HUE UNIVERSITY UNIVERSITY OF MEDICINE AND PHARMACY

NGUYEN THI THANH BINH

EARLY PREDICTORS OF NEONATAL HYPERBILIRUBINEMIA NEED PHOTOTHERAPY BY CORD BLOOD BILIRUBIN AND BILIRUBIN/ALBUMIN RATIO IN PRETERM INFANTS

MEDICAL DOCTORAL DISSERTATION

HUE, 2024

The name of postgraduate training institution: UNIVERSITY OF MEDICINE AND PHARMACY, HUE UNIVERSITY

Academic supervisor: PGS. TS. PHAN HUNG VIET

Reviewer 1:

Reviewer 2:

Reviewer 3:

The doctoral thesis was defended before the Hue University thesis review board at:

At the time:

The doctoral thesis can be found at:

- National library of Vietnam
- The library of Hue University
- The library of University of Medicine and Pharmacy, Hue University

HUE UNIVERSITY UNIVERSITY OF MEDICINE AND PHARMACY

NGUYEN THI THANH BINH

EARLY PREDICTORS OF NEONATAL HYPERBILIRUBINEMIA NEED PHOTOTHERAPY BY CORD BLOOD BILIRUBIN AND BILIRUBIN/ALBUMIN RATIO IN PRETERM INFANTS

Major: PEDIATRICS Mã số: 9 72 01 06

MEDICAL DOCTORAL DISSERTATION

HUE, 2024

INTRODUCTION

1. Rationale for the study

Indirect hyperbilirubinemia is a yellow staining of the skin and conjunctivae due to the accumulation of bilirubin in the skin and mucous membranes. About 80% of preterm newborns exhibit indirect hyperbilirubinemic jaundice during the first week of life. Characteristics of indirect hyperbilirubinemia in preterm infants may have a more unpredictable course. Premature birth is also a high risk of bilirubin-induced neurotoxicity; preterm infants born at 35-36 weeks have a 12.85 times higher risk of jaundice than full-term infants at 39-40 weeks; the time of peak bilirubin concentration usually occurs around day 5-7 after birth, when most babies in this age group have been discharged from the hospital; the clinical level of jaundice in premature babies does not always correspond with the severity of the disease.

With the desire to find new indicators to predict earlier the risk of jaundice requiring phototherapy, since the 90s of the twentieth century, some authors such as Rosenfeld in the United States (1986) and Knudsen in Denmark (1989) began research on the predictive value of indirect hyperbilirubinemia in newborns based on umbilical cord blood bilirubin and albumin concentrations. In recent years, some studies have mainly been conducted on healthy full-term newborns, with only a few studies involving preterm infants, and until now, there have been no reports on this research direction in Vietnam. Therefore, I conducted the research entitled "*Early predictors of neonatal hyperbilirubinemia need phototherapy by cord blood bilirubin and bilirubin/albumin ratio in preterm infants*" with the three following objectives:

+ Describe the clinical and subclinical characteristics of hyperbilirubinemia in preterm infants.

+ Survey of some factors related to cord blood bilirubin and bilirubin/albumin ratio in preterm infants.

1

+ Determine the predictability of hyperbilirubinemia needs phototherapy by using cord blood bilirubin and bilirubin/albumin ratio in preterm infants.

2. Scientific contributions and practical implications

The study was conducted for the first time in Vietnam with a large participant of preterm infants who were tested for cord blood and followed up to one week after birth for jaundice outcomes. From there, providing important information in clinical practice about the clinical characteristics of indirect hyperbilirubinemia in preterm infants. Basic information on total bilirubin, indirect bilirubin and total bilirubin/albumin ratio in preterm infants to serve as reference for future research in Vietnam. Furthermore, it is possible to apply these tests to predict preterm infants with hyperbilirubinemia who need phototherapy.

3. New contributions of the doctoral thesis

- A total of 176 cord blood samples: median total bilirubin was 1.77 (1.50 – 2.01) mg/dl (# 30.3 (25.7 – 34.4) μ mol/L), the median of total bilirubin/albumin ratio was 0.52 (0.42 – 0.60) mg/g.

- Some factors related to cord blood blood bilirubin and total bilirubin/albumin ratio in preterm infants with hyperbilirubinemia were gestational age, indication for phototherapy, children with early neonatal infections and respiratory failure, statiscally significant with p < 0.05.

- This is the first study in Vietnam on the value of cord blood bilirubin and total bilirubin/albumin ratio in predicting preterm infants with hyperbilirubinemia requiring phototherapy. At the cutoff point of cord blood bilirubin >1,82 mg/dl (# 31µmol/L) with AUC=0,854, p<0,0001 and at the cutoff point of cord blood total bilirubin/albumin ratio >0,52 mg/g with AUC=0,842, p<0,0001, had good and equivalent values in predicting preterm infants with hyperbilirubinemia requiring phototherapy.

