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A Retrospective Study on Clinical Features of Early Neonatal Jaundice in Term Babies at Ratchaburi Hospital, Thailand

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Authors' contributions

This work was carried out in collaboration among all authors. Author KLP designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors KZ and HHKS managed the analyses of the study. Author NNT managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Neonatal jaundice is a common condition that sometimes lead to devastating neurological consequence such as kernicterus.
Aim: This study was aimed to find out the clinical features and etiology of neonatal jaundice in term newborn admitted to Ratchaburi Hospital.
Study Design: Hospital-based retrospective study
Methodology: The study was conducted by reviewing 117 medical records of neonatal jaundice who were admitted at Ratchaburi Regional Hospital, Bangkok, Thailand from 1st October 2007 to

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30th September 2008. Both the patient's and their mother's profiles, etiology and clinical features of jaundice were extracted.

Results: The results showed that the most common etiology was inconclusive jaundice (64.9%) followed by ABO incompatibility (17.9%) and breast feeding jaundice (10.2%). 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 four cases. The maximum and minimum haematocrit was significantly lower while Nucleated Red Cell (NRC) count and percent of reticulocytes counts were significantly higher in haemolysis group than in non-haemolysis group,.

Conclusion: From our study, the most common etiology was inconclusive jaundice which is followed by ABO incompatibility but non-immune hemolysis and polycythemia were not encountered. There was significant difference of hematocrit, NRC and reticulocytes between hemolytic and non-hemolytic groups. Detailed approach of history taking and physical examination, early investigations of jaundice work up and septic work up are recommended in eliciting various etiologies and preventing complications.

Keywords: Neonatal jaundice; etiology; clinical feature; retrospective.

1. INTRODUCTION

The most common cause of readmission to hospital in healthy term infants is neonatal jaundice [1]. Paediatricians were aggressive in treating jaundice though several factors have changed the management of jaundice [2,3]. Effective approach and evaluations for management are crucial in preventing bilirubin induced encephalopathy and long term neurodevelopment outcomes [4]. The possible factors exaggerating physiological jaundice are shown in Table 1 [5].

Studies in the 1980s and 1990s suggested that kernicterus from jaundice was rare and that too many infants were being treated unnecessarily [6,7].

Early detection, effective intervention and new approaches to prevention have been also stimulated as it has a potential damage to developing brain [8]. Previous studies have indicated a relationship between neonatal hyperbilirubinemia and diverse factors including racial region, male gender, epidural anaesthesia, and instrumental delivery [9].

Risk factors for significant neonatal hyperbilirubinemia are:

1. Jaundice visible on the first day of life
2. A sibling of jaundice or anaemia
3. Unrecognized haemolysis (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 haematocrit >65% (polycythemia)
8. East Asian, Mediterranean, Native American heritage [10].

Pathological jaundice fulfils any of the following criteria:

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 [11].

The primary concern with respect to exaggerated hyperbilirubinemia is the potential for neurotoxic effects, but general cellular injury also occurs [12]. Bilirubin can interfere with neuroexcitatory signals, impair nerve conduction (particularly auditory nerve) inhibit ion exchange and water transport in renal cells. The infections, acidosis, hypoxia, sepsis, prematurity and hyperosmolarity can cause blood brain barrier more susceptible to the entry of bilirubin [13].

Table 1. Possible factors exaggerating physiological jaundice

Factor	Clinical correlate
1. Bilirubin load to liver	• Infants with polycythemia • Infants of diabetic mother • Collection of extravasated blood like cephalhematoma and intraventricular hemorrhage • Delayed cord clamping
2. Defective uptake from liver	• Decreased Y protein due to caloric deprivation
3. Defective bilirubin conjugation	• Due to decreased UDPG activity as seen in hypothyroidism and inhibitors in breast milk
4. Deceased hepatic excretion	• Congenital infections
5. Inadequate hepatic perfusion	• Hypoxia • Congenital heart diseases
6. Increased enterohepatic circulation	• Unfed babies • Delayed passage of meconium

