This is the infantile equivalent of adult starvation jaundice.

b) Breast milk jaundice (BMJ):

This condition is a type of neonatal jaundice associated with breastfeeding that is characterized by indirect hyperbilirubinemia (IHB) in an otherwise healthy breastfed NB that develops after the first 4-7 days of life, and has no other identifiable cause. The biochemical cause of breast milk jaundice remains under investigation. Some research reported that lipoprotein lipase, found in some breast milk, produces non-esterified long- chain fatty acids, which competitively inhibit glucuronyl transferase conjugating activity. Decreased (*UGT1A1*) activity may be associated with prolonged HB in BMJ.

2. **PATHOLOGICAL JAUNDICE:**

Pathologic jaundice is the most serious type of jaundice. ‘Pathological jaundice’ occurs when TSB concentrations are not in ‘physiological jaundice’ range. It occurs within 24-48 hours after birth.. Pathological jaundice includes the following:

a. ABO incompatibility:

A and B are two major erythrocyte membrane antigens. The incidence of the incompatibility of the ABO blood groups of the mother and foetus, when the mother has the blood group O and the NB has the A or B blood group, is 15–20% of all pregnancies. Jaundice owing to ABO incompatibility usually appears 24 h after the birth.

b. Rh factor incompatibility:

RHDN results from maternal red-cell alloimmunization. Rh is an antigen carried only on red blood cells. Most women are Rh-positive, however certain populations have a higher prevalence of Rh-negative women.

c. Cephalohematoma:

Cephalohematoma generally occurs during labor and delivery. In some instances, there is evidence of birth trauma, but in other cases, there is no indication of any sort of trauma. However, the use of forceps during delivery has been linked with a heightened risk of cephalohematoma.

d. Polycythaemia:

Neonatal polycythaemia, defined as a venous haematocrit ≥65% (0.65), is a common problem in NBs. Infants born post term or small for gestational age (GA), infants of diabetic mothers, recipient twins in twin-to-twin transfusion syndrome, and those who have chromosomal abnormalities are at higher risk.

e. Intestinal obstruction:

Intestinal atresia (IA) is a broad term used to describe a complete blockage or obstruction anywhere in the intestine. The frequencies, symptoms and methods of diagnosis differ depending on the site of intestinal involvement. The different types of intestinal atresia are Pyloric Atresia and Duodenal Atresia.

f. Sepsis:

Jaundice and hepatic dysfunction frequently accompany a variety of bacterial infections. Sepsis is more likely to manifest with jaundice in infants and children than in adults. Jaundice has been associated with infections caused by several organisms including aerobic and anaerobic gram-negative and gram-positive bacteria.

g. Jaundice Associated With G6PD Deficiency:

It is an inherited X-linked recessive disorder with varied clinical presentations including neonatal jaundice, haemolysis, acute icterus after exposure to chemicals and drugs, anaemia. Decreased bilirubin conjugation resulted from variation in the UGT1A1 and OATP2 genes play an important role in the progression of HB in G6PD deficient NBs.

h. Gilbert syndrome (GS):

GS is a relatively mild condition characterized by periods of elevated levels of a toxic substance called bilirubin in the blood (HB). This substance is removed from the body only after it undergoes a chemical reaction in the liver, which converts the toxic form of bilirubin (UCB) to a nontoxic form called conjugated bilirubin.

i. Crigler-najjar syndrome (CNSy):

CNSy. is a rare genetic disorder characterized by an inability to properly convert and clear bilirubin from the body. . Normally, bilirubin created in this process is converted from an unconjugated form to a form that can be dissolved in water and excreted from the body.

PARAMETER	**PHYSIOLOGICAL JAUNDICE**	**PATHOLOGICAL JAUNDICE**
Definition	Jaundice that occurs due to physiological changes in neonates.	Jaundice that occurs due to pathological changes in neonates.
Frequency	Most common	Less common when compared to physiological jaundice.