4. Outline of the thesis

The thesis has 130 pages including the problem statement, 2 pages with 3 research objectives, 4 chapters including an overview of the

research problem with 36 pages, objects and research methods with 20 pages, research results are available 33 pages, discussion has 34 pages, the conclusion has 2 pages and has 2 recommendations. The thesis has 55 tables, 12 charts, 01 diagrams and 10 illustrations. The Appendix has 165 references, including 24 Vietnamese documents and 141 English documents.

Chapter 1 OVERVIEW

1.1. CHARACTERISTICS OF INDIRECT YPERBILIRUBINEMIA IN PRETERM INFANTS

1.1.1. Defining preterm birth

Preterm birth is defined by WHO as all births before 37 completed weeks. Classification:

- Late preterm: 34- <37 weeks
- Moderate preterm: 32- <34 weeks
- Very preterm: 28- <32 weeks
- Extremely preterm: <28 weeks.

1.1.2. Some definitions of jaundice in neonates

1.1.3. Epidemiology of indirect hyperbilirubinemia neonates

According to WHO and NICE, about 80% of preterm infants develop jaundice in the first week after birth. The rate of premature infants with pathological jaundice requiring early intervention and treatment is up to 50% to 80%. Preterm infants born at 35-36 weeks have a 12.85 times higher risk of hyperbilirubinemia than full-term babies at 39-40 weeks. In addition, in the neonatal intensive care unit, research by Yismaw et al (2018) at a hospital in Northwest Ethiopia showed that premature infants with jaundice had a higher mortality rate. 3.4 times the group without jaundice (OR=3.39, 95%CI (1.90-6.05)).

1.1.4. Pathogenesis of indirect hyperbilirubinemia in neonates *1.1.4.1. Formation of bilirubin 1.1.4.2. Metabolism of bilirubin*



Figure 1.1. Diagram of bilirubin metabolism before and after birth *1.1.4.3. Role of bilirubin in the body*

1.1.4.4. Causes of indirect hyperbilirubinemia

1.1.5. The clinical and subclinical characteristics of hyperbilirubinemia in preterm infants.

1.1.5.1. Clinical characteristics

- Physical examination
- Time to detect jaundice
- Classification of jaundice in newborns
- Distinguishing between physiological and pathological jaundice

- Neurological dysfuntion complicated by bilirubin in preterm infants

1.1.5.2. Subclinical

1.1.6. Prevention and treatment of indirect hyperbilirubinemia in preterm infants

1.1.6.1. Prevention indirect hyperbilirubinemia in preterm infants

1.1.6.2. Hyperbilirubinemia screening in preterm infants

1.1.6.3. Hyperbilirubinemia treatment in preterm infants

- Phototherapy
- Exchange transfusion
- Other treatments

1.2. SCIENTIFIC BASIS OF STUDIES ON CORD BLOOD BILIRUBIN AND TOTAL BILIRUBIN/ALBUMIN

1.2.1. Role of bilirubin and total bilirubin/albumin ratio in the pathogenesis of bilirubin-induced neurological dysfunction in neonates

1.2.1.1. Neurotoxic potential of bilirubin

(Bilirubin anion)-Albumin + $2H^+ \rightleftharpoons$ (bilirubin acid-BH₂) + (albumin). According to this equation, when serum bilirubin levels are high, decreased serum albumin levels or high H+ levels (blood clotting) will affect the saturation as well as the binding of bilirubin to albumin, resulting in the formation of bilirubin acid that easily dissolves into the phospholipid layer of the cell membrane.

1.2.1.2. Role of serum total bilirubin/albumin ratio in pathogenesis of indirect hyperbilirubinemia in newborns

• Origin of fetal serum albumin

• Role of serum albumin in pathogenesis of indirect hyperbilirubinemia in newborns

• Role of serum total bilirubin/albumin ratio in pathogenesis of indirect hyperbilirubinemia in newborns

1.2.2. Characteristics of cord blood samples

1.2.2.1. Cord blood

1.2.2.2. Benefits of cord blood testing

1.3. RESEARCH SITUATION IN VIETNAM AND IN OTHER COUNTRIES

1.3.1. Studies in Vietnam

Until now, there has been no research in Vietnam on this topic.

1.3.2. Studies in other countries

Several studies on the value of cord blood bilirubin and total bilirubin/albumin ratio in predicting newborns with severe jaundice or jaundice requiring phototherapy or exchange transfusion. However, the studies were mainly in healthy full-term infants, with few studies focusing on premature infants.