Risk factors of severe hyperbilirubinemia: [14]

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 haemolytic disease
4. Previous sibling received phototherapy
5. Cephalhematoma or significant bruising
6. Exclusive breast feeding for whom with inadequate breastfeeding or excess brithweight (macrosomia, large for gestational age)
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

Factors associated with decreased risk factors of neonatal jaundice

1. Microbilirubin level in low risk zone
2. Exclusive bottle feeding
3. Black race
4. Discharge from hospital after 72 hour

Though hazardous (≥ 30mg/dL) hyperbilirubinemia is uncommon, timely recognition, potent work up and compelling management play pivotal roles in the prevention of chronic, bilirubin-induced neurotoxicity [15]. This study was aimed for detection of early neonatal jaundice and its various aetiology based on patients' profiles and investigations.

2. MATERIALS AND METHODS

This study was a hospital based retrospective review of 117 medical records, conducted at Ratchaburi regional hospital, Bangkok, Thailand from November 2008 to 2009 March. The clinical features of early neonatal jaundiced for newborns younger than 7 days whose gestational age ranges from 37 to 42 weeks were explored. Babies with onset of jaundice within 7 days requiring intervention for jaundice were included in the analysis. The sample size was calculated using the formula for single population proportion with the margin of error 10%, the assumption of 95% confidence level and prevalence of 60% of known etiology of neonatal jaundice in all pathological jaundice in Ratchaburi Regional Hospital. The minimum sample size required was 92. The exclusion criteria included preterm, low birth weights, major congenital anomalies and congenital infections, systemic infections before onset of jaundice, serious illness such as sepsis, meconium aspiration syndrome, and severe birth asphyxia.

Required data from the selected records were collected and transferred into a case record forms that was designed based upon the variables from Ratchaburi Regional Hospital and study objectives. The data obtained were calculated by SPSS version 11.5. The research was funded by the Faculty of Tropical Medicine, Mahidol University, Thailand in collaboration of SEAMEO TROPMED, Thailand.

3. RESULTS

Fig. 1 shows that inconclusive jaundice which is neonatal jaundice of unknown etiology that may require further investigations, 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 haemolysis and polycythemia in this study.

Table 2 shows that 47/76 cases (62%) 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.

Most of the cases had the maximum microbilirubin level in range 12-25 mg/dL. Similarly the majority of the cases had maximum unconjugated bilirubin level of 12-25 mg/dL. The cases that had the had the maximum microbilirubin level in range 12-25 mg/dL which correlates with the result of maximum unconjugated bilirubin level significantly with Pearson coefficient level at 0.699 (data not shown). All cases that had bilirubin level above 25 were in inconclusive etiology (Table 3).

Table 4 shows the mean values of CBC profile and bilirubin levels according to etiologies of hyperbilirubinemia. Maximum mean hematocrit (58.3%) was seen in babies with breast feeding jaundice. In all diagnosis, mean value of WBC and platelet count were within normal limit. Nucleated Red Cell Count was found in only ABO incompatibility and inconclusive jaundice and higher mean of Nucleated Red Cell Count 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 unconjugated bilirubin level was highest in minor blood group incompatibility (17.6 mg/dL). G6PD deficiency had the highest maximum value of microbilirubin (20.5 mg/dL) among other causes of neonatal jaundice. Only one blood film had hypochromic picture and this was in the inconclusive diagnosis group. Almost all patients had normal size of red blood cells. Anisocytosis accounted 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.

