Outcome Analysis of Jaundice Fast-Track System Implementation in Thammasat University Hospital

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Background: *Infants who were readmitted with high level of bilirubin (more than 20 mg/dL) should be treated as an acute medical emergency to prevent acute and chronic bilirubin encephalopathy.*
Objective: *To determine causes of severe neonatal hyperbilirubinemia, risk factors for exchange transfusion and outcomes of neonate after implementation of the Jaundice Fast-track System in Thammasat Hospital.*
Material and Method: *The medical records of neonates presenting with clinically significant hyperbilirubinemia to the outpatient department or emergency department after implementation of the Jaundice Fast-track System at Thammasat University from October 1, 2010 through September 30, 2012, were retrospectively reviewed.*
Results: *There were 76 infants included in the study. One infant had neurological abnormalities consistent with acute bilirubin encephalopathy at presentation. All infants received intensive phototherapy. Eight infants (10.5%) underwent an exchange transfusion. A cause of hyperbilirubinemia was identified in 66 cases (86%). Breastfeeding jaundice was the most common cause (47%). The mean peak MB level was higher in the exchange transfusion group than the phototherapy group (25.0±2.9 mg/dL vs. 21.2±1.8 mg/dL, p<0.001). Three infants in the exchange transfusion group had sepsis on admission compared to none in the phototherapy group, (p<0.001). No infant diagnosed as cephalhematoma underwent an exchange transfusion. The median (range) length of stay was significantly longer in the exchange transfusion group than the phototherapy group (9 (2-15) days vs. 2 (1-12) days, p<0.001). There were no statistical differences between the two groups in age at readmission and time to phototherapy. All infants in this study were discharged as no neurological abnormalities. Infants presented with peak MB ≥24 mg/dL had the greatest risk of exchange transfusion (OR = 26.6; 95% CI = 4.6, 153.7).*
Conclusion: *Initiating phototherapy within an hour of admission in infants who were readmitted with high levels of bilirubin is effective to prevent bilirubin encephalopathy. Physicians' early recognition of the risk factors to exchange transfusion is, therefore, crucial.*

Keywords: *Exchange transfusion, Hyperbilirubinemia, Jaundice fast track, Kernicterus, Neonate, Phototherapy*

J Med Assoc Thai 2014; 97 (5): 500-5
Full text. e-Journal: *http://www.jmatonline.com*

Neonatal hyperbilirubinemia remains the most common cause of readmission within the first two weeks of life, in spite of attempts to assess the risk of hyperbilirubinemia before discharge[1-5]. Although neonatal hyperbilirubinemia is usually a benign condition that resolves spontaneously, however the serum bilirubin concentration can rise to severe and even extreme levels, and cause acute and chronic bilirubin encephalopathy. Most infants with severe hyperbilirubinemia survive and recover from the acute phase of bilirubin encephalopathy under the treatment modalities for hyperbilirubinemia, including proper identification of at-risk infants through bilirubin testing, intensive phototherapy and exchange transfusion. However, some infants may develop permanent sequelae within the clinical spectrum of chronic bilirubin encephalopathy including choreoathetoid, cerebral palsy, hypertonia or hypotonia and sensorineural hearing loss[6-10]. In addition, recent studies have suggested that chronic bilirubin encephalopathy has a much broader spectrum of chronic neurological dysfunction such as speech delay, global developmental delay, and autism[11-13].

The American Academy of Pediatrics (AAP) Subcommittee on hyperbilirubinemia has recommended that if the total serum bilirubin (TSB) is at exchange transfusion level or ≥25 mg/dL at any time, it is a medical emergency and the infant should be admitted immediately for intensive phototherapy[14].

At our hospital, the authors experienced 82 cases of neonates presenting to the outpatient

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department (OPD) or emergency department (ED) with clinically significant hyperbilirubinemia during October 01, 2009 through September 30, 2010 in which the initiation of phototherapy was delayed for 4-7 hours. A medical history review of these cases identified the major causes of delay were the admission processes and the prioritization of the pediatric patients. In response to this delay, a multidisciplinary team has developed a Jaundice Fast-track System that stresses rapid nursing assessment, early serum bilirubin determination, and expedited transfer of high-risk patients to the neonatal intensive care unit (NICU) to receive intensive phototherapy.

The present study aimed to determine causes of severe neonatal hyperbilirubinemia, risk factors for exchange transfusion and outcomes of neonates after implementation of the Jaundice Fast-track System in Thammasat University Hospital.

