

**A RETROSPECTIVE STUDY ON CLINICAL FEATURES
OF EARLY NEONATAL JAUNDICE IN TERM BABIES
AT RATCHABURI HOSPITAL**



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Thematic Paper
Entitled
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**A RETROSPECTIVE STUDY ON CLINICAL FEATURES OF EARLY
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ABSTRACT

Neonatal jaundice is the common condition and sometimes it can lead to devastating neurological consequence like kernicterus. To recognize clinical features and to know etiology of term neonatal jaundice, a hospital based retrospective study was conducted by reviewing 117 medical records of neonatal jaundice who were admitted at Ratchaburi Regional Hospital from 1st October 2007 to 30th September 2008. Both the patient's and their mother's profiles, etiology and clinical features of jaundice were extracted. The results showed that female babies were more likely to contract jaundice. The most common etiology was inconclusive jaundice (64.9%) followed by ABO incompatibility (17.9%) and breast feeding jaundice (10.2%). In addition to those, other less common causes were G6PD deficiency, minor blood group incompatibility and cephalhematoma. The onset of the neonatal jaundice usually occurred on the 2nd to the 4th day of life and almost all newborns responded well to phototherapy. Most of interventions were started on the 2nd day of life. Moreover, exchange transfusion was needed in 4 cases. Maximum microbilirubin and unconjugated bilirubin levels were two factors associated with double side phototherapy and/or exchange transfusion.

KEY WORDS: NEONATAL JAUNDICE/ ETIOLOGY/ CLINICAL FEATURE

53 pages.

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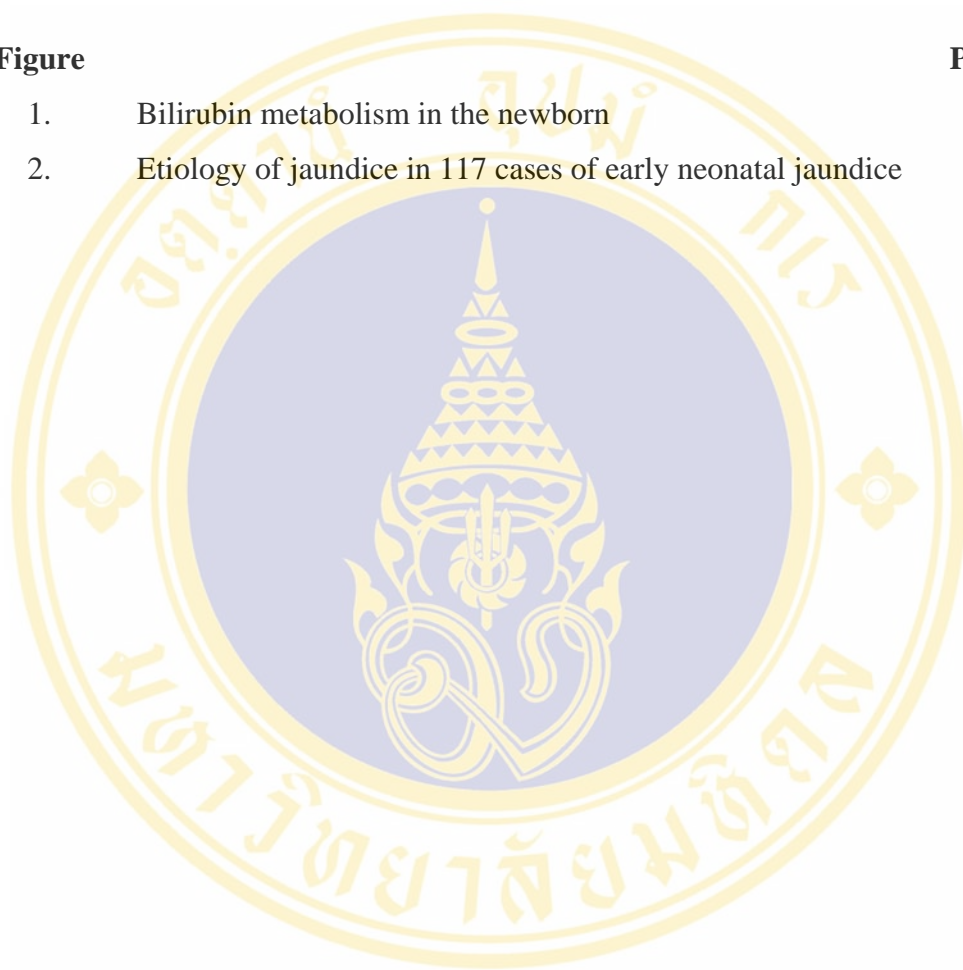
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LIST OF ABBREVIATIONS

Abbreviation or Symbol	Term
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CBC	Complete blood count
CI	Confidential interval
cm	Centrimeters
CPD	Cephalopelvis disproportion
DD/MM/YY	Day/Month/Year
def.	Deficiency
dL	Decilitre
e.g.	Exempli gratia
g	Grams
GA	Gestational age
GPA	Gavida/Partum/Abort
G6PD	Glucose 6 phosphate dehydrogenase
Hct	Hematocrit
HDN	Hemolytic disease of newborn
HIDA	Hydroxyl iminodiacetic acid
hr	Hour
ICU	Intensive Care Unit
Ig M	Immunoglobulin M
Ig G	Immunoglobulin G
kg	Kilograms
LDH	Lactate dehydrogenase
LFT	Liver function test
MB	Microbilirubin
mg	Miligrams

LIST OF ABBREVIATIONS (cont.)

Abbreviation or Symbol	Term
mL	Mililiter
mm ³	Cubic millimeter
n, N	Number
ND	No data
NRC	Nucleated red blood cells
RBCs	Red blood cells
RE system	Reticuloendothelial system
SD	Standard deviation
SGA	Small for gestational age
TcB	Transcutaneous measurement of bilirubin
UDPG	Uridine diphosphoglucose
VLBW	Very low birth weight
WBC	White blood cell
WHO	World Health Organization
wk	Week
<	Less than
>	Greater
%	Percent

CHAPTER I

INTRODUCTION

Icterus neonatorum or neonatal jaundice has long been recognized. From the 1950s through the 1970s, because of a high incidence Rh hemolytic disease and kernicterus, pediatricians were aggressive in treating jaundice (Brown AK, 1962). However, several factors have changed the management of jaundice (Watchko JF and Oksi FA, 1983). Studies in the 1980s and 1990s suggested that kernicterus from jaundice was rare and that too many infants were being treated unnecessarily (Newman TB and Klebanoff MA, 1993; Newman TB and Maisels MJ, 1990; Idem, 1992). And also, newborn infants were being discharged from the hospital sooner after birth, limiting the ability of physicians to detect jaundice during the period when the serum bilirubin concentration is likely to rise (Braveman P et al., 1995; Britton JR et al., 1994). It leads to an increase in reports of the almost forgotten cases of neonatal jaundice and sometimes deadly kernicterus.

Neonatal jaundice is most often caused by normal physiologic mechanism and not usually of significant concern. But, it has a potential for brain damage (Moyer VA et al., 2000). It is therefore important to know about different clinical course of neonatal jaundice and also etiologies. Therefore, early detection, effective intervention and new approaches to prevention have been also stimulated (Phyllis AD et al., 2001).

Although neonatal hyperbilirubinemia is a common event, it is of interest because at its extreme it has clinical significance. It also can be the source of considerable parental concern. All clinicians should be aware of multiple risk factors and causes for hyperbilirubinemia and also assess clinical course. Newborns with one or most risk factors should be followed closely.

Previous studies have indicated a relationship between neonatal hyperbilirubinemia and diverse factors including racial region, male gender, epidural anesthesia, and instrumental delivery (Sivasuriya M et al., 1978; Wood B et al., 1979; Campbell N et al., 1976). They also suggested a dose response relationship with

neonatal hyperbilirubinemia occurring only in association with very high dose of oxytocin (Davies DP et al., 1975; Jeffares Mj, 1977). Low birth weight, short gestation, neonatal infection and breast feeding have been reported to be associated with occurrence of neonatal hyperbilirubinemia (Newman AJ, 1983).

Risk factors for neonatal hyperbilirubinemia are

1. Jaundice visible on the first day of life
2. A sibling of jaundice or anemia
3. Unrecognized hemolysis (ABO, Rh and other blood incompatibility)
4. Nonoptimal feeding (Formula or breast feeding)
5. Deficiency of glucose 6 phosphate dehydrogenase
6. Infection, Infant of diabetic mother and immaturity
7. Cephalhematoma or bruise, Central hematocrit >65% (polycythemia)
8. East Asian, Mediterranean, Native American heritage (MMWR, 2001).

The primary concern with respect to exaggerated hyperbilirubinemia is the potential for neurotoxic effects, but general cellular injury also occurs (Chuniaud L et al., 2006). Bilirubin can interfere with neuroexcitatory signals and impair nerve conduction (particularly auditory nerve) (Bratlid D, 1990). It can also inhibit ion exchange and water transport in renal cells which may explain the neuronal swelling that occurs in the bilirubin encephalopathy associated with kernicterus (Sellinger M, 1990). Conditions that alter the blood brain barrier, such as infection, acidosis, hypoxia, sepsis, prematurity and hyperosmolarity may affect the entry of bilirubin in the brain. In immature rats, increased levels of lactate, decreased level of cellular glucose, and impaired cerebral glucose metabolism are associated with hyperbilirubinemia (Roger C et al., 1995).

According to the objectives of this study, clinical course of kernicterus should be well recognized by health workers including doctors and nurses.

Clinical course of kernicterus can be classified into acute and chronic form.