Onset	Appears after 24-48 hours of life.	Appears within 24-48 hours of life.
Persistence rate	Term neonates <8days Pre-term neonates <14days	Term neonates >8days Pre-term neonates >14days
Rate of increase in TSB	Less per 24hrs	More per 24hrs
Predominant type of bilirubin	UCB (α-bilirubin)	Conjugated (β-bilirubin) or unconjugated bilirubin (α-bilirubin)
Condition of neonate	Healthy	Unhealthy
Treatment	Disappears without treatment.	Requires treatment according to the cause.

Table A : Parameters of types of jaundice based on its aetiology

EPIDEMIOLOGY:

Babies who are either small or large for gestational age are at an increased risk of developing NNJ. Signs of NNJ are seen with in the first three days of birth in 80% of preterm babies and 60% of full term infants. NNJ is the commonest abnormal physical finding during the first week of life. Neonatal hyperbilirubinemia (NNH) is a significant cause of neonatal morbidity and prolongation of hospital stay, which in turn increases the chances of sepsis and mortality. HB is recognized as clinical jaundice in approximately 20-50% of full term and 80% of preterm neonates. About 10% of breast-fed babies are still jaundiced at 1 month of age. Identification of the risk factors, timely detection and optimal management of NNH are thus crucial to prevent brain damage and subsequent neuro motor retardation due to bilirubin encephalopathy.

PATHOPHYSIOLOGY:

Physiological hyperbilirubinemia;

Short lifespan of erythrocytes in the NB (during the first three months, fetal haemoglobin (HbF) is replaced by adult haemoglobin (HbA) as a result, haemoglobin levels drop and bilirubin levels rise) + Impaired bilirubin metabolism (due to immature hepatic conjugation and elimination pathways) + Enterohepatic circulation of bilirubin (UCB is reabsorbed and recycled into the circulation). All these factors lead to jaundice or hyperbilirubinemia in neonates.

Pathological hyperbilirubinemia;

It can be caused by multiple mechanisms:

- Increased production of bilirubin (E.g. conditions with increased haemolysis), Decreased

hepatic uptake (E.g. Crigler-Najjar syndrome),

- Decreased conjugation,
- Impaired excretion (E.g. cholestasis),
- Increased enterohepatic circulation (E.g. decreased intestinal motility, breast milk jaundice).

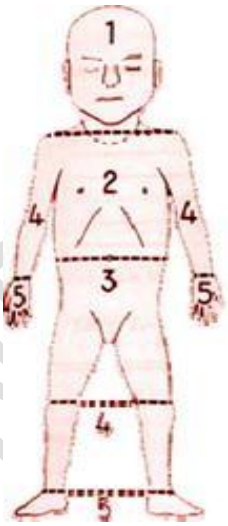
CLINICAL MANIFESTATIONS:

The most pervasive sign of infant jaundice is yellow skin and sclera (the whites of the eyes). This typically starts at the head, and spreads to the chest, stomach, arms, and legs. Yellowing of the skin and the whites of the eyes - the main sign of infant jaundice usually appears between the second and fourth day after birth. Drowsiness, pale stools - breast-fed babies should have greenish-yellow stools, while those of bottle fed babies should be a greenish-mustard colour, poor sucking or feeding, dark urine - a NB's urine should be colourless, yellow abdomen or limbs, inability to gain weight, poor feeding, irritability.

DIAGNOSIS:

- ***VISUAL INSPECTION:***

Visual inspection of neonatal jaundice is thought to be unreliable, but if is performed properly, then it is almost as good as transcutaneous bilirubinometry (TcB) especially if the TSB levels are less than 12-14 md/dl.



Grade	Extent of jaundice
0	None
1	Face and neck only
2	Chest and back
3	Abdomen below umbilicus to knees
4	Arms and legs below knees
5	Hands and feet

Figure A: Visual assessment scale of neonatal jaundice

- **MEASUREMENT OF SERUM BILIRUBIN:**

a. Bio-chemical: The gold standard for the estimation of TSB is high performance liquid chromatography (HPLC). But this can be used for research purpose only. Estimation of TSB is usually performed by Van den Bergh reaction in the laboratory.

b. Micro-method: It uses 10 microliter of blood sample and is based on spectrophotometry.