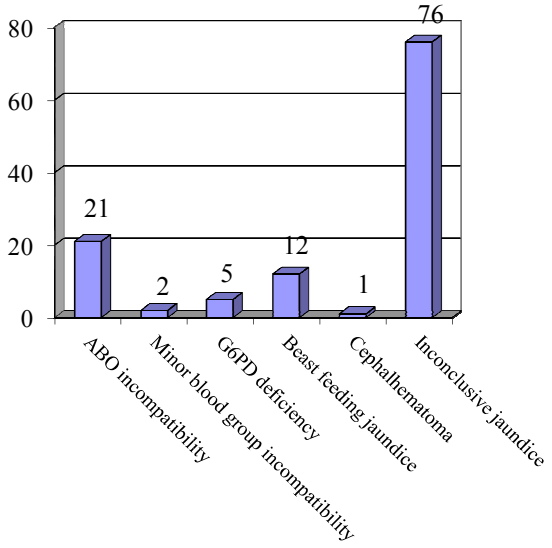

Fig. 1. Etiologies of Jaundice

Table 2. Characteristic maternal profile according to the etiology of jaundice

Maternal profile	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)				
Maternal age (n=113)							
15-20 years	26	5	0	0	1	0	20
21-35 years	76	15	2	5	7	1	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

Table 3. 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 unconjugated 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

As shown in Table 5, account for all diagnosis, onset of jaundice was most commonly on the 2nd day after delivery (n=49; 41.9%). It was followed by the 3rd day after birth (n=35; 29.9%) and the 4th day (n=12; 10.3%). Early onset jaundice (within 24 hours after birth) were seen in 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 7th day of birth. Conditions which have total bilirubin level greater than 15 mg/dL or requiring phototherapy at 5-7 days are defined as last onset hyperbilirubinemia. [16] According to onset of jaundice, treatment was started mostly on 2nd day after birth. Duration of phototherapy ranged from 1 to 4 days. There were four cases that needed exchange transfusion therapy for rescue. One case was ABO incompatibility with onset of jaundice on the second day of life, microbilirubin level was 16.4 mg/dL and reticulocyte count was 14.9%. Three cases were inconclusive jaundice with onset of jaundice on the 2nd, the 4th and the 5th day and the

microbilirubin levels were 38.5, 32.9 and 31.1 mg/dL respectively, without evidence of haemolysis.

Table 6 shows that the mean value of maximum and minimum haematocrit was significantly lower in haemolysis group than in non-haemolysis group (P= 0.013 and P<0.001). Nucleated Red Cell (NRC) count and percent of reticulocyte counts were higher in haemolysis group than in non-haemolysis group and the difference was statistically significant.

4. DISCUSSION

This study was conducted to describe the various clinical profiles of early neonatal jaundice. Careful history taking, physical examinations, early measurement of serum bilirubin and work up for jaundice were recorded to elicit the risk factors and different etiologies. Preterm babies and risk of kernicterus is highly associated shown in previous studies. Our study has limitation to illustrate neonatal jaundice in preterm and other conditions because preterm babies with neonatal jaundice were not studied.

It is crucial to assess characteristic maternal and neonatal profile during hospital stay and on discharge for risk of neonatal jaundice [17]. In our study, there was no difference between haemolytic and non-haemolytic group according to spontaneous delivery which was similar to the previous study finding [18]. We found that the minimum haematocrit was significantly lower and reticulocyte count is significantly higher in haemolytic group compared to non-haemolytic group which were compatible with pathogenesis of hyperbilirubinemia [19].

Table 4. Laboratory profile according to the etiology of jaundice

Laboratory profile (Mean; Range; SD)	Blood group incompatibility		G6PD def. (n=5)	Breast feeding (n=12)	Inconclusive (n=76)
	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)
Nucleated Red Cell count ($/mm^3$)	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	0.7	0.3	0.4	0.4	0.5
Conjugated (mg/dL)	0.2-6.0 (1.2)	0.3-0.4 (0.0)	0.2-0.4 (0.1)	0.2-0.7 (0.2)	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)