Acute form

Phase 1: (first 1 to 2 days) poor sucking, stupor, hypotonia, seizures

Phase 2: (middle of first week) hypertonia of extensor muscle, opisthotonus, retrocollis and fever

Phase 3: (after the first week) hypertonia

Chronic form

First year: hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills

After first year: movement disorders (choreoathetosis, ballismus, tremor), upward gaze, sensorineural hearing loss (Dennary PA et al., 2001).

Physiological jaundice is not always the great problem. Nevertheless, significant hyperbilirubinemia contributes short and long term complications like kernicterus which in turn may give potential adverse effect such as cerebral palsy.

This study was designed to get a various clinical profiles of early neonatal jaundice. Careful history taking, physical examinations to elicit information on risk factors were recommended for preventing development of pathological jaundice. Moreover, early measurement of serum bilirubin and work up for jaundice were necessary to know different etiologies.

Effective therapies with timely intervention which based on clinical course and etiologies of neonatal jaundice can prevent devastating bilirubin toxicity, kernicterus.

CHAPTER III

REVIEW OF LITERATURE

DEFINITION AND INCIDENCE OF NEONATAL JAUNDICE:

Neonatal jaundice refers yellow coloration of skin and sclera of newborn that results from hyperbilirubinemia (David E, 2007). The yellow color usually results from the accumulation of unconjugated, nonpolar, lipid-soluble bilirubin pigment in the skin (Anthony JP and Barbara JS, 2007).

Incidence:

Hyperbilirubinemia is a common and in most cases benign problem in neonates (Anthony JP and Barbara JS, 2007).

General incidence:

Jaundice within the 1st week of life is observed in approximately 60% of term infants and 80% of preterm infants. Jaundice may be present at birth or may appear at any time during the neonatal period, depending on the etiology.

Many normal infants have a degree of physiological jaundice which tends to begin on 2nd or 3rd days of life and thereafter begins to fade and finally disappears by 8th to 10th days of age.

In icterus neonatorum, bilirubin level rises at the rate of <5 mg/dL/24 hr; thus, jaundice becomes visible on the 2nd-3rd day, usually peaking between the 2nd and 4th days at 5-6 mg/dL and decreasing to below 2 mg/dL between the 5th and 7th days of life.

Jaundice associated with these changes is designated physiologic and is believed to be the result of increased bilirubin production from the breakdown of fetal red blood cells combined with transient limitation in the conjugation of bilirubin by the immature neonatal liver (Anthony JP and Barbara JS, 2007).

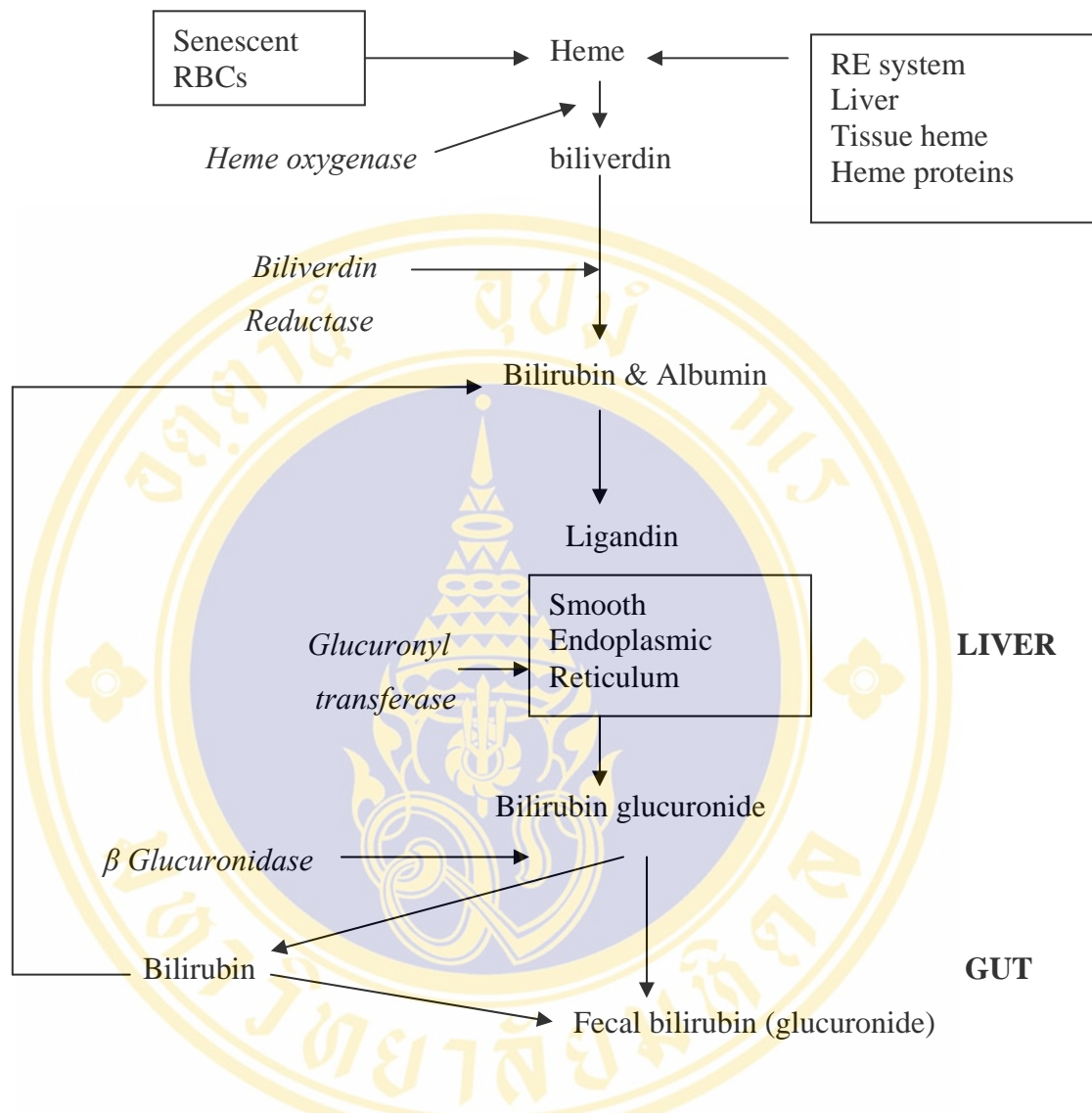


Figure 1: Bilirubin metabolism in the newborn (Tan KL, 1983)

Possible mechanism involved in physiological jaundice

1. Increase bilirubin load on liver cells
 - Increased erythrocyte volume
 - Increased labile bilirubin
 - Increased enterohepatic circulation
 - Decreased erythrocyte survival
2. Defective hepatic uptake of bilirubin from plasma
 - Decreased ligandin (Y protein)
 - Increased binding of Y protein by other anions

- Decreased hepatic uptake especially in Phase II
3. Defective bilirubin conjugation
 - Decreased UDPG activity
 4. Defective bilirubin excretion

Table 1: Possible factors exaggerating physiological jaundice (Lalitha KG, 1993)

Factor	Clinical correlate
1. Bilirubin load to liver	<ul style="list-style-type: none"> • Infants with polycythemia • Infants of diabetic mother • Collection of extravasated blood like cephalhematoma and intraventricular hemorrhage • Delayed cord clamping
2. Defective uptake from liver	<ul style="list-style-type: none"> • Decreased Y protein due to caloric deprivation
3. Defective bilirubin conjugation	<ul style="list-style-type: none"> • Due to decreased UDPG activity as seen in hypothyroidism and inhibitors in breast milk
4. Decreased hepatic excretion	<ul style="list-style-type: none"> • Congenital infections
5. Inadequate hepatic perfusion	<ul style="list-style-type: none"> • Hypoxia • Congenital heart diseases
6. Increased enterohepatic circulation	<ul style="list-style-type: none"> • Unfed babies • Delayed passage of meconium

In infants without these variables, indirect bilirubin levels rarely rise above 12 mg/dL whereas infants with several risk factors are more likely to have higher bilirubin level. Prediction of which neonates are at risk for exaggerated physiologic jaundice can be based on hour-specific bilirubin levels in the 1st 24-72 hr of life. Indirect bilirubin levels in full-term infants decline to adult levels (1 mg/dL) by 10-14 days of life (Hansen TWR, 2003).

PATHOLOGICAL JAUNDICE:

Jaundice and its underlying hyperbilirubinemia are considered pathologic if the time of appearance, duration, or pattern varies significantly from that of physiologic jaundice.

If the course is compatible with physiologic jaundice but other reasons exist to suspect that the infant is at special risk for neurotoxicity.

Definition

Any of the following features characterizes pathological jaundice;

1. Clinical jaundice appearing in the first 24 hour.
2. Increase on level of total bilirubin by more than 0.5 mg/dL/hr or 5mg/dL/24 hr.
3. Total serum bilirubin > 12 mg/dL in term infants and total serum bilirubin level 10-14 mg/dL in preterm infants.
4. Direct reacting bilirubin > 2.0 mg/dL (Anthony JP and Barbara JS, 2007).

Onset of jaundice before 24 hours of age suggests pathological hyperbilirubinemia requires investigation and immediate attention. It may be due to

- Immune hemolysis such as rhesus disease, ABO incompatibility, rare blood group antibodies
- Non-immune hemolysis such as G6PD deficiency, pyruvate kinase deficiency, congenital spherocytosis
- Sepsis

Jaundice secondary to extensive ecchymosis or hematoma may occur during the first day or later.

Jaundice appearing after 3rd day of life and within first week should suggest bacterial sepsis or urinary tract infections.

Familial non-hemolytic icterus (Crigler Najjar syndrome) and early onset breast feeding jaundice are seen initially on the 2nd and 3rd day.