MANAGEMENT:

I. PHOTOTHERAPY (PT):

Phototherapy remains the mainstay of treating HB in neonates. It acts by converting insoluble bilirubin (unconjugated) into soluble isomers that can be excreted in urine and feces. The decrease of TSB during PT is a result of formation of photo-isomers. Light absorption in the skin transforms the toxic nonpolar Z,Z-bilirubin molecule into more extractable polar photo-isomers: the configurational isomers Z,E-bilirubin and E,Z-bilirubin and the structural isomers Z-lumirubin and E-lumirubin. In addition, a small amount of photo-oxidation products is formed. Generally photo-isomers are induced shortly after phototherapy is initiated. Presumably they are less toxic than bilirubin and less able to cross the blood-brain barrier. The most commonly used PT units include blue compact florescent lamps (CFL), high intensity light emitting diodes (LED) and fibroptic units.

II. EXCHANGE TRANSFUSION:

Double volume exchange transfusion (DVET) should be performed if the TSB levels reach to age specific cut-off for exchange transfusion or the infant shows signs of bilirubin encephalopathy irrespective of TSB levels.

III. INTRAVENOUS IMMUNOGLOBULINS (IVIG):

IVIG was used quite commonly for reducing hemolysis and consequent HB in Rh.I and ABO incompatibility. However, subsequent studies did not prove the efficacy and its use. We do not use Intravenous immunoglobulins (IVIG) for treating iso-immune HJ.

IV. HYDRATION:

Infants with severe HB and evidence of dehydration (e.g. excessive weight loss) should be given IV hydration. An extra fluid of 50 mL/kg of N/3 saline over 8hr 11 decreases the need for exchange transfusion.

OBJECTIVES:

- To determine incidence rate of neonatal jaundice.
- To evaluate the commonest cause and determine the efficacy of continuous phototherapy.
- To detect adverse reactions associated with continuous phototherapy.

METHODOLOGY:

The study was conducted in Avis Ankura hospital for women and children. It is a well recognized, authorized hospital where gynaecological and neonatal care is provided. A total of 162 neonates were considered. Informed consent was obtained from all the subject's care takers. Subjects enrolled in the study were admitted in NICUs'. This study appraises the conventional cause of NNJ, evaluates the efficacy of continuous phototherapy and detects the phototherapy induced adverse reactions by using Naranjo's causality assessment scale.

Fig B: Jaundiced neonate on phototherapy

RESEARCH PARTICIPANTS:

A total of 162 neonates comprising of 94 males and 68 females were considered and the disease condition was evaluated after obtaining the informed consent from each of their care takers. Patient details including demographics, maternal details, chief complaints, history of present illness, past medical history, family history, other co-morbidities, physical examination, laboratory investigations, phototherapy, contact details and other relevant information has been collected from case reports. The obtained clinical data and the test results were re-examined and entered in the data collection forms and further results obtained were tabulated. The subject's caretakers were counselled which helped them to improve and prevent their disease condition, improve quality of life and to a certain extent helped in prevention of adverse reactions.

RESULTS:

DISTRIBUTION OF PATIENTS BASED ON THE GESTATIONAL AGE:

Gestational age	No. of neonates	Percentage
Extremely Pre-term (< 28 weeks)	8	4.93%
Very Pre-term (28-32 weeks)	42	25.9%
Late Pre-term (32-37 weeks)	60	37.03%
Early Term (37-39 weeks)	22	13.5%
Full Term (39-41 weeks)	28	17.2%
Late Term (41-42 weeks)	2	1.2%

