The Value of Routine Bilirubin Screening to Detect Significant Hyperbilirubinemia in Thai Healthy Term Newborns

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Objective: *To evaluate the clinical value and the predictive usefulness of the routine pre-discharge bilirubin screening in term newborn at 48-72 hours after birth.*
Material and Method: *Blood samples of 1983 healthy term newborns for measuring total serum bilirubin level were drawn at the same time as the routine metabolic screening at Prapokklao Hospital. Newborns with total serum bilirubin levels ≥ 5 mg/dL in the first 24 hours, ≥ 10 mg/dL at 25 to 48 hours, ≥ 13 mg/dL at 49-72 hours, and ≥ 15 mg/dL at > 72 were defined to have hyperbilirubinemia and were started on phototherapy.*
Results: *Two hundred and seventy-nine newborns (14.07%) with hyperbilirubinemia, including seven (0.35%) with severe hyperbilirubinemia were detected by the bilirubin screening program. Newborns without hyperbilirubinemia at the time of screening test were unlikely to develop subsequent significant hyperbilirubinemia. The costs for detecting hyperbilirubinemia and severe hyperbilirubinemia were 6.22 US$ and 247.87 US$ per case, respectively.*
Conclusion: *The bilirubin screening program was cost-effective and could detect a number of unexpected severe hyperbilirubinemia. Newborns without hyperbilirubinemia were unlikely to develop subsequent significant hyperbilirubinemia.*

Keywords: *Hyperbilirubinemia, Bilirubin screening, Universal metabolic neonatal screening, Prediction*

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In recent years, early discharge of healthy term newborns after delivery has become a common practice for medical, social, and economic reasons. This limits the ability of physicians to detect jaundice before discharge. Normally, jaundice is observed in the first days of life, usually reaching peak values at about the third day after birth[1]. With early discharge from hospital, hyperbilirubinemia is the most common cause for readmission during the early neonatal period[2-4] and 0.36% of healthy term newborns discharged with no more than mild hyperbilirubinemia may subsequently develop severe neonatal hyperbilirubinemia in the first postnatal week[5]. Therefore, in this situation, there is a need for early detection of hyperbilirubinemia and good follow-up programs after discharge.

A follow-up for a newborn discharged before 48 hours of life at 2 to 3 days post natally, as recommended by the American Academy of Pediatrics[6], is not always possible in clinical practice. A routine pre-discharge screening for total serum bilirubinemia was claimed be a good practical guideline to identify the newborns at risk for developing significant hyperbilirubinemia during the first days of life[7-9]. A screening program for metabolic and endocrine diseases in the newborn has been established in Thailand since 1998. For this purpose, a blood sample of the newborn is usually drawn at about 48-72 hours after birth, a time which serum bilirubin concentration is likely to rise. The purpose of the present study was to investigate whether including into the metabolic screening pro-

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gram a sample for measuring the serum bilirubin concentration may detect some infants with unexpectedly high bilirubinemia levels in need for treatment before hospital discharge and its value in identification of infants at risk for the development of subsequent significant hyperbilirunemia.

Material and Method

Subjects

The populations of normal full-term newborn with a birth weight ≥ 2500 grams delivered at Prapokklao Hospital during the period of March 2004 to November 2004 were included. The authors excluded newborns admitted to the intensive care unit for neonatal illness and those with severe perinatal asphyxia, congenital anomalies, congenital infection, or conjugated hyperbilirubinemia.

Prapokklao Hospital is the regional government hospital in Chantaburi province. Chantaburi is situated in eastern Thailand about 245 km from Bangkok and near the Cambodian border. The main occupation of the people is agriculture and there are few industries.

Study design

The present study was approved by the ethics committee of Prapokklao Hospital. It included the newborns who met the eligible criteria. An informed consent was obtained from the parent. A blood sample for measuring total serum bilirubin levels was drawn at the same time as the routine metabolic screening, which was usually about 48-72 hours after birth.