Jaundice after the 1st week of life:

1. Breast milk jaundice
2. Neonatal hepatitis

3. Septicemia
4. Congenital biliary atresia
5. Paucity of bile ducts
6. Hypothyroidism
7. Cystic fibrosis
8. Galactosemia
9. Spherocytosis
10. Crisis of hemolytic anemia

Rh incompatibility rarely causes complications in a first pregnancy and does not affect the health of the mother. But Rh antibodies that develop during subsequent pregnancies can be potentially dangerous to mother and child. Rh disease can result in severe anemia, jaundice, brain damage, and heart failure in a newborn. In extreme cases, it can cause severe complication and the death of the fetus (Barbara PH, 2008).

TYPE OF HYPERBILIRUBINEMIA:

Unconjugated hyperbilirubinemia:

- Physiological
- Breast milk
- Cephalhematoma
- Urinary tract infection
- Galactosemia (early)
- Hypothyroidism/ Hypopituitarism
- Polycythemia
- Hemolytic

Hemolytic disease of the newborn (Rh, ABO):

- Membrane defects: Spherocytosis, Elliptocytosis
- Enzyme defects: G6PD, pyruvate kinase deficiency
- Enzyme dysfunction
 - Gilbert's syndrome
 - Crigler Najjar syndrome

Conjugated hyperbilirubinemia:

- Hepatic
 - Neonatal hepatitis
 - Hypothyroidism/Hypopituitarism
 - Galactosemia
 - Cystic fibrosis
 - Alpha 1 antitrypsin deficiency
 - Parenteral nutrition
 - Amino/organic aciduria
- Post hepatic
 - Biliary atresia
 - Biliary duct obstruction (choledochal cyst)

ABO INCOMPATIBILITY:

It is the most common iso-immune hemolytic disease, but is generally less severe than that caused by rhesus incompatibility.

The naturally occurring anti A or anti B antibody is of the Ig M type, which does not cross the placenta. Approximately 10% of women carry immune anti A or anti B of the Ig G class. It is in the pregnancies of these women that ABO incompatibility occurs, as the Ig G crosses the placenta to hemolyse fetal red cells. The mechanisms of development of these antibodies are disputed. ABO incompatibility may occur in the first pregnancy and subsequent pregnancies may be relatively unaffected.

ABO incompatibility generally occurs with the blood group combinations are listed in following table (Liley AW, 1961; Scoff F and Chan FY, 2008; Queenan JT et al., 1993).

Table2: Relation of maternal and neonate blood group in ABO incompatibility

Mother	Infant	Frequency
O	A and B	Common
A	B or AB	Rare
B	A or AB	Rare

Rh INCOMPATIBILITY:

It can develop only after maternal exposure to fetal cells at birth, as in abortion, antepartum hemorrhage, or amniocentesis, or after incompatible transfusion. Usually, first pregnancies cause no reaction, and the disease worsens in second and later pregnancies after recurrent exposure of the mother's immune system to foreign red cells proteins (Mupanemuda R and Watkinson M, 2005).

Ig G remains present in the neonatal circulation for up to 3 months and neonatal hemolysis may continue to occur for some weeks after birth (Liley AW, 1961; Scoff F and Chan FY, 2008; Queenan JT et al., 1993).

Following the introduction of anti D prophylaxis in the late 1960s, there was a rapid decline in the number of mothers who became sensitized. The risk of rhesus sensitization and hence disease is greatly reduced by the administration of anti D immunoglobulin to affected mothers at 28 weeks and again within 24 hours of delivery. Overall, the incidence of several diseases has now fallen to about one per 1,000 births. Thus, prophylaxis has had a considerable on the consequences of rhesus incompatibility.

Although the Rh antibodies is the most common cause of severe hemolytic disease of newborn (HDN), other alloimmune antibodies belonging to Kell, Duffy, Kidd and MNSs system causes severe HDN, but rare. This kind of hemolysis is also known as non immune hemolysis.

G6PD DEFICIENCY:

It is the most common red cell morphology abnormality associated with increased risk of hemolysis (Jeffery M et al., 2004).

It is also known to be associated with neonatal jaundice, kernicterus and even death (Mupanemuda R and Watkinson M, 2005).

In newborns with significant hyperbilirubinemia, looking for G6PD deficiency is very important. Moreover, G6PD deficient infants require intervention at lower total serum bilirubin levels. G6PD level can also be elevated in the presence of hemolysis and it may obscure the diagnosis in newborn period. Therefore, in a hemolyzing infant with normal levels cannot rule out the deficiency. If G6PD deficiency is strongly suspected, a repeat level should be measured when the infant is 3 months old (Cesar PT, 2003).

POLYCYTHEMIA:

Polycythemia in the newborn is common and is defined as venous hematocrit of 65% or more during the first week of life. It should only be diagnosed on a free flowing venous specimen and not from a heel prick sample.

The causes of polycythemia are listed as below:

1. Chronic intrauterine hypoxia such as SGA, post maturity
2. Excessive transfusion of blood such as delayed cord clamping, maternofetal transfusion and twin to twin transfusion
3. Infants of diabetic mother
4. Down syndrome
5. Neonatal thyrotoxicosis
6. Congenital adrenal hyperplasia (Liley AW, 1961; Scoff F and Chan FY, 2008; Queenan JT et al., 1993)

INFECTION:

Infections increase RBCs destruction, liberating more bilirubin, and impair the ability of the liver to clean bilirubin from plasma. Infection should always suspected in any neonate with a sudden onset of jaundice not due to hemolytic disease or red cell abnormalities (Rennie JM and Robertson NRC, 2002).

INVESTIGATION OF HYERBILIRUBINEMIA:

Investigation of in patients with unconjugated hyperbilirubinemia

- Indirect and direct acting bilirubin
- Hemoglobin
- Blood film for red cell morphology
- Maternal and infant blood group
- Direct Coombs' test
- Infection screen
- Urine reducing sugar
- G6PD screening
- Serum thyroxin and thyroid stimulating hormone (Malcolm IL et al., 2008)

Investigation in patients with conjugated hyperbilirubinemia

- Liver enzyme
- Alkaline phosphatase level
- Serum bilirubin level
- Alpha fetoprotein level
- Abdominal ultrasonogram
- Sweat test
- TORCH serology
- Amino acid screen
- Percutaneous liver biopsy
- HIDA scan (hydroxyl iminodiacetic acid) (Malcolm IL et al., 2008)

Clinical assessment for hyperbilirubinemia

History

The following points should be noted;

1. Family history of jaundice and anemia
2. History of jaundice and need exchange transfusion in sibling
3. Family history of neonatal or early infant death due to liver disease suggesting galactosemia, Crigler Najjar syndrome or alpha 1 antitrypsin.

4. Maternal illness suggestive of viral infection, fever, rash and lymphadenopathy

5. Maternal drugs such as sulphonamide or antimalarials causing hemolysis in a G6PD deficiency (Lalitha KG, 1993)

Physical examination

1. Extra vascular blood e.g. bruising, cephalhematoma, petechiae
2. Plethora or pallor
3. Hepatosplenomegaly
4. Evidence of intrauterine infection: small for gestational age, cataract and microcephaly, etc
5. Infection: umbilicus, skin
6. Neurological sign: hypertonic, opisthotonus, fits, abnormal eye movement
7. Abdominal distension; associated with bowel obstruction, bowel stasis or hypothyroidism (Malcolm IL et al., 2008)

Jaundice can be detected in the immediate postnatal period at the bilirubin level more than 5 mg/dL. This level manifests as clinical jaundice or icterus where as in the adults the skin look icterus with as little as 2 mg/dL (Lalitha KG, 1993).

As jaundice is common, it is essential to have a clinical method for determining its severity. Proper lighting is important for detection of subtle level of jaundice (Malcolm IL et al., 2008).

Table 3: Kramar's rule (Kramar LI, 1969)

Dermal zone	mg/dL
Face and neck	5
Upper trunk	10
Lower trunk and thigh	12
Arms, legs, below knees	15
Hands and feet	>15

Whereas jaundice from deposition of indirect bilirubin in the skin tends to appear bright yellow or orange, jaundice of the obstructive type (direct bilirubin) has a

greenish or muddy yellow cast. But, visual assessment of serum bilirubin level may lead to error (Lalitha KG, 1993).

Noninvasive techniques for transcutaneous measurement of bilirubin (TcB) that correlate with serum levels may be used to screen infants but determination of serum bilirubin level is indicated in patients with

- elevated age-specific transcutaneous measurement
- Progressing jaundice
- Risk for either hemolysis
- Sepsis (Maisels MJ and Kring E, 1998)

RISK FACTORS OF SEVERE HYPERBILIRUBINEM IA: (Pamela GL, 2003)

Major Risk Factors:

1. Pre discharge microbilirubin level in high risk zone
2. Jaundice observed in 1st 24 hour
3. Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease
4. Previous sibling received phototherapy
5. Cephalhematoma or significant bruising
6. Exclusive breast feeding if nursing is not going well and weight is excess
7. East Asian Race

Minor Risk Factors:

1. Pre discharge microbilirubinemia level in the high intermediate risk zone
2. Jaundice observed before discharge
3. Previous sibling with jaundice
4. Macrosomic infant of diabetic mother
5. Male Gender

Decreased risk factors:

1. Microbilirubin level in low risk zone
2. Exclusive bottle feeding
3. Black race

4. Discharge from hospital after 72 hour

The greatest risk associated with indirect hyperbilirubinemia is the development of bilirubin-induced neurologic dysfunction which typically occurs with high indirect bilirubin levels. The development of kernicterus (bilirubin encephalopathy) is depended on the level of indirect bilirubin duration of exposure to elevated levels, the cause of jaundice, and the infant's well-being.