Table 1.1: Distribution of Patients Based On The Gestational Age

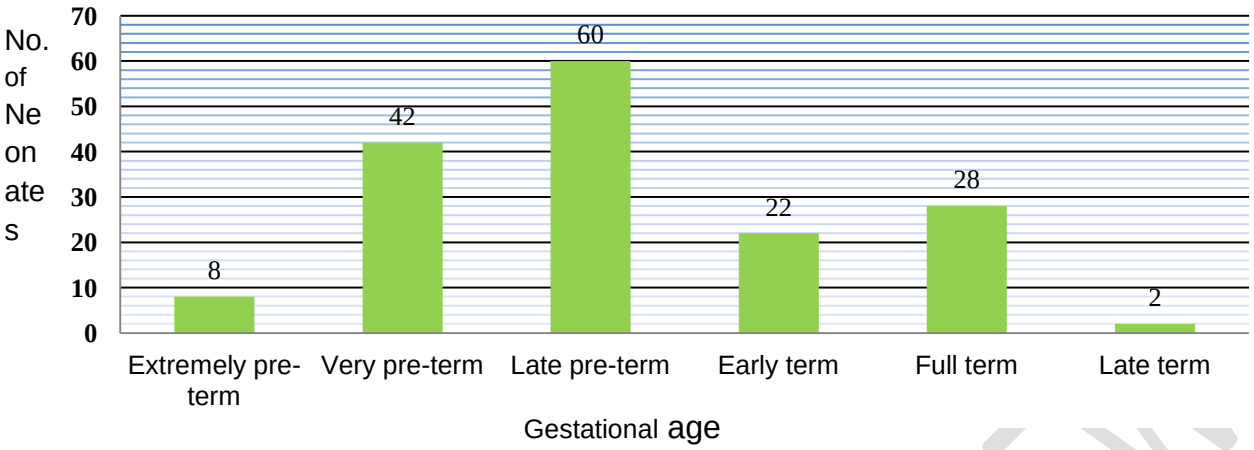


Figure 1.1: Distribution Of Patients Based On The Gestational Age

DISTRIBUTION OF PATIENTS BASED ON THE BLOOD GROUP:

Blood group	A	B	AB	O
A	14	2	-	6
B	8	38	4	14
AB	4	6	2	-
O	14	14	2	34

Table 1.2: Distribution of Patients Based On Blood Groups

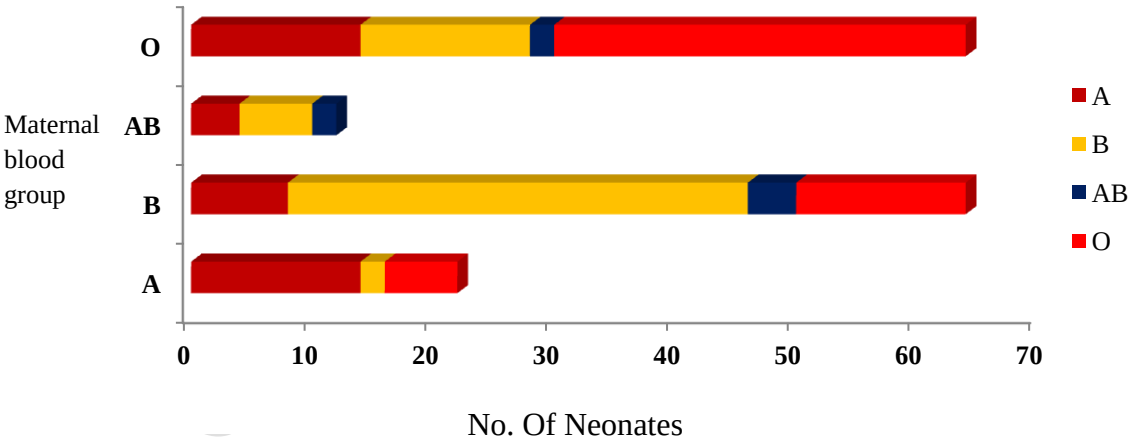


Figure 1.2: Distribution of Patients Based On Blood Groups

DISTRIBUTION OF PATIENTS BASED ON THE BIRTH WEIGHT:

Birth weight	No. of patients	Percentage
NBW (2500-4200g)	52	32.09%
LBW	70	43.20%

(1500-2499g)		
VLBW (1000-1499g)	24	14.81%
ELBW (< 1000g)	16	9.87%

Table 1.3: Distribution Of Patients Based On The Birth Weight

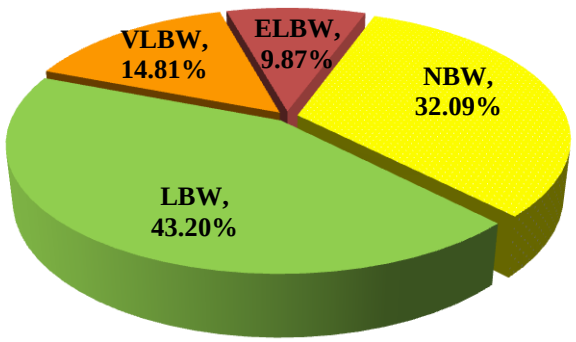


Figure 1.3 : Distribution Of Patients Based On The Birth Weight

RELATION BETWEEN BIRTH WEIGHT & AVERAGE DURATION OF PHOTOTHERAPY:

Birth weight	Avg. duration of phototherapy
NBW	29 hours
LBW	30 hours
VLBW	31 hours
ELBW	34 hours

Table 1.4: Relation between Birth Weight & Average Duration Of Phototherapy

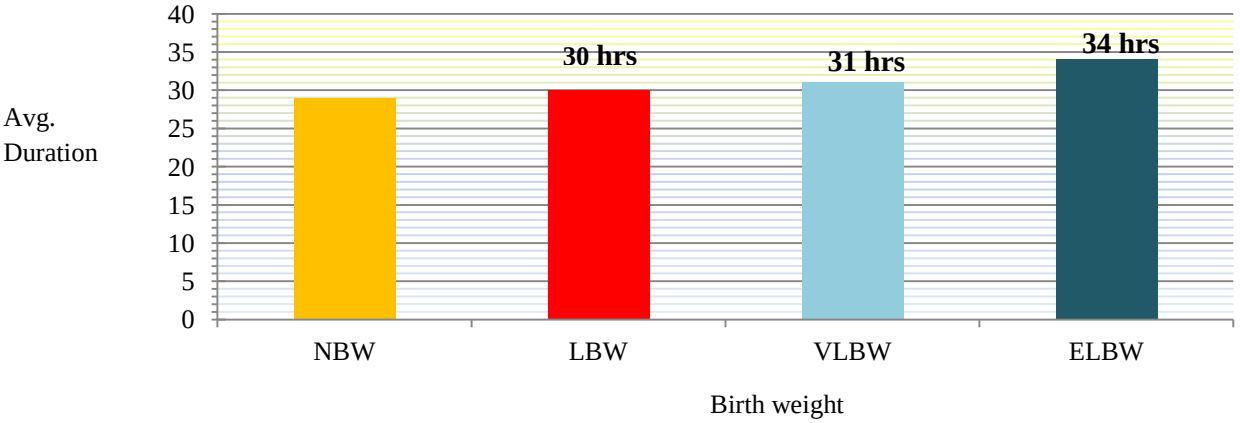


Figure 1.4: Relation between Birth Weight & Average Duration Of Phototherapy

RELATION BETWEEN GESTATION PERIOD & AVERAGE DURATION OF PHOTOTHERAPY:

Gestation Period	Avg. Duration Of Phototherapy
Pre-Term	31 hrs
Term	27 hrs

Table 1.5: Relation between Gestation Period & Average Duration of Phototherapy

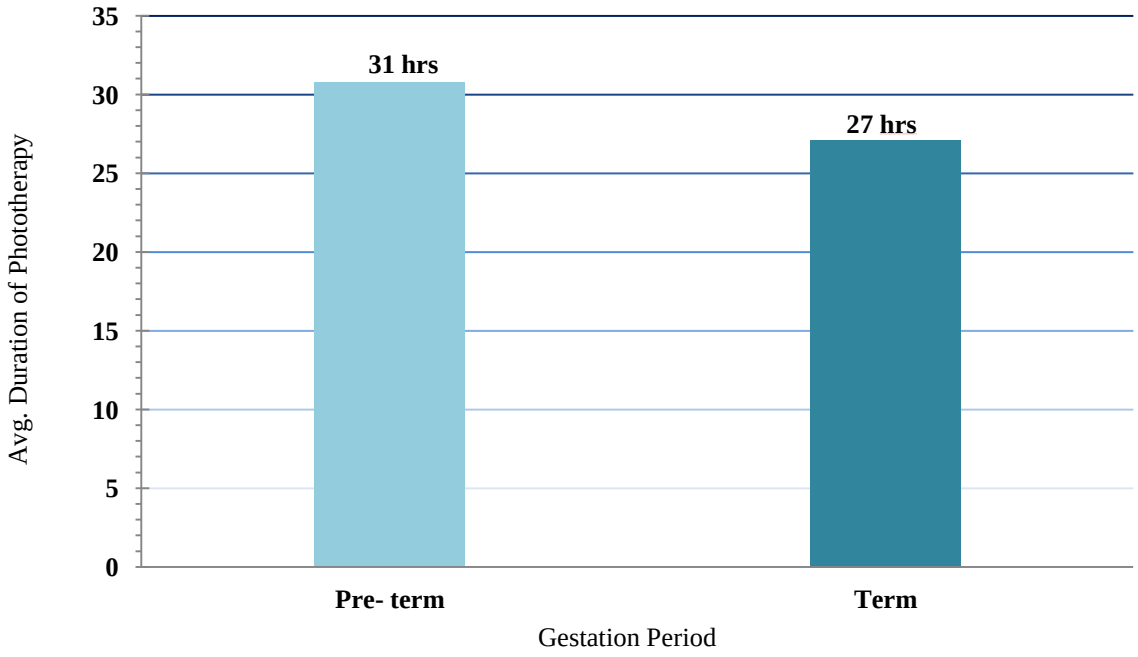


Figure1.5 : Relation between Gestation Period & Average Duration Of Phototherapy

DISTRIBUTION OF PATIENTS BASED ON THE CAUSE:

Cause	No. of patients	Percentage
Physiological	92	56.79%
ABO incompatibility	18	11.11%
Rh incompatibility	12	7.40%
Sepsis	10	6.17%
Breast feeding jaundice	10	6.17%
Intestinal obstruction	6	3.70%
Polycythemia	4	2.46%
Idiopathic neonatal hepatitis	4	2.46%
Cephalohematoma	2	1.23%
Haemolysis	2	1.23%
Tyrosinemia	2	1.23%

Table 1.6: Distribution Of Patients Based On The Cause.

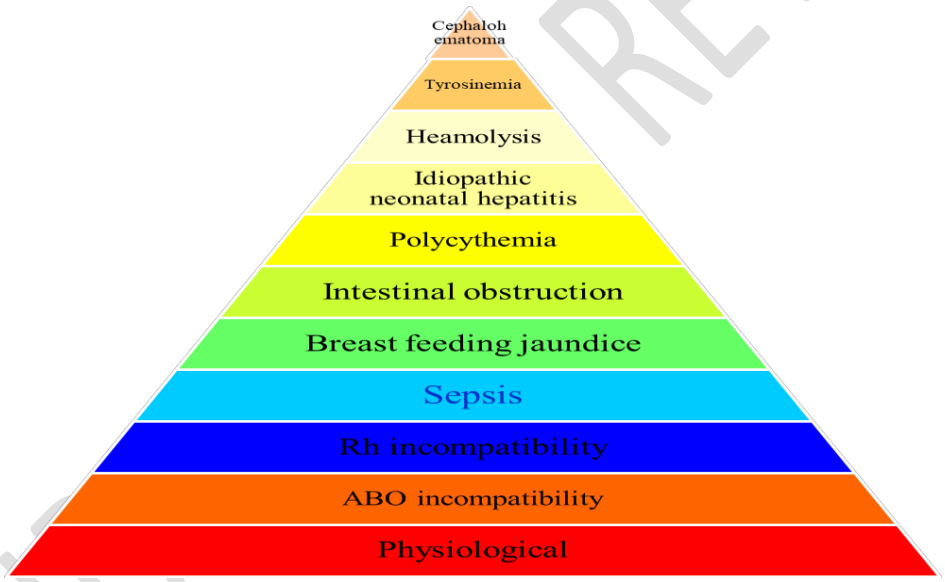


Figure.1.6: Distribution Of Patients Based On The Cause.