Prapokklao guidelines for management of neonatal hyperbilirubinemia

The authors define a newborn as hyperbilirubinemia in the first 24 hours of life if the total serum bilirubin measurement was ≥ 5 mg/dL, at 25 to 48 hours if the total serum bilirubin measurement was ≥ 10 mg/dL, at 49-72 hours if the total serum bilirubin measurement was ≥ 13 mg/dL, and > 72 hours if the total serum bilirubin measurement was ≥ 15 mg/dL. Severe hyperbilirubinemia is defined as total serum bilirubin level ≥ 20 mg/dL. Newborns with total serum bilirubin met or exceeded these levels are recommended to start on phototherapy and work up for hemolysis including reticulocyte count, direct Coomb's test, G-6-PD level and maternal and infant blood group. Exchange transfusion is recommended in well term newborns failing to respond to intensive phototherapy at a total serum bilirubin level of ≥ 25 mg/dL without any evidence of hemolysis or ≥ 20 mg/dL with evidence of hemolysis. The authors' criteria for hyperbilirubinemia and consideration for phototherapy are modified from the 1994 American Academy of Pediatrics (AAP) clinical practice parameter for management of hyperbilirubinemia in the healthy term newborn[10]. In the authors' practice, the follow-up program to decrease the risk of kernicterus recommended by the AAP cannot be performed. Therefore, the authors selected to lower threshold level in the presented newborn.

Bilirubin measurement

Total serum bilirubin measurements were performed using Jendrassik and Grof Method[11].

Statistical analysis

The descriptive statistics: mean and standard deviation (SD) describe maternal and newborn characteristic.

The receiver operating characteristic (ROC) curve analysis of the various screening bilirubin levels of the newborns without hyperbilirubinemia at the screening program was done to predict the development of subsequent significant hyperbilirubinemia.

Results

One thousand nine hundred and eighty three newborns were included in the present study. The mean maternal age was 26.6 ± 6.3 years. Over half of the newborns were the first or second offspring. The mean age of the newborns at the time of hospital discharge was 4.0 ± 1.6 days (3.6 ± 1.3 for vaginal delivery and 4.7 ± 1.8 for caesarian delivery).

Four hundred and sixty nine newborns (23.7%) had hyperbilirubinemia before discharge from the hospital. Table 1 show various ages at the time that hyperbilirubinemia was identified. Severe hyperbilirubinemia (a maximum total serum bilirubin level ≥ 20 mg/dL) was identified in 12 newborns (0.6%) and levels ≥ 25 mg/dL in none. Four hundred and forty eight newborns (22.6%) were treated with phototherapy. Total blood exchange transfusions were performed in nine newborns (0.5%). G6PD deficiency was found in 68 newborns, ABO blood group incompatibility in 56 newborns and minor blood group incompatibility in one newborn.

The presented bilirubin screening program could detect unexpected hyperbilirubinemia in 279 newborns, including seven patients with severe hyperbilirubinemia (Table 1). After the screening program, 728 newborns without hyperbilirubinemia remained in

Table 1. Various ages at the time that hyperbilirubinemia was identified

	Postnatal age in hours				Total
	≤ 24	25-48	49-72*	> 72	
Hyperbilirubinemia	17	132	279	41	469
Severe hyperbilirubinemia	0	3	7	2	12
Exchange transfusion	0	4	5	0	9
G6PD deficiency	3	17	40	8	68
ABO incompatibility	5	14	32	5	56

* The time that blood samples for measuring total serum bilirubin level were drawn

Table 2. Sensitivity, Specificity and Positive and Negative Predictive values of various screening bilirubin levels of newborns without hyperbilirubinemia at the screening program in predicting the development of subsequent hyperbilirubinemia

Screeningtotal bilirubin level (mg/dl)	Outcome: subsequent hyperbilirubinemia (Total = 728)				Predictive characteristics %			
	False negative	True positive	True negative	False positive	Positive predictive value	Negative predictive value	Sensitivity	Specificity
9	4	37	262	425	8.0	98.5	90.2	38.1
10	8	33	372	315	9.5	97.9	80.5	54.1
11	13	28	500	187	13.0	97.5	68.3	72.8
12	26	15	604	83	15.3	95.9	36.6	87.9

the hospital, and 41 newborns developed subsequent hyperbilirubinemia. The receiver operating characteristic (ROC) curve analysis of the various screening bilirubin levels of 728 newborns without hyperbilirubinemia was done. The area under the ROC curve, as shown in Fig. 1, is calculated to be 76%. Table 2 lists the predictive ability of these bilirubin levels in predicting the development of subsequent hyperbilirubinemia. At a higher level of total serum bilirubin, the sensitivity decreases and specificity increases. However, at any level, the positive predictive (8.0%-15.3%) is very low and the negative predictive value (98.5%-95.9%) is very high.

The authors found three infants were readmitted to Prapokklao Hospital due to hyperbilirubinemia. The hospital readmission due to neonatal hyperbilirubinemia was decreased compared with the same interval of the previous year, during which nine infants were readmitted.