1.4. A COMBINED OBSTETRIC AND PEDIATRIC MANAGEMENT APPROACH AT HOSPITAL OF UNIVERSITY OF MEDICINE AND PHARMACY, HUE UNIVERSITY

1.4.1. Introduction Obstetrics and Gynecology Department at Hospital of University of Medicine and Pharmacy, Hue University **1.4.2.** A combined obstetric and pediatric management approach at the Obstetrics and Gynecology Department

During the time of studying, thanks to the combined obstetricspediatrics model, PhD students had many advantages in collecting research data, such as taking umbilical cord blood samples immediately after birth in the delivery room or operating room, continuing to monitor the newborns at the Department of Obstetrics and Gynecology or treating the newborns at the Neonatal room care.

Chapter 2 PARTICIPANTS AND METHODS

2.1. PARTICIPANTS

A total of 176 preterm infants were born at Hue University of Medicine and Pharmacy Hospital.

2.1.1. Selection criteria

- Preterm infants < 37 weeks of gestation age.

- Cord blood bilirubin and albumin were tested immediately after birth.

- Infants had jaundice in the first 7 days after birth.

- The infant's parents agreed to participate in the research.

2.1.2. Exclusion criteria

- Preterm infants were transferred to a central hospital for the duration of the study.

2.1.3. Research time and location

a. Research period: From April 2018 to August 2020.

b. Research location: at the Department of Obstetrics and Gynecology and at the neonatal room care, Hue University of Medicine and Pharmacy Hospital.

2.2. METHODS

2.2.1. Design of the study

The study describes a series of cases.

2.2.2. Sample size

Convenient sample size. During the study period, 176 preterm infants had all of the above selection criteria.

2.2.3. Research variables

2.2.4. Definition of the research variables

2.2.4.1. Variables of general characteristics

2.2.4.2. Maternal and family history variables

2.2.4.3. Variables of the clinical characteristics

2.2.4.4. Variables of the subclinical characteristics

2.2.5. Research organization and data collection

2.2.5.1. Steps of research

Step 1: Prepare a research form. Explain to the mother and/or family members about the research. If the preterm infant's family agrees, the research steps will continue.

Step 2: Approach preterm infants immediately after birth in the delivery room or operating room. Assess and resuscitate the infant (if necessary) and provide routine care.

Step 3: Take a sample of cord blood from the mother's side immediately after birth to measure serum bilirubin and albumin levels.

Step 4: Record information about the mother's and family's medical history and history. Examine the baby and follow clinical symptoms from birth until discharge. Depending on gestational age and health status, premature infants are monitored in two groups:

(1) Preterm infants were cared for in the neonatal room if they have one of the following health problems: <34 weeks of gestation or >34 weeks of gestation but have at least one of the following health problems such as: respiratory distress, infection, vomiting, poor feeding, birth defects, clinically evident jaundice...

(2) Preterm infants are routinely cared for by their mothers at the Obstetrics and Gynecology Department and are monitored by a neonatologist. Clinical symptoms: if the child does not have problems like group 1.

- Time to test for venous blood bilirubin and albumin:

(1) First time: if the infant appeared jaundiced <24 hours, test for venous blood bilirubin at the time of jaundice detection to decide on treatment.

(2) Second time: if the infant was monitored in the neonatal room, a synchronous test of bilirubin and albumin of venous blood was prescribed on day 2 after birth (24-48 hours after birth).

(3) After the second time, the venous blood bilirubin test was ordered to be repeated one or more times depending on the level and progression of the infant's jaundice for therapeutic intervention.

- Cases with venous blood serum bilirubin test: refer to the value of total venous blood bilirubin concentration with the treatment threshold graph of indirect hyperbilirubinemia according to each gestational age of NICE 2016 and divided into 2 groups:

(1) Phototherapy group: if total venous blood bilirubin at one or more times during the study period reached the threshold for phototherapy or exchange transfusion (but the infant responded to phototherapy) and did not have to perform exchange transfusion).

(2) Without a phototherapy group: if total venous blood bilirubin during the study period was below the phototherapy threshold, or mild jaundice did not require testing for venous blood bilirubin concentration and jaundice progress gradually subsided.

- Record additional information and test results (such as complete blood count, blood glucose test, etc.) in the research form.

- Step 5: Analyze data
- Step 6: Write the thesis

2.2.5.2. Personnel

2.2.6. Research diagram



Diagram 2.1. Research diagram

2.2.7. Statistical methods

- Determine risk factors related to the indication for phototherapy using the odds ratio (OR) with a 95% confidence interval. Risk factors are not determined when OR=1 or p>0.05. In case p<0.05, if OR>1, then exposure is a risk factor; if OR<1, then exposure is a protective factor.

- Determine the correlation between quantitative variables such as total bilirubin concentration, indirect bilirubin, albumin and total bilirubin/albumin ratio of cord blood with venous blood using Pearson correlation (symbolized by r). The value of r ranges from 0 to 1.