Neurologic injury including kernicterus occurs at lower bilirubin levels in preterm infants and in the presence of asphyxia, intraventricular hemorrhage, hemolysis, or drugs that displace bilirubin from albumin. The exact serum indirect bilirubin level that harmful for very low birth weight (VLBW) infants is unclear (Ip S et al., 2004).

KERNICTERUS:

The term "kernicterus" refers to an anatomic diagnosis made at autopsy based on characteristics pattern of staining found in babies who had marked hyperbilirubinemia before they succumbed. Most effected regions include; basal ganglion, hippocampus, geniculate bodies and cranial nerves, not sparing to the cerebellum. Despite the lack of clear cut cause and effect relationship between Kernicterus and hyperbilirubinemia, that many laboratory investigations have demonstrated that bilirubin is neurotoxic at cellular level.

Kernicterus is now recognized to occur in premature infants and rarely in healthy term infants. In contrast to infants with hemolytic disease, there is little evidence showing adverse neurologic outcome in healthy term babies with bilirubin level lower than 25 to 30 mg/dL. Evidence favors the hypothesis that bilirubin interferes with oxygen utilization by cerebral tissue possibly by injuring the cell membrane. However there are some situations that bilirubin staining can occur in the absence of hyperbilirubinemia. In these situations, factors influencing the permeability of blood-brain barrier and the amount of unbound bilirubin may play a role (Robert MK, 2007).

TREATMENT:*Indications of treatment*

- **Age of the baby**

Rate of increment of bilirubin can be estimated from age and further rise for next 24 hours and thus decide whether treatment is necessary. The relative susceptibility of the nervous system is greatest during the first days of life; the risk of bilirubin toxicity is also greatest during this period.

- **General condition of the baby**

The healthy baby can tolerate high level of bilirubin with any damage. However, this ability declines with deteriorating general conditions and maturity. Hence, the needs for treatment at lower bilirubin level for those who are ill or/and premature.

- **Underlying cause of jaundice**

Where the etiology is known, it is possible to predict the pattern of bilirubin curve over next few days. In severe hemolytic conditions a rapid increase can be anticipated which is not the case with non hemolytic jaundice. This will help in decision making.

- **Bilirubin level**

The bilirubin level finally determines the need for treatment. However, the decision should always be taken in relation to other three factors. In ill babies, treatment may be necessary at low bilirubin level whereas in healthy babies, similar level can be easily tolerated (Tan KL, 1983).

Choice of treatment

- **Phototherapy**

It is the most widely form of treatment for unconjugated hyperbilirubinemia and has considerably lessened the need of exchange transfusion.

Geometric photoisomerization of unconjugated bilirubin results in more soluble form of bilirubin. This accounts for 80% of conversion.

Converting bilirubin to lumirubin through structural isomerization can be excreted in the bile without the need for hepatic conjugation.

Oxidation mechanism results in colorless by products and excreted by liver and kidney without conjugation. This is the last important mechanism (Lalitha KG, 1993).

Phototherapy can be commenced when the bilirubin level exceeds 13 mg/dL in first 48 hours. For older babies the therapy is only stated when the bilirubin level exceeds 15 mg/dL. Phototherapy should be continued for a minimum period of 24 hours, and be discontinued to below 11 mg/dL. During phototherapy bilirubin level should be monitored 6 or 12 hourly intervals. After cessation of phototherapy, bilirubin level should be monitored for two successive days to detect any rebound without exposure. If the rebound in bilirubin level equal or exceed than that of pre phototherapy level, second exposure is needed. However, in the vast majorities of babies only one exposure is necessary (Tan KL, 1983).

Distance of baby from light source also affects the effectiveness of phototherapy. Typically, a distance of 45 cm used to be followed, although lesser distance is being used. Babies are kept naked except for diapers as larger the surface area exposed, more effective is the phototherapy. Skin pigmentation does not alter effectiveness. Eyes must be covered with eye patches to prevent potential adverse effect on retina (Lalitha KG, 1993).

Risk of phototherapy (Anthony JP and Barbara JS, 2007)

Generally, phototherapy is very safe, and it may have no long term serious effects in neonates. However some adverse may be noted. There may be potential for retinal damage if the eyes are not shielded. Other complications are

- loose stool
- erythematous macular rash
- papular rash associated with transient porphyrinemia
- overheating: hypothermia from exposure and dehydration (insensible water loss and diarrhea) (Anthony JP and Barbara JS, 2007)
- bronze baby syndrome, the baby turns to dark bronze color as a result of exposure to phototherapy. In such babies there is always evidence of obstructive jaundice and hepatic dysfunction though the converse is not true. The discoloration may be due to photo induced modification of porphyrin. Despite the bronze baby

syndrome, phototherapy can continue if needed. Fortunately the dark color fades within 2 to 3 month without any ill effects on infants (Rubaltelli FF et al., 1996).

Clinical experience suggests that long term adverse effects of phototherapy are absent, minimal or unrecognized (Anthony JP and Barbara JS, 2007).

- **Exchange transfusion**

This is the standard therapy for immediate treatment for severe hyperbilirubinemia to prevent fatal and most dangerous complication like kernicterus and to correct anemia in erythroblastosis fetalis (Lalitha KG, 1993).

With the advent of phototherapy, the need of exchange transfusion is declined. But in severe hemolytic jaundice, exchange transfusion is necessary. It is not only remove the excess bilirubin but also circulating antibodies and sensitized cells in severe hemolytic jaundice (Tan KL, 1983).

Therapeutic guideline for exchange transfusion (Lalitha KG, 1993)

1. When phototherapy level fails to prevent rise of bilirubin level in toxic level.
2. To correct anemia and congestive heart failure in hydrop infants.
3. To stop hemolysis and production of remaining antibodies and sensitized RBCs.
4. Repeat exchange are done for same indications as initial exchange.

To perform exchange effectively, following conditions should be satisfied:

- Use of compatible blood within 4 to 5 days of storage. The volume of blood is twice that of infant circulating blood volume (80 to 85 mL/kg).
- Blood should be warm to body temperature before transfusion.
- The aliquot should exactly replace the volume extract thus avoiding any over or under infusion. This aliquot should range from 5 to 10 mL so as not to cause any circulating disturbance.
- Absolute sterility should be maintained throughout the procedure.
- 1 mL of 10% calcium gluconate should be infused after 100 mL exchange to prevent hypocalcemia (Tan KL, 1983).

The total volume amount of blood exchanged is equal to twice of the infant's blood volume, calculated as

Weight (kg) x 85 mL/kg x 2 (Pamela GL, 2003)

An exchange transfusion may range 1.5 to 2 hours and more prolong in sicker neonates.

The exchange transfusion causes 50% decline in bilirubin level. However, rapid rebound will occur resulting bilirubin level reach 90% of pre exchange level by 6 hours post exchange. In order to reduce the rebound, phototherapy should start immediately after exchange transfusion (Tan KL, 1983).

The exchange transfusion is effective but not free of risk. The substantial potential complications in up to 12% include;

- Cardiac-arrhythmia, volume overload, congestive heart failure and cardiac arrest
- Hematological- over heparinization, neutropenia, thrombocytopenia and graft versus host syndrome
- Metabolic-acidosis, hypocalcemia, hypernatremia and hyperkalemia
- Vascular-embolization, thrombosis, necrotizing enterocolitis and perforation of vessel
- Systemic-hypothermia.
- **Intravenous immunoglobulin**

The administration of immunoglobulin is an adjuvant therapy hyperbilirubinemia due to iso-immune hemolytic anemia. Intravenous Ig (0.5 to 1 g/kg/dose, repeat in 12 hours) has been shown to reduce the need for exchange transfusion in both ABO and Rh incompatibility presumably by reducing hemolysis (Anthony JP and Barbara JS, 2007).

- **Hemoxygenase inhibitor (Metalloporphyrin)**

It may reduce hyperbilirubinemia by competitive enzymatic inhibition of rate limiting conversion of heme to biliverdin. Single intramuscular dose on first day of life reduce the need of phototherapy. It remains unclear whether it will alter the risk of kernicterus and long term neurodevelopment impairment. Data on efficacy, toxicity and long term benefits are currently evaluated (Anthony JP and Barbara JS, 2007).

- **Phenobarbitone**

Administration of this drug to pregnant woman and babies has been shown to reduce serum bilirubin by more than 50% in physiologic jaundice. But, it is effective only if given to mother before delivery. Since onset of labour cannot predict, it does not gained popularity. It leads to excessive sleep in neonates and can be potentially addiction. Combination of phototherapy and phenobarbitone is no more effective than phototherapy alone. Hence, less commonly used in clinical practice (Lalitha KG, 1993).

- **Miscellaneous agents**

Frequent breast feeding will prevent reabsorption of unconjugated bilirubin from gut reducing enter hepatic circulation. Bilirubin binding agent like charcoal and agar in the gut may prevent reabsorption of unconjugated bilirubin (Lalitha KG, 1993).

Use of blood filters containing fungal bilirubin oxidase is still experimental therapy.

Moderate alkalization (pH not over 7.55) has been recommended as a mean of preventing neurotoxicity (Dennerly PA et al, 2001).

PREVENTION:

Preventing of neonatal jaundice is confined to maintenance of the general well being and nutrition of the baby and preventing complications of sepsis, anoxia, hypercapnia and acidosis (Tan KL, 1983).

Early feeding reduces the incidence of jaundice by preventing dehydration and the elevation of free fatty acids. The maintenance of an adequate fluid intake is an essential part of the care of a jaundiced baby (Malcolm IL, 2008).