The total costs of the bilirubin screening were calculated as 35 Thai baht (0.87 US$) per one serum bilirubin measurement[12]. The cost for detecting

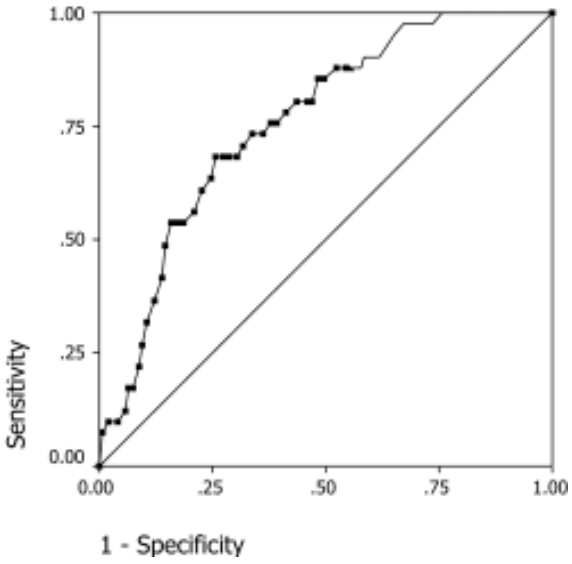

Fig. 1 The ROC analysis of the various screening bilirubin levels of newborns without hyperbilirubinemia at the screening program in predicting the development of subsequent hyperbilirubinemia

unexpected hyperbilirubinemia was 249 Thai baht (6.22 US$) per newborn and 9915 Thai baht (247.87 US$) per newborn for severe hyperbilirubinemia.

Discussion

In the presented prospective study, the authors found a higher incidence of hyperbilirubinemia in the presented newborns compared with other studies. Newman et al data in one study, 18% of the infants met standard textbook criteria for non-physiologic hyperbilirubinemia (the incidence varied from 9% in blacks to 31% in Asian infants)[13] and in another study, 9.3% of all births had a maximum total serum bilirubin level $\geq$ 15 mg/dL[14]. Some studies using the age-specific criteria recommended in the American Academy of Pediatrics (AAP) 1994 guideline[10], hyperbilirubinemia was found in 10.5% of the term newborns excluding those with any evidence of hemolysis[15] and 2.74% excluding those with total serum bilirubin level > 10 mg/dL in the first 24 hours of life[16]. The high incidence of hyperbilirubinemia in the present study may be attributable to Asian race of the newborns, exclusively breast-feeding in Prapokklao Hospital, and the lower threshold levels for definitions of hyperbilirubinemia and starting phototherapy.

Although the authors had a large number of phototherapy in the present study (22.6%) because of starting phototherapy at lower threshold levels, the newborns were less likely to have severe hyperbilirubinemia and as a result decreasing risk for kernicterus. The authors found only 0.6% of the newborns with total serum bilirubin level $\geq$ 20 mg/dL and none with level $\geq$ 25 mg/dL compared with 2% and 0.15% in Newman et al study, respectively[14]. Chou et al also claimed that they could attribute a lower incidence of newborns with total serum bilirubin level $\geq$ 20 mg/dL to their more rigorous bilirubin screening, follow-up, and treatment program[16]. Therefore, the authors speculated that the lower rates of severe hyperbilirubinemia in the present study were due to the authors' management protocols.

In traditional practice, the determination of total serum bilirubin level is indicated when jaundice is clinically significant by medical judgment. This practice relies on the ability of the physician to recognize significant jaundice and there is considerable variability in the accuracy among observers[17,18]. The AAP suggests detecting jaundice by blanching the skin with digital pressure to reveal the underlying color of the skin and subcutaneous tissue. As the total serum bilirubin level rises, the extent of cephalocaudal progression may be helpful in quantifying the degree of jaundice[10]. However, there were several instances when the early appearance of jaundice was missed, and often attributable to skin coloring and the physician awareness. Madlon-Kay evaluated by the ability of nurses and physicians to detect jaundice and concluded that nurses and physicians may not feel the need to attempt to assess carefully jaundice severity clinically when accurate blood levels were so readily available[19].

Many studies could demonstrate the predictive usefulness and clinical value of the pre-discharge bilirubin screening in term newborn[7-9,20,21]. They could predict nearly all of the term newborns who had significant hyperbilirubinemia and determined all those who required phototherapy later during the first days of life. The most concerning problem about the routine bilirubin screening is its cost-effectiveness and it may be questioned whether hyperbilirubinemia fulfils the basic criteria of being an important health problem[22]. Following the AAP guidelines, Newman et al study suggested the selective total serum bilirubin test-ordering policy[14]. They could save on venipuntures and their associated costs and discomfort, with little increased risk of missing extreme hyperbilirubinemia, if the infants still received appropriate follow-up.