 $|\mathbf{r}| \ge 0.5$: strong correlation

 $|\mathbf{r}| < 0.5$: average correlation

 $|\mathbf{r}| < 0,3$: weak correlation

 $|\mathbf{r}| < 0,1$: very weak correlation

0 < r < 1: positive linear correlation (X increases, Y increases) -1 < r< 0: negative linear correlation (X increases, Y decreases) r=0: two variables are not related

- Determine the value of cord blood bilirubin concentration and total bilirubin/albumin ratio in predicting indirect hyperbilirubinemia requiring phototherapy using ROC curve with corresponding cutoff point and sensitivity (Se), specificity optimal performance (Sp). Accuracy was measured by the area under the ROC curve (AUC).

AUC	Meaning
>0,90	Excellent
0,80-0,90	Good
0,70 - 0,80	Fair
0,60 - 0,70	Poor
0,50-0,60	Fail

Table 2.4. Value of area under the ROC curve (AUC)

2.2.8. Ethical considerations

The study was approved by the Medical Ethics Council of the University of Medicine and Pharmacy, Hue University, on January 4, 2018. The study was conducted with the consent of the Board of Directors and the Board of Directors of the Department of Obstetrics and Gynecology, Hospital of Hue University of Medicine and Pharmacy. Cord blood sample testing was paid for by the PhD student. All information about the newborn and their mother is kept confidential and is only used for research purposes, not for other purposes. The newborn's name is abbreviated in the patient list.

Chapter 3 RESULTS

3.1. GENERAL CHARACTERISTICS

A total of 176 preterm infants <37 weeks of gestation with hyperbilirubinemia in first week of life:

- Males were higher than females, the male/female ratio is 1.26:1; mean gestation age is $34,5 \pm 1,4$ weeks, mean birth weight is 2190.0 $\pm 425,5g$, 83,0% appropriate-for gestation age.

- 41,5% cesarean section, 83,5% preterm infants did not need resuscitation after birth.

- 84,7% of mothers were aged 18-35 years old, 60,8% had at least 1 risk factor for early-onset sepsis.

3.2. CLINICAL AND SUBCLINICAL CHARACTERISTICS OF HYPERBILIRUBINEMIA IN PRETERM INFANTS

3.2.1. Clinical characteristics

Table 3.7. Time of jaundice appearance

Time of jaundice appearance	n	%
< 24	11	62
24 - < 48	89	50.6
48 - 72	23	13.1
> 72	53	30,1
Total	176	100,0
Median $(25^{\text{th}}-75^{\text{th}})$	44,0 (33	0-80,0)

Table 3.8. Kramer's scale at the time detected jaundice

Kramer score	n	%
1	83	47,2
2	37	21,0
3	34	19,3
4	15	8,5
5	7	4,0
Total	176	100,0

During the research period, 88/176 preterm infants were prescribed phototherapy, accounting for 50.0%.

Photothe (n=88	n	%				
	< 24	2	2,3			
	24 - < 48	60	68,2			
Time to start	48 - 72	17	19,3			
phototherapy	> 72	9	10,2			
	Total	88	100,0			
	Mean $(25^{th}-75^{th})$	38,0 (30),0 – 53,0)			
Duration of phototherapy (days)X ± SD		2,96	±0,94			
	Effective	88	100,0			
Outcomes	Ineffective	0	0,0			
	Total	88	100,0			

 Table 3.10.
 Phototherapy time and outcomes

3.2.2. Subclinical characteristics

3.2.2.1. Some cord blood parameters off pretem infants with indirect hyperbilirubinemia

 Table 3.12. Cord blood bilirubin, albumin and total bilirubin/albumin ratio

Cord blood parameters	X±SD or
(n=176)	Mean (25 th -75 th)
Total bilirubin (mg/dl)	1,77 (1,50 - 2,01)
Indirect bilirubin (mg/dl)	1,23 (0,95-1,52)
Albumin (g/dl)	$3,44 \pm 0,35$
Total bilirubin/albumin ratio (mg/g)	0,52 (0,42-0,60)

3.2.2.2. Some venous blood parameters on day 2 after birth of preterm infants with indirect hyperbilirubinemia

During the study period, 131/176 preterm infants were monitored and treated in the neonatal pediatric room with indications for venous blood testing.

Table 3.13. Some venous blood parameters on day 2 after birth of preterm infants with indirect hyperbilirubinemia

Venous blood parameters on day 2 after	$X \pm SD$ or
birth (n=131)	Median $(25^{\text{tn}}-75^{\text{tn}})$
Total bilirubin (mg/dl)	6,98 (5,76 - 7,82)
Indirect bilirubin (mg/dl)	6,50 (5,49 - 7,48)
Albumin (g/dl)	3,51 ± 0,32
Total bilirubin/albumin ratio (mg/g)	1,90 (1,64 - 2,30)

3.2.3. The relationship between clinical characteristics of indirect hyperbilirubinemia and total bilirubin concentration in venous blood on day 2 after birth in premature infants

Table 3.16. The relationship between clinical characteristics of indirect hyperbilirubinemia and total bilirubin concentration in venous blood on day 2 after birth in premature infants