DISTRIBUTION OF PATIENTS BASED ON ADVERSE REACTIONS BY USING NARANJO'S SCALE:

Type of adverse reaction	No. of patients	Causality
Electrolyte disturbances	20	Possible
Diarrhoea	8	Possible
Hypocalcaemia	6	Possible

Table 1.7: Distribution Of Patients Based on Adverse Reactions By Using Naranjo's Scale

BASED ON THE VARIANCE OF TSB VALUES IN RELATION TO DURATION OF PHOTOTHERAPY:

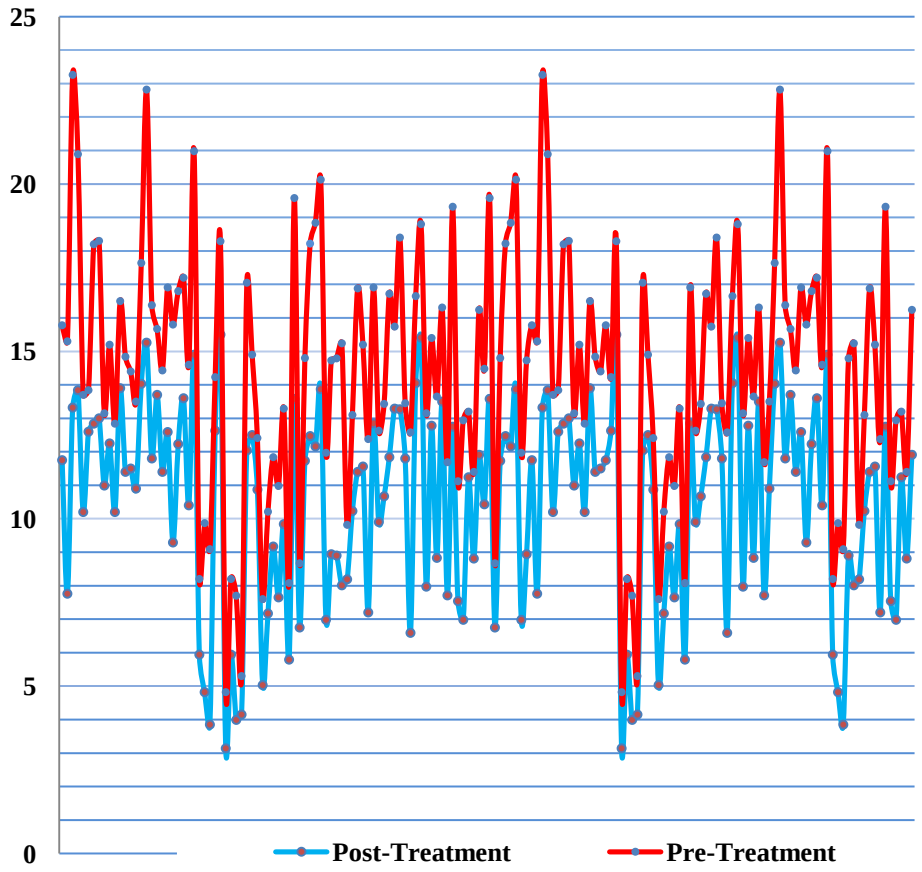


Figure 1.7: Variance of TSB Values In Relation To Duration Of Phototherapy

RISK ASSESSMENT BASED ON TSB VALUES IN RELATION TO AGE & GESTATIONAL AGE OF THE PATIENT:

Age	Risk classification based on TSB values		
	HIGH RISK (<28-32 weeks)	INTERMEDIATE RISK (32-39 weeks)	LOW RISK (39-42 weeks)
24 hours	8	9.9	11.7
48 hours	11.4	13.1	15.3
72 hours	13.6	15.5	17.7
96 hours	14.5	17.5	19.9
> 120 hours	15	18	21

Table 1.8: Risk Assessment Based On TSB Values In Relation To Their Age &Gestational Age of The Patient