Both neonatal clinicians and researchers may find this study beneficial in understanding how and why fast-track jaundice systems can be implemented in clinical practice for all variations of hospital.

Material and Method

Study population

Medical records of neonates presenting with clinically significant hyperbilirubinemia to the OPD or ED, after implementation of the Jaundice Fast-track System at Thammasat University from October 01, 2010 through September 30, 2012, were retrospectively reviewed. Neonates were excluded if they had incomplete data or required exchange transfusion as a result of other indications apart from hyperbilirubinemia.

Clinical pathway of the Jaundice Fast-track System and prospective study data collection.

1. Neonates presenting with clinically significant hyperbilirubinemia to OPD or ED are identified by the registered nurse (RN).

2. The RN immediately (with a physician's authorization) obtains a microbilirubin (MB) level via a heel stick.

3. The RN requests laboratory for the immediate result (within 15 minutes).

4. Neonates with any of the following results: MB ≥20 mg/dL or within 2 mg/dL of exchange threshold are immediately sent to the physician for full evaluation and admission orders including fast-track phototherapy within an hour.

5. The OPD RN calls the nurse in charge in NICU to prepare equipments for intensive phototherapy and intravenous (IV) placement.

6. The neonate is taken to NICU, and is placed on double phototherapy using a bilirubin blanket and fluorescent lamp phototherapy on top, while obtaining additional blood tests (blood group, complete blood count (CBC), etc.) and the IV line.

7. The parents are sent to the admission centers to complete the admission process.

Data including gestational age, sex, birth weight, route of delivery, feeding methods, Apgar score, causes of hyperbilirubinemia, age at readmission, peak MB, percentage of weight loss, time to phototherapy, length of hospital stay, treatment modalities and complications of exchange transfusion were recorded. The time to phototherapy is defined as admission order time to time of documentation of the phototherapy initiation. All infants received treatment according to the guidelines of the American Academy of Pediatrics for management of hyperbilirubinemia in the newborn infant of 35 or more weeks of gestation[14]. Exchange transfusion is indicated when phototherapy fails to reduce the bilirubin load to 25 mg/dL in healthy term infants or to lower level in the presence of neurotoxicity risk factors (according to the American Academy of Pediatrics guidelines).

The present study was approved by the Ethics Committee of the Faculty of Medicine, Thammasat University: Number MTU-EC-PE-6-001/57.

Data analysis

Data were expressed as median and ranges for non-normal distributions or means and standard deviations for normal distributions. Continuous variables were analyzed using an independent sample t-test, and categorical data were analyzed using Fisher's exact test or Chi-square analysis where appropriate. Non-parametric variables were calculated by the Mann-Whitney U test. Statistical significance was designated at $p<0.05$.

Results

During the present study period, 76 infants were included in the Jaundice Fast-track System. Of these, one infant had neurological abnormalities consistent with acute bilirubin encephalopathy at presentation. All infants received intensive phototherapy. Eight infants (10.5%) underwent an exchange transfusion. Causes of hyperbilirubinemia were identified in 66 cases (86%) (Table 1). Breast-feeding jaundice was the most common cause (47%), followed by cephalhematoma (10.5%). Of those with blood group incompatibility, 7.8% was ABO and 2.6%

was minor blood groups. No cause was identified for hyperbilirubinemia in 10 infants (13%). Demographic characteristics were not significantly different between the infants received phototherapy and infants undergoing exchange transfusion. Sixty-five infants (85.5%) were exclusively breast fed (Table 2).

The mean peak MB level was higher in the exchange transfusion group than those in the phototherapy group were (25.0±2.9 mg/dL vs. 21.2±1.8 mg/dL, $p<0.001$). Three infants in the exchange transfusion group had sepsis compared to zero infants in the phototherapy group ($p<0.001$). No infant who was diagnosed as cephalhematoma underwent an exchange transfusion. Infants who had weight loss of more than 10% of birth weight were found in 25% and 10.5% in the exchange transfusion group and the phototherapy group, respectively. The median length of stay was significantly longer in the exchange transfusion group than the phototherapy group (9 (2-15) days vs. 2 (1-12) days, $p<0.001$). There were no statistical differences between the two groups in age at readmission and time to phototherapy. All infants in this study were discharged with no neurological abnormalities (Table 3).