Clinical chara (n=13	acteristics 1)	n (%)	Total bilirubin concentration in venous blood on day 2 (mg/dl) Median (25 th - 75 th)	р
Time of	< 24	11 (8,4)	7,33 (7,04 - 8,81)	
jaundice	24 - < 48	89 (67,9)	7,14 (6,35 – 7,84)	-0 0001
appearance	48 - 72	23 (17,6)	5,78 (4,71 - 6,54)	<0,0001
(hour)	> 72	8 (6,1)	4,92 (4,62 - 5,84)	
V	1	38 (29,0)	6,60 (5,15 - 7,34)	
scale at the time detected	2	37 (28,2)	6,77 (5,79 - 7,86)	
	3	34 (26,0)	6,72 (5,54 - 7,62)	0,004
	4	15 (11,5)	7,63 (6,51 - 8,70)	
Jaunuice	5	7 (5,3)	8,91 (7,72 - 9,68)	

3.2.4. Some factors related to indications for phototherapy in preterm infants

- Some factors in preterm infants themselves that were related to indirect hyperbilirubinemia requiring phototherapy were gestational age, birth weight, early-onset sepsis and respiratory distress. Preterm infants with gestational age <35 weeks were 4.61 times more likely to need phototherapy than infants 35-<37 weeks. Preterm infants with birth weight <2000g were 3.28 times more likely to need phototherapy than those weighing \geq 2000g. Preterm infants with early-onset sepsis were 7.15 times more likely to need phototherapy than others. Preterm infants with postpartum respiratory distress were 4.37 times more likely to need phototherapy than others.

- Premature infants who appear to have jaundice before 48 hours had a 23.40 times higher risk of needing phototherapy than the group whose jaundice appeared after 48 hours. At the time of detection, if an infant had jaundice from Kramer score 3 or higher, the risk of needing phototherapy was 4.83 times higher than in the jaundice group with Kramer's score of 1 or 2.

- Maternal factors related to indirect hyperbilirubinemia require phototherapy for premature infants whose mothers had a risk of early-onset sepsis. When the mother had risk factors for early-onset sepsis, the infant was 1.87 times more likely to need phototherapy than the other group (p<0.05).

3.3. SOME FACTORS RELATED TO CORD BLOOD BILIRUBIN AND TOTAL BILIRUBIN/ALBUMIN RATIO IN PRETERM INFANTS WITH HYPERBILIRUBINEMIA

3.3.1. The relationship between cord blood bilirubin concentration and total bilirubin/albumin ratio with some clinical characteristics and risk factors of indirect hyperbilirubiniemia in premature infants.

Some factors related to cord blood bilirubin concentration and total bilirubin/albumin ratio were gestational age, birth weight, time of jaundice appearance, jaundice area, indication for phototherapy, early-onset sepsis and respiratory distress.

3.3.2. The relationship between cord blood bilirubin concentration and total bilirubin/albumin ratio with some subclinical characteristics of indirect hyperbilirubiniemia in premature infants.

 Table 3.26.
 Correlation between cord blood total bilirubin

 concentration and some biochemical parameters of venous blood on

Venous blood on day 2 after birth (n=131)	Cord bl bilin concer (g	ood total rubin ntration /dl)	Correlation equation		
	r	р			
Total bilirubin (mg/dl)	0,406	<0,0001	y = 3,8000 + 1,7212x		
Indirect bilirubin (mg/dl)	0,412	<0,0001	y = 3,4967 + 1,6757x		
Total bilirubin/albumin ratio (mg/g)	0,385	<0,0001	y = 1,1722+ 0,4451x		

day 2 after birth

Table 3.29. Correlation between cord blood total bilirubin/albumin ratio and some biochemical parameters of venous blood on day 2

alter birth						
Venous blood on day 2 after birth (n=131)	Cord blo bilirubin/ ratio (ood total /albumin mg/g)	Correlation equation			
	r	р				
Total bilirubin (mg/dl)	0,378	<0,0001	y = 3,9122 + 5,7001x			
Indirect bilirubin (mg/dl)	0,383	<0,0001	y = 3,6139 + 5,5353x			
Total bilirubin/albumin ratio (mg/g)	0,423	<0,0001	y = 1,0528 + 1,7411x			

3.4. VALUE OF CORD BLOOD BILIRUBIN AND TOTAL BILIRUBIN/ALBUMIN RATIO IN PREDICTING PRETERM INFANTS WITH HYPERBILIRUBINEMIA REQUIRING PHOTOTHERAPY

3.4.1. Value of cord blood total bilirubin in predicting preterm infants with hyperbilirubinemia requiring phototherapy

Table 3.30. Value of cord blood total bilirubin in predicting preterm infants with hyperbilirubinemia requiring phototherapy