Specific preventive measure e.g. phenobarbitone therapy have not been practiced widely. Such preventive measures will involve the large number of babies who will not need any treatment. This is partly due to the inability to predict the likelihood of severe jaundice occurring. It would therefore seem unwise to use such preventive measures but rather confine treatment to those infants who develop jaundice of sufficient severity (Tan KL, 1983).

CHAPTER IV

MATERIALS AND METHODS

STUDY DESIGN AND STUDY SITE:

It was a hospital based retrospective record study.

STUDY AREA:

The study was done at Ratchaburi Regional Hospital.

STUDY PERIOD:

The study was conducted from 1st November 2008 to 31st March 2009.

STUDY POPULATION:

Neonates who were admitted at Ratchaburi Regional Hospital with the problem of early neonatal jaundice (onset within 7 days) during 1st October 2007 to 30th September 2008.

Inclusion criteria

1. Neonates aged less than 7 days who admitted to Ratchaburi hospital.
2. Gestational age was 37 to 42 weeks.
3. Patient who needed intervention for jaundice.
4. Patient whose onset of jaundice within 7 days.
5. Neonates who were available for assessing microbilirubin level.

Exclusion criteria

1. Preterm neonate
2. Low birth weight (less than 2.5 kg)
3. Major congenital anomalies
4. Serious illness requiring ICU care, severe birth asphyxia, meconium aspiration syndrome
5. Systemic infection before onset of jaundice such as sepsis, pneumonia

6. Suspected congenital infection such as cataract, microcephaly.

SAMPLE SIZE: (Reference from WHO sample size determination)

n = minimum require sample size

$Z = 1.96$ (where confidence interval is 95%)

P = estimated prevalence of known etiology of neonatal jaundice in all pathological jaundice = 60% (information from Ratchaburi Regional Hospital)

$q = p - q = 40\%$

d = precision=0.1

$n = (1.96) (1.96) \times 0.6 \times 0.4 / 0.1 \times 0.1 = 92$ (approximately 100)

DATA COLLECTION METHOD:

Case record forms were constructed based upon the variables from Ratchaburi Regional Hospital and study objectives. First of all, medical records of neonatal jaundice who was admitted from 1st October 2007 to 30th September 2008 were collected. Among them, medical records of early neonatal jaundice were selected according to inclusion and exclusion criteria. Required data from the selected records were collected and transferred into case record form. Finally collected data from case record forms were entered into SPSS 11.5 for statistical analysis.

STATISTICAL ANALYSIS:

Descriptive analysis was used for this study. Student T-test for continuous variables and Chi square and Odds ratio for categorical variables were used according to the type of data collection. The statistical significance in all tests was accepted at two-tailed with the 95% confidence level ($p < 0.05$).

PARAMETERS:

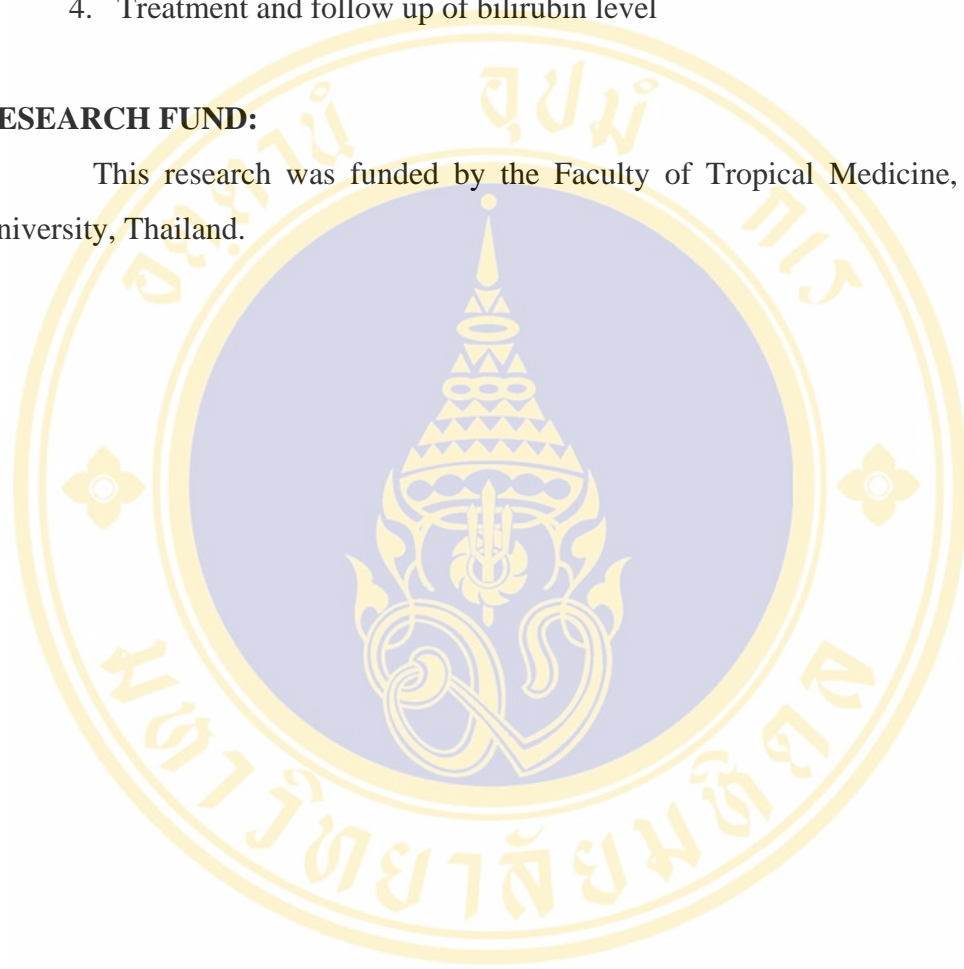
The following parameters were collected from the patient's medical records and laboratory results

1. Demographic data: age, gender, birth weight, gestational age

2. Maternal history: age, GPA, obstetric history, medication, previous neonatal jaundice
3. Newborn history and laboratory investigation for etiology: CBC, blood group, G6PD assay, liver function test
4. Treatment and follow up of bilirubin level

RESEARCH FUND:

This research was funded by the Faculty of Tropical Medicine, Mahidol University, Thailand.



CHAPTER V

RESULTS

Characteristic of neonatal profile in this study

Table 4: Characteristic of neonates in this study

Neonatal profile	No.	(%)
Gender distribution (n=117)		
Male	56	49.9
Female	61	52.1
Mode of delivery (n=117)		
Spontaneous	61	52.1
Cesarean section		
Elective	22	18.8
Emergency	20	17.1
Vacuum extraction	13	11.1
Forceps extraction	1	0.9
Birth weight (g) (n=117)		
2,500-3,000	51	43.6
3,001-3,500	45	38.5
3,501-4,000	21	17.9

Among 117 neonates, 56 (49.9%) neonates account for male and 61 (52.1%) were females. Most of the babies were born by normal spontaneous vaginal delivery (n=61, 52.1%) which was followed by cesarean section (elective, n=22, 18.8%), (emergency, n=20, 17.1%). Vacuum extraction was 13 cases (11%) and there was only 1 case of forceps extraction among 117 patients.

Most of the neonates had birth weight in range of 2,500-3,000 g (n= 51, 43.6%). This value was followed by body weight range within 3,001–3,500 g. The least common was group within 3,501 to 4,000 g.

Characteristic of mother profile in this study

Table 5: Characteristic of mothers in this study

Maternal profile	No.	(%)
Maternal age (years) (n=113)		
15-20	26	23.0
21-35	76	67.3
36-45	11	9.7
Maternal complication(n=116)		
CPD	18	15.5
Hypertension	2	1.8
Diabetic	1	0.9
Hypertension and Diabetic	1	0.9
Oxytocin using (n=115)	3	2.6
Any medication during pregnancy (n=115)	2*	1.7
Previous neonatal jaundice history (n=67)	5	7.5

*one case of methyl dopa + hydralazine and one case of insulin used.

Most of the maternal age was low risk maternal age group (21 to 35 years) (n= 76; 67.3%). Maternal aged more than 35 years was 11 cases (9.7%) and less than 20 years was 26 cases (23%) which were included in high risk group.

Among maternal complications, CPD/difficult labor was the most encountered. Mother who had history of hypertension alone were only 2 cases (1.8%) where as those with diabetes mellitus were only 1 case (0.9%). There was 1 mother who had hypertension and diabetes mellitus. Only 2 mothers had history of medication during pregnancy, one case used methyl dopa and hydralazine, and

another case used insulin. Five cases (7.5%) had history of previous baby with jaundice.