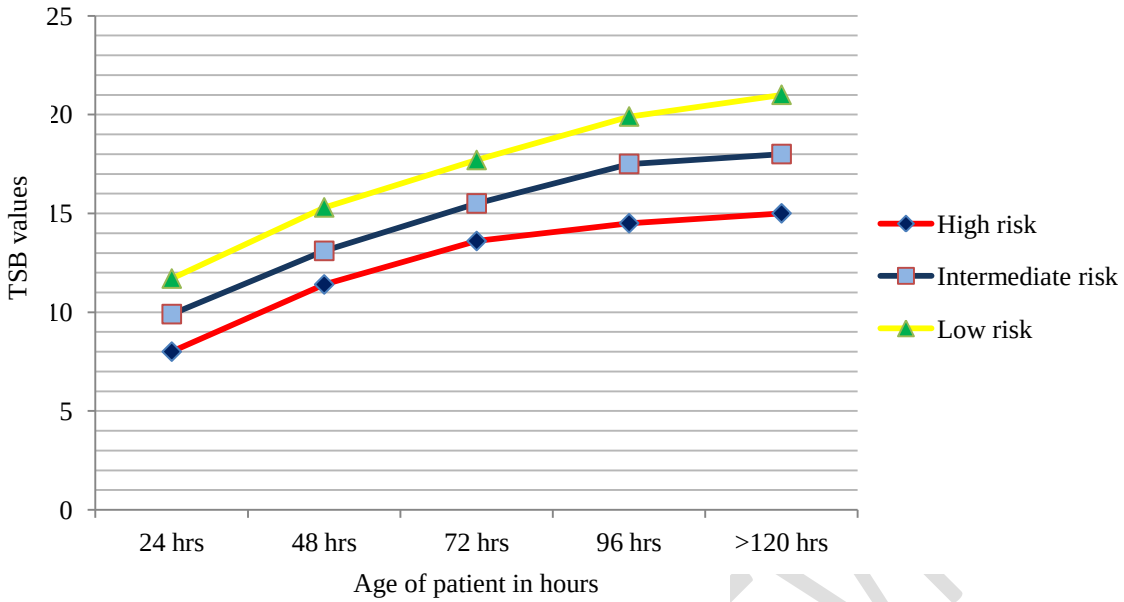


Figure 1.8: Risk Assessment Based On TSB Values In Relation To Their Age &Gestational Age Of The Patient

CONCLUSION:

The incidence of neonatal hyperbilirubinemia was assessed in a tertiary care hospital. Through this study, we systematically estimated the number of infants with severe hyperbilirubinemia and the underlying causes. From this study, it was concluded that males were more prone to develop neonatal jaundice when compared with females. 1-3 days aged preterm neonates were found to be more prone to neonatal jaundice.

Physiological jaundice contributes maximum number of cases among the total cases. Physiological cause occurs mostly due to immaturity of bilirubin-conjugating system, increased entero-hepatic circulation, decreased calorie intake (breast feed), higher rate of hemolysis. Neonates with 'A' and 'B' blood groups contributed maximum to ABO incompatibility. The impact of birth weight on the duration of continuous phototherapy required to treat NNJ was significant. The use of phototherapy was inversely related to gestational age and birth weight. The duration was significantly longer in the lowest birth weight and gestational age groups and decreased with increasing birth weight and gestational age.

The causality assessment was done using Naranjo's scale which showed higher number of possible adverse reactions. As a result, regular adverse reaction monitoring is required to evaluate and prevent short term and long term side effects respectively in patients with NNJ. Neonates received phototherapy through devices with LEDs'. So, primary outcomes included the rate of fall of total bilirubin (mg/dl) which was indicated by the pre and post treatment serum bilirubin values. We categorised the neonates into high, intermediate and low risk categories based on the hour-specific nomogram for risk stratification published in 'Management of hyperbilirubinemia in the new-born infant' (2004) by the AAP journal.

Every effort should be made to identify at-risk new-borns during admission and even before their discharge. This assessment should include measurement of serum bilirubin levels in infants who appear jaundiced or who have risk factors before they are discharged, preferably in the first few days of life. We recommend screening of infants born to mothers with type 'O' blood, for blood type and Coomb's testing. Appropriate follow-up needs to be arranged before the infants are discharged, including repeat serum bilirubin testing (if necessary) based on predictive hour specific serum bilirubin nomograms used when the infants are discharged.

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