Total	Cutoff	AUC	Se %	Sp %	SE	95% CI	Р
(mg/dl)	1,82	0,854	72,7	84,1	0,0277	0,793 - 0,903	<0,0001

3.4.3. Value of cord blood total bilirubin/albumin ratio in predicting preterm infants with hyperbilirubinemia requiring phototherapy

Table 3.32. Value of cord blood total bilirubin/albumin ratio in predicting preterm infants with hyperbilirubinemia requiring

phototherapy

Total bilirubin/	Cutofff	AUC	Se %	Sp %	SE	95% CI	Р
albumin ratio (mg/g)	0,52	0,842	76,1	81,8	0,0298	0,780 - 0,893	<0,0001

3.4.4. Compare the values of cord blood total bilirubin, indirect bilirubin concentration and total bilirubin/albumin ratio in predicting preterm infants with hyperbilirubinemia requiring phototherapy

Table 3.33. Compare the values of cord blood total bilirubin, indirect bilirubin concentration and total bilirubin/albumin ratio in predicting preterm infants with hyperbilirubinemia requiring phototherapy

Cord blood sample	AUC	SE	95% CI	р
Total bilirubin ^a	0,854	0,0277	0,793- 0,903	a với b: = 0,023
Indirect bilirubi ^b	0,809	0,0319	0,743 - 0,864	a với c: = 0,530
Total bilirubin/albumin ratio ^c	0,842	0,0298	0,780 - 0,893	b với c: = 0,166

Cord blood total bilirubin concentration and total bilirubin/albumin ratio had equivalent values in the prediction of indirect bilirubin requiring phototherapy in premature infants with p>0.05.

Chapter 4 DISCUSSION

4.1. GENERAL CHARACTERISTICS

The ratio of male/female premature babies is 1.26/1. The research group's gestational age classification is similar to WHO statistics, with the 35-<37 weeks gestational age group accounting for the highest rate of 58.5% and decreasing proportionally with the gestational age group. The average birth weight is 2190.0 - 425.5g, which also corresponds to the weight at about the 50th percentile for each gestational age weeks as follows: weight at 32 weeks gestation is 1650g, 34 weeks is 2100g and 35 weeks is 2600g.

4.2. CLINICAL AND SUBCLINICAL CHARACTERISTICS OF HYPERBILIRUBINEMIA IN PRETERM INFANTS

4.2.1. Clinical characteristics

- Time of jaundice appearance: 56.8% of children appeared jaundice 48 hours before. The time to detect jaundice in my study

was earlier than other authors because the premature infants in the study were monitored daily and focused on jaundice symptoms, so it was detected early.

- Jaundice area at the time of detection: 47.2% of children were detected with jaundice only in Kramer score 1. However, 12.5% of children were also detected with jaundice in Kramer score 4 and 5. Even though all babies have been monitored daily, there were still some of them with a rapid rate of jaundice. By the time it was detected, the patient scores already reached scores 4 and 5. Therefore, if we can find the cutoff point of cord blood bilirubin concentration and total bilirubin/albumin ratio in predicting jaundice requiring treatment, it will help clinicians plan to monitor infants at risk of rapid jaundice progression for timely treatment.

- The incidence of preterm infants with indirect hyperbilirubinemia who were prescribed phototherapy was 50.0%. The rate of phototherapy in other studies was higher than in my study because of differences in research participants. Most of my research participants belong to the late preterm group, while other studies have a higher rate of babies at <32 weeks or <28 weeks and the rate of phototherapy in these participants was over 90.0%.

- The average phototherapy time was 2 days and there were no cases requiring exchange transfusion. This was the advantage of the combined obstetrics-pediatrics model. Preterm infants were monitored for jaundice symptoms since birth, so they could be detected early and treated early, avoiding complications.

4.2.2. Subclinical characteristics

4.2.2.1. Some cord blood parameters off pretem inffants with indirect hyperbilirubinemia

The result of cord blood sample testing in my study showed a median total bilirubin concentration of 1.77 (1.50 - 2.01) mg/dl (#30.3 (25.7 - 34.4) μ mol /l), the total bilirubin/albumin ratio is 0.52 (0.42-0.60) mg/g, also similar to that recorded by some authors studying cord blood bilirubin concentration and total

bilirubin/albumin ratio in premature infants. Other authors' studies on full-term infants have a higher median of these two metrics than my study. However, there are currently no studies in Vietnam on bilirubin and umbilical albumin levels, so these parameters are valuable references for new topics in the future.

4.2.2.2. Some venous blood parameters on day 2 after birth of preterm infants with indirect hyperbilirubinemia

Bilirubin concentration and total bilirubin/albumin ratio in peripheral venous blood in premature infants prescribed phototherapy were higher than in the control group. Physiologically, preterm infants typically have peak bilirubin levels at 5-7 days after birth. But my study tested bilirubin concentration and the total bilirubin/albumin ratio on the second day after birth, so it had lower levels than other studies that had a later sampling time.