Etiology of Jaundice

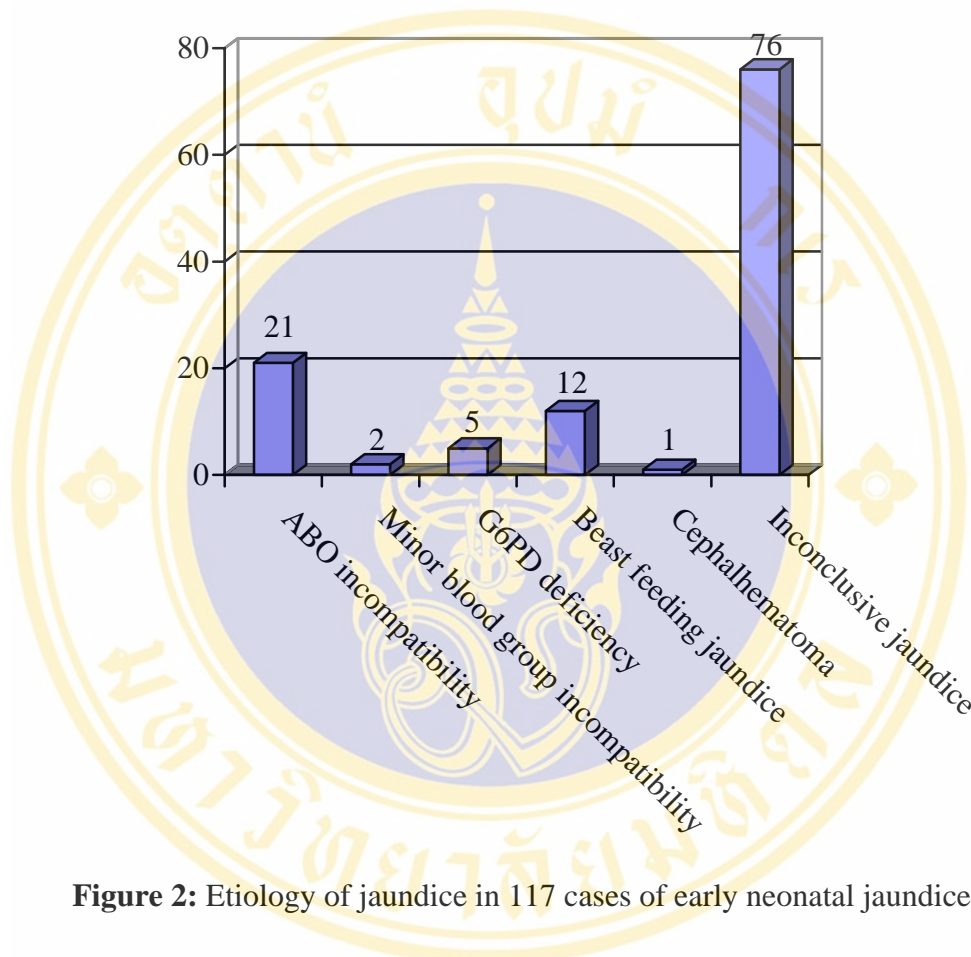


Figure 2: Etiology of jaundice in 117 cases of early neonatal jaundice.

In this figure, inconclusive jaundice was the most common etiology in this study (n=76, 64.9%), which was followed by ABO incompatibility (17.9%). Other diagnoses were breast feeding jaundice (10.2%), G6PD deficiency (4.2%) and minor blood group incompatibility (1.7%). There was one case of cephalhematoma. There were no cases of non immune hemolysis and polycythemia in this study.

*Characteristic neonatal and maternal profiles according to the etiology of jaundice***Table 6:** Characteristic neonatal profile according to the etiology of jaundice

Neonatal profile	No.	Blood group incompatibility		G6PD def. (n=5)	Breast feeding (n=12)	Cephal-hematoma (n=1)	Incon-clusive (n=76)
		ABO (n=21)	Minor (n=2)				
Gender distribution							
Male	56	7	1	5	10	0	33
Female	61	14	1	0	2	1	43
Mode of delivery							
Spontaneous	61	12	2	3	6	1	37
Cesarean section							
Elective	22	2	0	1	4	0	15
Emergency	20	4	0	1	2	0	13
Vacuum extraction	13	3	0	0	0	0	10
Forceps extraction	1	0	0	0	0	0	1
Birth weight (g)							
2,500-3,000	51	13	0	1	3	0	34
3,001-3,500	45	4	2	3	5	1	30
3,501-4,000	21	4	0	1	4	0	12

Most of the female babies were seen in ABO incompatibility and inconclusive jaundice. 11/14 (78.6%) cases of instrumental deliveries such as vacuum and forceps extraction were found in group of inconclusive jaundice. Only 3/13 (23.0%) cases of vacuum extraction were found in group of ABO incompatibility, there was no cephalhematoma found in instrumental delivery. 13/21(61.9%) cases of ABO incompatibility had birth weight between 2,500-3,000 g, whereas only 34/76 (44.7%) cases of inconclusive jaundice.

Table 7: Characteristic maternal profile according to the etiology of jaundice

Maternal profile	No.	Blood group		G6PD def. (n=5)	Breast feeding (n=12)	Cephal-hematoma (n=1)	Inconclusive (n=76)
		ABO (n=21)	Minor (n=2)				
Maternal age (n=113)							
15-20 years	26	5	0	0	1	0	20
21-35 years	76	15	2	5	7	0	47
36-45 years	11	1	0	0	4	0	6
Maternal complication (n=116)							
CPD	18	5	0	1	1	0	11
Hypertension	2	0	0	0	0	0	2
Diabetic	1	0	0	0	1	0	0
Hypertension and diabetic	1	0	0	0	0	0	1
No complication	94	16	2	3	10	1	62
Oxytocin using (n=115)							
Yes	3	0	0	0	0	0	3
No	112	21	2	5	11	1	72
Any medication during pregnancy (n=115)							
Yes	2	0	0	0	1	0	1
No	113	21	2	4	11	1	74
Previous neonatal jaundice history (n=67)							
Yes	5	0	0	0	1	0	4
No	62	13	0	4	5	1	39

In table 7, 47/76 cases (62%) were born from mother aged between 21 to 35 years were diagnosed as inconclusive jaundice. In this study, oxytocin was used in 3 mothers and diagnoses of their infants were inconclusive jaundice.

Among 5 cases that had previous history of neonatal jaundice, 1 case was breast feeding jaundice and other 4 cases were inconclusive jaundice.

Other findings such as bruise/petechiae, hepatosplenomegaly were not observed in this study.

Table 8: Maximum bilirubin level according to the etiology of jaundice

Maximum bilirubin level	No.	Blood group incompatibility		G6PD def. (n=5)	Breast feeding (n=12)	Cephal-hematoma (n=1)	Inconclusive (n=76)
		ABO (n=21)	Minor (n=2)				
Maximum microbilirubin level (mg/dL)							
<12	5	0	0	0	1	0	4
12-25	106	21	2	5	11	1	66
>25	6	0	0	0	0	0	6
Maximum unconjugate bilirubin level (mg/dL)							
<12	10	1	0	0	1	0	8
12-25	103	20	2	5	11	1	64
>25	4	0	0	0	0	0	4

Most of the case had the maximum microbilirubin level in range 12-25 mg/dL which a correlate to the result of maximum unconjugated bilirubin level significantly with Pearson coefficient level at 0.699. All cases that had bilirubin level above 25 were in inconclusive etiology.

Table 9: Laboratory profile according to the etiology of jaundice

Laboratory profile (Mean; Range; SD)	Blood group		G6PD def. (n=5)	Breast feeding (n=12)	Incon- clusive (n=76)
	incompatibility				
	ABO (n=21)	Minor (n=2)			
CBC profile					
Maximum of Hct (%)	53.1 38-68 (7.3)	54.5 48-61 (9.2)	58.2 52-70 (7.2)	58.3 50-66 (5.9)	56.4 32-70 (6.7)
Minimum of Hct (%)	43.9 31-57 (7.4)	47.5 38-57 (13.4)	51.6 47-63 (6.5)	51.1 38-60 (6.6)	49.9 30-62 (7.1)
WBC count (X10 ³ /mm ³)	14.4 6.9-24.5 (4.7)	14.8 13.9-15.7 (1.3)	11.6 7.8-20.5 (5.1)	13.3 9.1-20.5 (3.6)	15.9 6.0-17.3 (23.3)
Platelet count (X10 ³ /mm ³)	291.0 145-494 (93.6)	345.5 314-377 (44.5)	234.8 165-357 (89.9)	236.3 66-398 (98.7)	275.8 89-599 (84.2)
NRC (/mm ³)	131.5 0-1470 (321.4)	0	0	0	9.9 0-232 (40.5)
% Reticulocyte count	8.6 3-14.9 (3.8)	13.6 3.5-23.6 (14.2)	4.6 2.8-8.0 (2.4)	7.1 0.7-13.4 (4.1)	6.0 0-15.1 (3.4)
Bilirubin					
Conjugated (mg/dL)	0.7 0.2-6.0 (1.2)	0.3 0.3-0.4 (0.0)	0.4 0.2-0.4 (0.1)	0.4 0.2-0.7 (0.2)	0.5 0.0-10.6 (1.2)
Unconjugated (mg/dL)	16.0 11.9-21.4 (2.6)	17.6 16.4-18.8 (1.7)	16.6 12.4-21.1 (3.7)	15.6 9.4-19.1 (2.8)	16.8 7.3-37.8 (4.9)
Maximum of MB	17.4 12.4-24.1 (2.8)	18.1 17.5-18.7 (0.8)	20.5 17.7-22.2 (1.9)	17.1 10.3-21.5 (3.0)	18.3 8.9-38.5 (4.9)

From table 9, the mean values of CBC profile and bilirubin level according to etiologies were demonstrated. Among mean value of maximum hematocrit (58.3%) was highest in breast feeding jaundice. In all diagnosis, mean value of WBC and platelet count were within normal limit. NRC was found in only ABO

incompatibility and inconclusive jaundice and higher mean of NRC in ABO incompatibility (131.5%). Mean of reticulocyte count percentage was 13.6 in minor blood group incompatibility which was the highest in all etiologies.

Mean value of conjugated bilirubin was highest (0.7 mg/dL) in ABO incompatibility while as unconjugated was highest in minor blood group incompatibility (17.6 mg/dL).

The diagnosis of G6PD deficiency had the highest maximum value of microbilirubin (20.5 mg/dL) among other cause of neonatal jaundice.