Table 5. 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)	Inconclusive (n=76)
		ABO (n=21)	Minor (n=2)				
Onset of Jaundice							
1st day of birth	10	2	0	0	1	0	7
2nd day of birth	49	14	1	4	6	0	24
3rd day of birth	35	5	0	0	3	1	26
4th day of birth	12	0	1	1	1	0	9
5th day of birth	5	0	0	0	0	0	5
6th day of birth	1	0	0	0	0	0	1
7th day of birth	5	0	0	0	1	0	4
Treatment							
Day of start therapy							
1st day of birth	10	2	0	0	1	0	7
2nd day of birth	51	15	2	4	6	0	24
3rd day of birth	32	3	0	0	3	0	26
4th day of birth	11	0	0	1	1	0	9
5th day of birth	4	0	0	0	0	0	4
6th day of birth	3	1	0	0	0	0	2
7th day of birth	4	0	0	0	1	0	3
8th 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

Increased frequency of jaundice is obviously associated with maternal usage of epidural anaesthesia [data not shown]. According to etiologies and maternal profile, nearly 50% of ABO incompatibility are primigravida in this study which is similar to the previous study establishing that approximately 50% of the ABO haemolytic jaundice cases occur in first born infants and there is no predictable pattern of recurrence in subsequent infants [20]. Rh haemolytic disease and sepsis are etiologies that have increased risk of bilirubin encephalopathy than ABO incompatibility [21]. Previous research showed inconclusive jaundice was the most common etiology as demonstrated in our study.

Theoretically, G6PD deficiency usually occurs in males although heterozygous females may manifest the mild features of disease [22]. In our study, newborns diagnosed as G6PD deficiency were all males (4.2%).

Infection is one of the risk factors of hyperbilirubinemia [23]. Unexplained unconjugated hyperbilirubinemia may be a first sign of neonatal sepsis as bacterial sepsis can contribute to neonatal jaundice [24]. Our study did not demonstrate a higher WBC count in the non-haemolytic group compared to the haemolytic group. One of the possible explanations was that unidentified non-infectious etiologies may also play a significant role in the aetiology of non-haemolytic group.

Measuring serum bilirubin concentrations exactly 24hours after delivery or at a later time just before discharge may improve the sensitivity of this predictor for hyperbilirubinemia [25]. Predictive bilirubin nomogram is an effective

Table 6. Laboratory profile according to etiology of jaundice

Laboratory	Haemolysis (n=24)	Non haemolysis (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
Nucleated Red Cell 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

predictor for significant hyperbilirubinemia according to their risks, high, intermediate and low [26].

Among four cases for whom exchange transfusion was done, one case was ABO incompatibility and the rest three cases were inconclusive jaundice. Three cases of inconclusive jaundice had no evidence of haemolysis and onset of jaundice were on 2nd, 4th and 5th day while microbilirubin level are 38.5, 32.9 and 31.1 mg/dL respectively. All neonatal jaundice with high bilirubin levels would require aggressive treatment (such as exchange transfusion and double phototherapy) to prevent complications of hyperbilirubinemia [27]. In newborn with bilirubin level above 20 mg/dL, there is noticeable association with kernicterus which has 70% long term consequences [28].

5. CONCLUSION

Our study has shown than the most common etiology was inconclusive jaundice closely followed by ABO incompatibility. Further septic work up and investigations are required to identify accurate diagnosis. Neonatal jaundice caused by non-immune hemolysis and polycythemia were not found in this study. High WBC count in inconclusive jaundice support the possibility of neonatal sepsis and infections that are also main concern for neonatal jaundice. There is no decrease in mean values of platelet count. Mean value of reticulocyte count was highest in the diagnosis of minor blood group incompatibility. There was significant difference of haematocrit, Nucleated Red Cell count and reticulocytes between haemolytic and non-haemolytic groups. As the study was the hospital based retrospective record study, the subjective

data such as progression of jaundice and other clinical findings were not observed. To retrieve the comprehensive data, the prospective study is suggested. Our study has limitation to illustrate neonatal jaundice in preterm and other conditions because it is only focused on babies born from 37 to 42 weeks. As prematurity is one of the main cause of neonatal jaundice, further research with different inclusion criteria is suggested. Nevertheless, the study highlighted the etiologies of neonatal jaundice of study group, laboratory profiles with significance in haemolysis, onset of jaundice and duration of different managements.

CONSENT

It is not applicable.

ETHICAL APPROVAL

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

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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