4.2.3. The relationship between clinical characteristics of indirect hyperbilirubinemia and total bilirubin concentration in venous blood on day 2 after birth in premature infants

In table 3.16, the research results show that the earlier the jaundice appears, the higher the jaundice area at the time of detection, the higher the total bilirubin concentration in venous blood on day 2 at p < 0.0001. Preterm infants had jaundice at Kramer score 1, have a median day 2 venous blood total bilirubin concentration of 6.60 mg/dl and increases to 8.91 mg/dl if the infant had jaundice at Kramer score 5 at the time of detection. According to Kramer's scale, the higher the total bilirubin concentration in the blood, the more jaundiced the skin becomes. However, the value of the total bilirubin concentration in my study was lower than Kramer's scale because my research participants were preterm infants, and the amount of subcutaneous fat was thinner than full-term infants, so jaundice could be detected early.

4.3. SOME FACTORS RELATED TO CORD BLOOD BILIRUBIN AND TOTAL BILIRUBIN/ALBUMIN RATIO IN PRETERM INFANTS WITH HYPERBILIRUBINEMIA

4.3.1. relationship between cord blood bilirubin The concentration and total bilirubin/albumin ratio with some clinical characteristics and risk factors of indirect hyperbilirubiniemia in premature infants.

Some factors related to cord blood bilirubin concentration and total bilirubin/albumin ratio were gestational age, birth weight, time of jaundice appearance, jaundice area, indication for phototherapy, early-onset sepsis and respiratory distress.

4.3.2. The relationship between cord blood bilirubin concentration and total bilirubin/albumin ratio with some subclinical characteristics of indirect hyperbilirubiniemia in premature infants.

There was a moderate positive correlation between cord blood bilirubin concentration and total bilirubin/albumin with the concentration of the corresponding substances in venous blood on the 2nd day after birth at p < 0.0001.

The bilirubin metabolism of the fetus is different from that of the newborn. In the womb, the fetus's liver is barely functional. Most of the indirect bilirubin produced in the fetus is eliminated through the placenta and enters the mother's liver. After birth, preterm infants may have one or more causes or risk factors that lead bilirubin concentration in the blood to increase. My research results have shown that there was a moderate positive correlation between cord blood and venous blood samples, helping to identify preterm infants at risk of continuing to increase bilirubin levels in the blood to plan for diagnosis and proper follow-up.

4.4. VALUE OF CORD BLOOD BILIRUBIN AND TOTAL BILIRUBIN/ALBUMIN RATIO IN PREDICTING PRETERM INFANTS WITH HYPERBILIRUBINEMIA REQUIRING PHOTOTHERAPY

4.4.1. Value of cord blood total bilirubin in predicting preterm infants with hyperbilirubinemia requiring phototherapy

In table 3.30, at the cutoff point of cord blood total bilirubin > 1,82 mg/dl (# 31μ mol/L) with AUC=0,854, p<0,0001, Se 72,7%, Sp 84,1%, there was a good prognostic value of preterm infants with hyperbilirubinemia requiring phototherapy.

The value of the cutoff point in my study is at a lower limit than most other studies. This is explained by the fact that my research subjects were only conducted on preterm infants, while most of the studies by other authors were conducted mainly on full-term infants.

4.4.3. Value of cord blood total bilirubin/albumin ratio in predicting preterm infants with hyperbilirubinemia requiring phototherapy

In table 3.32, at the cutoff point of cord blood total bilirubin/albumin ratio >0,52 mg/g with AUC=0,842, p<0,0001, Se 76,1%, Sp 81,8%, there was a good prognostic value of preterm infants with hyperbilirubinemia requiring phototherapy.

Several other studies have noted that cord blood total bilirubin/abumin ratio had good to very good values in predicting pathological indirect hyperbilirubinemia in newborns. However, the cutoff point of cord blood total bilirubin/abumin ratio in these studies is higher than the results of my study. Because the participants in my study were preterm infants, while most of the studies by other authors were mainly full-term infants. Furthermore, cord blood albumin concentration in my study had a higher average value than in other studies, but the total bilirubin concentration was lower.

4.4.4. Compare the values of cord blood total bilirubin, indirect bilirubin concentration and total bilirubin/albumin ratio in predicting preterm infants with hyperbilirubinemia requiring phototherapy

The results in table 3.33 and chart 3.4 show the value of 3 indicators (cord blood total bilirubin, indirect bilirubin concentration and total bilirubin/albumin ratio) in predicting jaundice requiring phototherapy in preterm infants. Among them, cord blood total bilirubin concentration had the highest predictive value with an AUC of 0.854, followed by cord blood total bilirubin/albumin ratio with AUC = 0.842 and finally, cord blood indirect bilirubin concentration with AUC = 0.809, p<0.05. However, when comparing the difference in the predictive ability of these three indices, it was noted that cord blood total bilirubin concentration and total bilirubin/albumin ratio with p>0.05.