Only one blood film had hypochromic picture in which was the inconclusive diagnosis. Almost all patients had normal size of red blood cells. Anisocytosis account for 11.9% and microcytes were 3.4%. On the other hand, only 11% of newborns had normal shape of red blood cells. The rest 89% of them had abnormal shape such as poikilocytosis, burr cells, target cells, spherocyte, ovalocyte, schistocyte and polychromasia.

Characteristic of jaundice and treatment according to their etiologies

Table 10: Onset and treatment of neonatal jaundice

Characteristic of jaundice	No.	Blood group incompatibility		G6PD def. (n=5)	Breast feeding (n=12)	Cephal-hematoma (n=1)	Incon-clusive (n=76)
		ABO (n=21)	Minor (n=2)				
ONSET OF JAUNDICE							
1 st day of birth	10	2	0	0	1	0	7
2 nd day of birth	49	14	1	4	6	0	24
3 rd day of birth	35	5	0	0	3	1	26
4 th day of birth	12	0	1	1	1	0	9
5 th day of birth	5	0	0	0	0	0	5
6 th day of birth	1	0	0	0	0	0	1
7 th day of birth	5	0	0	0	1	0	4
TREATMENT							
Day of start therapy							
1 st day of birth	10	2	0	0	1	0	7
2 nd day of birth	51	15	2	4	6	0	24
3 rd day of birth	32	3	0	0	3	0	26
4 th day of birth	11	0	0	1	1	0	9
5 th day of birth	4	0	0	0	0	0	4
6 th day of birth	3	1	0	0	0	0	2
7 th day of birth	4	0	0	0	1	0	3
8 th day of birth	2	0	0	0	0	1	1
Phototherapy duration (Days) (Mean; Range; SD)							
Single phototherapy	1.4	1	1.2	1.3	1	1.1	
	0-2		1-2	0-3		0-4	
	(0.6)		(0.4)	(0.9)		(0.7)	
Double phototherapy	0.5	1	0.8	0.3	0	0.5	
	0-2	0-2	0-1	0-1		0-2	
	(0.7)	(1.4)	(0.4)	(0.5)		(0.7)	
All type	1.9	2.0	2.0	1.7	1	1.6	
	1-4	1-3	1-3	1-4		1-6	
	(0.7)	(1.4)	(0.7)	(1.0)		(0.9)	
Exchange transfusion	4	1	0	0	0	0	3

Account for all diagnosis, onset of jaundice mostly started on the 2nd day after delivery (n=49; 41.9%). It was followed the 3rd day after birth (n=35; 29.9%) and the 4th day (n=12; 10.3%).

Early onsets of jaundice (within 24 hours after birth) were 10 cases (8.5%) and most of them (70%) were inconclusive jaundice. One case of breast feeding jaundice and 5 cases of inconclusive jaundices presented with late onset of jaundice on the 6th and the 7th day of birth. According to onset of jaundice, treatment was started mostly on 2nd day after birth. Duration of phototherapy was range from 1 to 4 days.

There were four cases need exchange transfusion therapy for rescue, One case was ABO incompatibility which onset of jaundice on the second day of life, microbilirubin level as 16.4 mg/dL and 14.9% reticulocyte count observed. Three cases were inconclusive jaundice which onset of jaundice on the 2nd, the 4th and the 5th day and the microbilirubin level were 38.5, 32.9 and 31.1 mg/dL respectively, without evidence of hemolysis.

According to ABO blood group examination of the mothers and the babies who were diagnosed as ABO incompatibility (n=11), All blood group O mothers and blood group A and group B in newborn were 10 (47.6%) and 11 (52.4%) respectively.

Risk factors and correlation factors of hemolytic jaundice of newborn**Table11:** Comparing risk factors of hemolytic and non-hemolytic jaundice

Factors	Hemolysis	Non hemolysis	Odd ratio (95% CI)	P value
Male	8/24 (33.3%)	48/93 (51.6%)	0.47 (0.18-1.2)	> 0.05
Birth weight < 3,000 g	12/24 (50.0%)	35/93 (37.6%)	1.66 (0.67-4.09)	> 0.05
Maternal age <21 or >35 years	6/24 (25.0%)	31/89 (34.8%)	0.624 (0.23-1.73)	> 0.05
Maternal complication	6/24 (25.0%)	13/92 (14.1%)	2.03 (0.68-6.05)	> 0.05
Jaundice onset within first 3 days	22/24 (92.0%)	72/93 (77.4%)	3.21 (0.70-14.7)	> 0.05

Male was more in non hemolysis group (51.6% Vs 33.3%). Birth weight<3,000 g, maternal complication and onset of jaundice within first 3 days were more common in hemolysis group, however there was no statistically significant.

Table12: Comparing laboratory finding of hemolytic and non-hemolytic jaundice

Laboratory	Hemolysis (n=24)	Non hemolysis (n=93)	P value
CBC profile			
Maximum of Hct (%)	53.0 38-68 (7.2)	56.8 32-70 (6.5)	0.013
Minimum of Hct (%)	44.2 31-57 (7.7)	50.1 30-63 (6.9)	<0.001
WBC count (X10 ³ /mm ³)	14.5 6.9-24.5 (4.4)	15.3 6.0-17.3 (21.2)	>0.05
Platelet count (X10 ³ /mm ³)	304.1 145-497 (98.1)	265.4 66-599 (83.4)	>0.05
NRC count (/mm ³)	115.0 0-1470 (303.0)	8.1 0-232 (36.8)	0.001
% Reticulocyte count	8.7 3.0-23.6 (4.9)	6.0 0-15.1 (3.5)	0.003
Bilirubin			
Conjugated (m/dL)	0.7 0.16-6.0 (1.2)	0.5 0-10.6 (1.1)	>0.05
Unconjugated (m/dL)	16.4 11.9-21.4 (2.7)	16.6 7.3-37.8 (4.6)	>0.05
Maximum of MB	17.6 12.4-24.1 (2.7)	18.2 8.9-38.5 (4.6)	>0.05

Mean value of maximum and minimum hematocrit was lower in hemolysis group than in non hemolysis group significantly (P= 0.013 and P<0.001). NRC count and percent of reticulocyte counts were higher in hemolysis group than in non hemolysis group with statistically significant.

Risk factor for aggressive treatment of jaundice**Table13:** Comparing risk factors of intensive and non-intensive care

Factors	Intensive* care	Non intensive care	Odd ratio (95% CI)	P value
Male	22/51 (43.1%)	34/66 (50.7%)	0.71 (0.34-1.49)	> 0.05
Birth weight < 3,000 g	23/51 (45.1%)	24/66 (36.4%)	1.44 (0.68-3.02)	> 0.05
Maternal age <21 or >35 years	14/49 (28.6%)	23/64 (35.9%)	0.71 (0.32-1.59)	> 0.05
Maternal complication	6/50 (12.0%)	13/66 (19.7%)	0.56 (0.20-1.58)	> 0.05
Jaundice onset within first 3 days	39/51 (76.5%)	55/66 (83.3%)	0.65 (0.26-1.62)	> 0.05

*Intensive care means double photo therapy or exchange transfusion

Concerning with risk factors of intensive care need, this study could not demonstrated the difference of profile statistically significant.

Table14: Comparing laboratory finding of intensive and non-intensive care

Laboratory	Intensive* care (n=51)	Non intensive care (n=66)	P value
CBC profile			
Maximum of Hct (%)	55.1 32-70 (7.3)	56.8 38-66 (6.4)	>0.05
Minimum of Hct (%)	47.4 30-63 (7.4)	50.1 31-62 (7.2)	>0.05
WBC count (X10 ³ /mm ³)	15.8 6.9-17.3 (22.8)	14.7 6.0-13.5 (15.6)	>0.05
Platelet count (X10 ³ /mm ³)	283.2 118-599 (90.3)	266.4 66-497 (85.3)	>0.05
NRC count (/mm ³)	8.1 0-207 (40.3)	47.0 0-1470 (189.3)	>0.05
% Reticulocyte count	6.9 0-23.6 (4.7)	6.4 0.7-14.6 (3.3)	>0.05
Bilirubin			
Conjugated (m/dL)	0.6 0.2-10.6 (1.4)	0.4 0-6.0 (0.7)	>0.05
Unconjugated (m/dL)	19.3 13.0-37.8 (4.3)	14.5 7.3-23.2 (2.9)	<0.001
Maximum of MB	21.0 15-38.5 (4.2)	16.0 8.9-22.8 (2.7)	<0.001

*Intensive care means double phototherapy or exchange transfusion

Concerning with laboratory profiles, unconjugated bilirubin and maximum of microbilirubin level were higher statistically significant in intensive care group. Although mean value of maximum and minimum hematocrit were lower in intensive group than non intensive group but there was no significance.

CHAPTER VI

DISCUSSION

Neonatal profile

Among 117 neonates, 49% account for male and 52% are female. In ABO incompatibility, female newborns are more dominant than male. Only term newborns were included in this study. Therefore, we could not demonstrate the neonatal jaundice in preterm as the previous study which showed jaundice occurred in 60% of term infants and 80% of preterm infants. (Anthony JP and Barbara JS, 2007).

Among mode of deliveries, most of the babies in this study were born by normal spontaneous vaginal delivery (52.1%). There was no difference between hemolysis and non hemolysis group according to spontaneous delivery which was similar to the previous study finding (Sarci SU et al, 2002). The second most common mode of deliveries was cesarean section (18.8%) followed by vacuum extraction (11%) and there was only 1 case of forceps extraction among 117 patients.

Maternal profile

Among 116 patients, mother who had hypertension are 1.8% where as those with diabetes mellitus are only 1 case (0.9%). And also only 1 case (0.9%) of mother had both history of hypertension and diabetes mellitus. All of them were mothers of baby with diagnosis of inclusive jaundice. There were no cases of eclampsia and preclampsia. Cephalopelvic disproportion was account for 15.5%. About 7% of mother has history of previous baby with neonatal jaundice.