In the present study, the authors preferred to perform the pre-discharge bilirubin screening together with universal metabolic screening at about 48-72 hours after birth as bilirubin levels were likely to rise at this time. The calculations of the cost-benefit for detecting hyperbilirubinemia justified the bilirubin screening. According to the present findings, the bilirubin screening could identify a large number of unexpectedly high bilirubinemia levels in need of treatment before hospital discharge. The authors also found that newborns without hyperbilirubinemia at the time of screening test were unlikely to develop subsequent significant hyperbilirubinemia (95.9% negative predictive value at the level of 12 mg/dL in predicting the development of subsequent hyperbilirubinemia).

Most of the presented newborns were discharged after 48-72 hours of age. This may be due to the exclusively breast-feeding policy in Prapokklao Hospital that the authors would not discharge the newborns with their mothers until their lactations were approved. Late discharge from hospital combining with the presented bilirubin screening program decreased the risk of readmission and kernicterus because the authors could observe and detect most cases of hyperbilirubinemia in the hospital. With early discharge, we

questioned whether the bilirubin screening alone can do the same.

In conclusion, it was cost-effective to perform bilirubin screening at the time of routine metabolic screening in Prapokklao Hospital. The bilirubin screening could detect a number of unexpected severe hyperbilirubinemia. The screening of newborns without hyperbilirubinemia was unlikely to develop subsequent significant hyperbilirubinemia. The modified AAP guideline by lowering the threshold levels for definitions of hyperbilirubinemia and consideration of phototherapy contributed to a high incidence of hyperbilirubinemia in the presented newborns but who were less likely to have severe hyperbilirubinemia.

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การศึกษาประโยชน์ของการตรวจวัดระดับบิลิรูบินในเลือด เพื่อคัดกรองภาวะตัวเหลืองในทารกแรกเกิดครบกำหนด

ทนง ประสานพานิช, สุภรณ์ สมหล่อ

วัตถุประสงค์*: เพื่อศึกษาประโยชน์ของการตรวจวัดระดับบิลิรูบินในเลือดเพื่อคัดกรองภาวะตัวเหลืองมากในทารกแรกเกิดก่อนการจำหน่ายกลับบ้าน เมื่ออายุ 48-72 ชั่วโมงหลังคลอด*

วัสดุและวิธีการ*: ทารกแรกเกิดจำนวน 1,983 คนที่เกิดในโรงพยาบาลพระปกเกล้า น้ำหนักตั้งแต่ 2,500 กรัม ได้รับการเจาะเลือดเพื่อตรวจวัดระดับบิลิรูบินในเลือดร่วมกับการตรวจคัดกรองหาภาวะพร่องไทรอยด์ฮอร์โมนเมื่ออายุ 48-72 ชั่วโมง ระดับบิลิรูบิน ≥ 5 mg/dL ที่อายุ 24 ชั่วโมงแรก, ≥ 10 mg/dL ที่อายุ 25 - 48 ชั่วโมง, ≥ 13 mg/dL ที่อายุ 49-72 ชั่วโมง, และ ≥ 15 mg/dL ที่อายุ > 72 ชั่วโมง จะถือว่ามีภาวะตัวเหลืองมากและได้รับการรักษาด้วย phototherapy*

ผลการศึกษา*: การตรวจคัดกรองสามารถตรวจพบภาวะตัวเหลือง 279 คน (14.07%) ในจำนวนนี้เป็นภาวะตัวเหลืองมากระดับรุนแรง 7 คน (0.35%) ทารกที่ตรวจไม่พบภาวะตัวเหลืองมากจากการตรวจคัดกรองมีโอกาสน้อยมากที่จะเกิดภาวะนี้ในภายหลัง คำนวณต้นทุนในการตรวจพบภาวะตัวเหลืองและภาวะตัวเหลืองระดับรุนแรงต่อหนึ่งคน เท่ากับ 249 บาท และ 9,915 บาท ตามลำดับ*

สรุป*: ระดับบิลิรูบินในเลือดที่ตรวจร่วมกับการตรวจคัดกรองภาวะพร่องไทรอยด์ฮอร์โมนในทารกแรกเกิด สามารถพบทารกที่มีภาวะตัวเหลืองมากได้จำนวนมาก การนำมาประยุกต์ใช้เพื่อเป็นแนวทางในการดูแลทารกแรกเกิดหลังคลอดน่าจะได้ประโยชน์และคุ้มกับต้นทุนที่เสียไป*