CONCLUSIONS

A total participants of 176 preterm infants were born at Hue University of Medicine and Pharmcy Hospital. The study leads to the following conclusions:

1. Clinical and subclinical characteristics of hyperbilirubinemia in preterm infants

- The male/female ratio is 1.26:1; mean gestation age is $34,5 \pm 1,4$ weeks, mean birth weight is $2190.0 \pm 425,5g$.

- 56.8% present jaundice before 48 hours after birth, 50.0% of infants requiring phototherapy.

- A total of 176 cord blood samples: median total bilirubin was 1.77 (1.50 – 2.01) mg/dl (# 30.3 (25.7 – 34.4) μ mol/L), the median of total bilirubin/albumin ratio was 0.52 (0.42 – 0.60) mg/g.

- A total of 131 samples of venous blood on the second postpartum: mean total bilirubin concentration was 6.98 (5.76 - 7.82)

mg/dl (#119.4 (98.5 - 133.7) μ mol/L), median of total bilirubin/albumin ratio was 1.90 (1.64 - 2.30) mg/g.

2. Some factors related to cord blood bilirubin and total bilirubin/albumin ratio in preterm infants with hyperbilirubinemia

Some factors related to cord blood blood bilirubin and total bilirubin/albumin ratio in preterm infants with hyperbilirubinemia were gestational age, indication for phototherapy, children with early neonatal infections and respiratory failure, statiscally significant with p < 0.05.

3. Value of cord blood bilirubin and total bilirubin/albumin ratio in predicting preterm infants with hyperbilirubinemia requiring phototherapy

- Cord blood total bilirubin and total bilirubin.albumin ratio had good and equivalent values in predicting preterm infants with hyperbilirubinemia requiring phototherapy.

- At the cutoff point of cord blood bilirubin >1,82 mg/dl (# 31 μ mol/L) with AUC=0,854, p<0,0001 and at the cutoff point of cord blood total bilirubin/albumin ratio >0,52 mg/g with AUC=0,842, p<0,0001, there were a good prognostic value of preterm infants with hyperbilirubinemia requiring phototherapy.

ADVANTAGES AND LIMITATIONS OF THE STUDY

1. Advantages of the study

- Up to present, there has not been any research on this topic in Vietnam.

- The research was conducted at Hue University of Medicine and Pharmacy Hospital, a hospital with a coordinated obstetrics and pediatrics model. Therefore, all cases of premature birth are synchronously tested for cord blood bilirubin and albumin and continue to monitor or treat the baby while the mother and their child are still in the hospital. - The patients of this study were preterm infants, unlike many other studies in the world that mainly focus on full-term newborns.

- The study results have found three valuable indicators in predicting indirect hyperbiliruninemia requiring phototherapy in premature infants: cord blood total bilirubin, indirect bilirubin concentration and total bilirubin/albumin ratio at specific cut points.

2. Limitations of the study

- This study did not include premature infants without jaundice.

- My research location has not yet implemented facilities to nurture and treat extremely premature newborns under 28 weeks and/or under 1500g, as well as newborns in very severe condition. This may be one of the reasons why my research results have not recorded the value of umbilical cord blood albumin in predicting pathological jaundice in newborns like some other studies.

SUGGESTIONS

Through research on 176 premature infants with indirect hyperbilirubinemia in the first week after birth, I found that cord blood bilirubin and albumin testing were a non-invasive test, quick results and valuable in prediction of indirect hyperbilirubinemia requires phototherapy in premature infants. Therefore, I have some suggestions as follows:

1. The concentration of cord blood bilirubin and albumin should be tested for premature newborns immediately after birth to help predict cases that are likely to progress to increased indirect hyperbilirubinemia requires phototherapy.

2. From the limitations of this study, I would also like to have more in-depth studies to determine the value of cord blood bilirubin and the ratio of total bilirubin/albumin in predicting indirect hyperbilirubinemia requiring phototherapy in premature infants at smaller gestational ages.

SCIENTIFIC ARTICLES HAVE BEEN PUBLISHED RELATED TO THE DOCTORAL THESIS

- 1. Nguyen Thi Thanh Binh, Phan Hung Viet (2023), "Cord blood albumin and bilirubin concentration in preterm newborns with hyperbilirubinemia", *Journal of Clinical Medicine Hue Central Hospital*, No.85, pp.124-131.
- 2. Nguyen Thi Thanh Binh, Phan Hung Viet (2023), "Early predictors of neonatal hyperbilirubinemia requiring phototherapy by cord blood bilirubin, albumin and bilirubin/albumin ratio in preterm infants", *Hue Journal of Medicine and Pharmacy Hue University of Medicine and Pharmacy*, Special issue, November 2023, pp.98-103.