Hemolytic jaundice

In this study the minimum hematocrit was lower and NRC count and reticulocyte count higher in hemolytic group compare to non hemolytic group which were compatible with pathogenesis of hyperbilirubinemia. (David E, 2007).

ABO incompatibility

In this study, nearly 50% (11/21 cases) of ABO incompatibility were primigravida which was similar finding to the previous study (Hinkes MT and Cloharty JP, 1998) that showed approximately 50% of the ABO hemolytic jaundice cases occur in first born infants and there is no predictable pattern of recurrent in subsequent infants.

Meanwhile in ABO incompatibility group, all mothers had blood group O. This finding suggest ABO incompatibility is common if mother blood group is O and the baby is A or B as previous study (Hughes- Jones NC, 1980; Dacie JV, 2006).

G6PD deficiency

Theoretically G6PD deficiency usually occurs in males although heterozygous females may manifest the mild features of disease (Malcolm IL et al., 2008). In this study, newborns who diagnosed as G6PD deficiency were all males (4.2%) which female with G6PD deficiency could not demonstrate.

Breast feeding jaundice

Most of maternal aged between 21-35 years, the average of age was 26.8 years old. There were 11 cases maternal age greater than 35 years which could be defined as high risk pregnancy. This study was observed the breast feeding jaundice occurred in the older mothers (aged greater than 35 years old) more than other caused of jaundice significantly ($p=0.016$, odd ratio 6.71, 95% CI 1.30-34.36).

Cephalhematoma

Cephalhematoma (collection of extravasated blood) itself could be cause increase in unconjugated bilirubin and it is included in major risk factors (Balagangadhar R and Tarbati D, 2005) as was demonstrated one case of our study.

Inconclusive jaundice

Whether infection was one of the risk factor of hyperbilirubinemia (Rennie JM and Robertson NRC, 2002) in this study could not demonstrate the higher WBC in

non hemolytic group compared to hemolytic group, one of possible explanation was not only infection include in group of non hemolytic but also unidentified non infectious causes were mixed up to non hemolytic group.

Treatment

There were four cases need exchange transfusion therapy for rescue. One case was ABO incompatibility which onset of jaundice on the second day of life, microbilirubin level as 16.4 mg/dL on the 1st day after delivery that compatible with pathological jaundice and reticulocyte count was also increased (14.9% even on 1st day).

Three cases were inconclusive jaundice which onset of jaundice on the 2nd, the 4th and the 5th day and the microbilirubin level are 38.5, 32.9 and 31.1 mg/dL respectively, without evidence of hemolysis. All neonatal jaundice with high bilirubin level would be treated with aggressive treatment (such as exchange transfusion and double side phototherapy) to prevent complication of hyperbilirubinemia (Tan KL, 1983). And also it was recommended to follow up the case to detect the neurological sequelae.

CHAPTER VII

CONCLUSION

In this study, according to objectives, various etiologies of hyperbilirubinemia were found. The most common etiology was inconclusive jaundice because it was only rely on medical record. As we know before, the second common etiology was ABO incompatibility. Neonatal jaundice caused by non immune hemolysis and polycythemia were not found in this study.

According to the baseline data, female were found more than male group. Most of the neonates were within birth weight 2,500 to 3,000 grams.

We found vacuum extraction 11% and only one forceps deliveries among mode of deliveries. It may show instrumental delivery rates are declined. Obstetric history revealed cephalopelvic disproportion was presented in 15.5% of mothers. No maternal eclampsia, pre-eclampsia and premature rupture of membrane. About 3% of hypertension and 2% of diabetes mellitus were encountered. Among 68 mothers, only 5 mothers had history of previous babies of neonatal jaundice.

In laboratory diagnosis, the WBC count was highest in the inconclusive jaundice. In all diagnosis, mean values of platelet count were within normal limit. Mean value of reticulocyte count was highest in the diagnosis of minor blood group incompatibility.

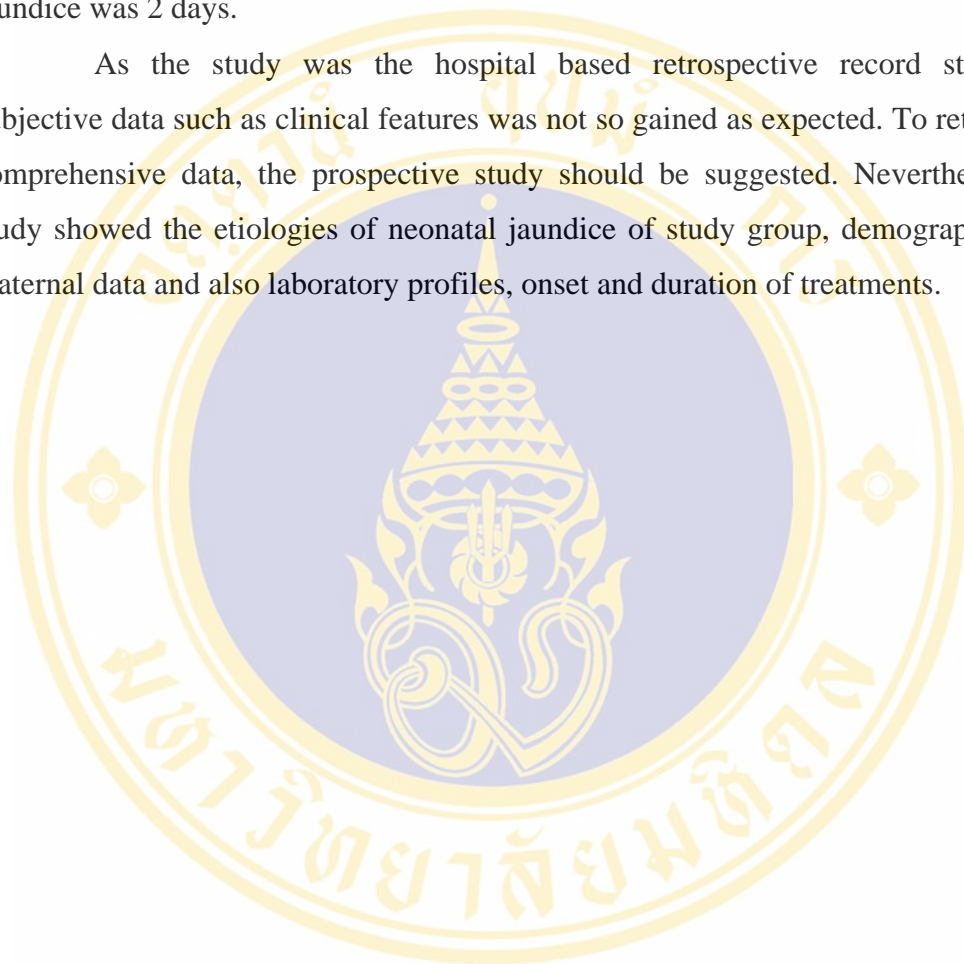
Diagnosis of inconclusive jaundice had highest mean value of maximum hematocrit. The lowest mean value of minimum hematocrit was found in ABO incompatibility. Unconjugated bilirubin was highest in minor blood group incompatibility. Inclusion and Heinz bodies were not detected in all babies.

Almost all patients had normal size of red blood cells. About 10% had anisocytosis and 3% had microcytes. On the other hand, only 11% of newborns had normal shape of red blood cells. Abnormal shape of red blood cells included poikilocytosis, burr cells, target cells, spherocyte, ovalocyte, schistocyte and polychromasia.

Concerning with risk factors and laboratory profiles, there was no statistically significant between intensive care group and non intensive care group.

Onset of jaundice starts mostly on the 2nd day after delivery. According to onset of jaundice, treatment was started on the 2nd day. The most frequent duration of jaundice was 2 days.

As the study was the hospital based retrospective record study, the subjective data such as clinical features was not so gained as expected. To retrieve the comprehensive data, the prospective study should be suggested. Nevertheless, the study showed the etiologies of neonatal jaundice of study group, demographic data, maternal data and also laboratory profiles, onset and duration of treatments.



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APPENDIX A

CASE RECORD FORM

Case Record Form: A retrospective study on clinical features of early neonatal jaundice in terms babies at Ratchaburi Hospital

1. Baseline data

1. Date of birth / / (DD/MM/YY)
Time : :
2. Gender of baby Male [1] / Female [2]
3. Gestation Term (37-42 wk)[1], Post term (>42 wk) [2], ND[99]
4. Birth Weight g
5. Mode of delivery Spontaneous [1] Forceps [2] Vacuum Extraction[3]
 Elective Cesarean section [4]
 Emergency Cesarean section [5] ND[99]

2. Maternal History

6. Age years old ; ND[99]
7. Blood group [ABO] A[1] B[2] AB[3] O[4] ND[99]
8. Blood group [Rh] positive [1] negative [2] ND[99]
9. GPA G(2.4.1) P(2.4.2) A(2.4.3)
10. Obstetric history difficult labour/CPD (2.5.1)
 Gestational hypertension(2.5.2)
 - pre-eclampsia [1]
 - eclampsia [2]
 - hypertension alone [3]
 Gestational diabetes mellitus(2.5.3)
 Rupture of membrane >18 hours (2.5.4)
 Other (2.5.5)
Define _____
11. Oxytocin using Yes[1] No[2] ND[99]
12. Any medication during pregnancy _____
13. Previous baby with neonatal jaundice Yes [1] No[2] ND[99]
 If yes
 Diagnosis _____

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