Univariate logistic regression analysis identified that infants who presented with peak MB ≥24 mg/dL had the greatest risk of exchange transfusion (OR = 26.6; 95% CI = 4.6, 153.7). Other factors including hemolysis, weight loss more than 10% of birth weight on readmission, time to phototherapy of more than 15 minutes, and age at readmission of more than 5 days were no statistical increase risk of exchange transfusion (Table 4).

Table 1. Causes of neonatal hyperbilirubinemia

Causes	Number (%)
Breast feeding jaundice	36 (47.4)
Cephalhematoma	8 (10.5)
ABO incompatibility*	6 (7.9)
G6PD deficiency	6 (7.9)
Sepsis (proven or suspected sepsis)	5 (6.6)
Minor blood group incompatibility*	2 (2.6)
Hypothyroid	2 (2.6)
Red cell membrane defect	1 (1.3)
Unidentified	10 (13.2)

* Positive direct Coombs test and hemolytic findings on peripheral blood smear
G6PD = glucose-6-phosphate dehydrogenase deficiency

Table 2. Comparison baseline characteristics between infants required phototherapy (phototherapy group) and those who underwent exchange transfusion (exchange transfusion group)

Characteristics	Phototherapy group (n = 68)	Exchange transfusion group (n = 8)	*p*-value
Gestational age (week), mean (SD)	37.8 (1.2)	37.8 (1.7)	0.95
Male, n (%)	37 (48.6)	5 (62.5)	0.66
Birth weight (gm), mean (SD)	2,969 (622.6)	3,187 (413.2)	0.36
Normal delivery, n (%)	41 (53.9)	4 (50.0)	0.57
Exclusive breastfeeding, n (%)	57 (75.0)	8 (100)	0.47
Apgar score, median (range)			
At 1 min	9 (8-9)	9 (6-9)	0.18
At 5 min	10 (10-10)	10 (9-10)	0.20

Table 3. Comparison data during readmission between the two groups

	Phototherapy group (n = 68)	Exchange transfusion group (n = 8)	*p*-value
Peak MB (mg/dL), mean (SD)	21.2 (1.8)	25.0 (2.9)	<0.001
Sepsis, n (%)	0 (0)	3 (37.5)	<0.001
Cephalhematoma, n (%)	8 (11.7)	0 (0)	0.34
Weight loss ≥10%, n (%)	8 (10.5)	2 (25.0)	0.29
Time to phototherapy (min), median (range)	9 (3-40)	9 (5-25)	0.90
Length of stay (days), median (range)	2 (1-12)	9 (2-15)	<0.001
Age at readmission (day), median (range)	6 (2-12)	7 (4-18)	0.28

MB = microbilirubin

Table 4. Univariate logistic regression analysis for exchange transfusion

	Exchange transfusion group n (%)	Phototherapy group n (%)	Odds ratio	95% CI	*p*-value
Hemolysis	3 (37.5)	12 (17.6)	2.8	0.6-13.3	0.18
Age at readmission ≥5 days	6 (75.0)	47 (69.1)	1.3	0.2-7.1	0.73
Peak MB ≥24 mg/dL	5 (62.5)	4 (6.2)	26.6	4.6-153.7	<0.001
Weight loss ≥10%	2 (25.0)	8 (10.5)	2.5	0.4-14.5	0.29
Time to phototherapy ≥15 minutes	4 (50.0)	31 (45.5)	1.2	0.3-5.1	0.81

Seven infants who underwent exchange transfusion had complications associated with the procedure. Four infants had venous hematocrit lower than 42% (anemia) and three infants had fever (temperature more than 37.8°C) after exchange transfusion including one infants had *Staphylococcus aureus* septicemia, necrotizing enterocolitis, and thrombocytopenia. Others complication included hypotension during procedure, hypocalcemia, and hyperkalemia.

Discussion

These results have demonstrated that infants who are readmitted with high levels of bilirubin (more than 20 mg/dL) continue to be a challenge in our hospitals. Fortunately, we achieved our goal of initiating phototherapy within an hour of admission for every infant. The main value of phototherapy is to reduce the risk that serum bilirubin levels will reach the level of exchange transfusion. However, eight infants (10.5%) underwent exchange transfusion with the mean peak bilirubin level of 25.0±2.9 mg/dL at presentation. The most common causes of hyperbilirubinemia were breastfeeding jaundice and blood group incompatibility, which are different from the study of Sgro M and Manning DM who founded that the common causes were ABO incompatibility and glucose-6-phosphate dehydrogenase deficiency (G6PD)[4,15]. The explanation for this is that our hospital has high rates of mothers, who exclusively breastfeeding with early discharge. Breastfeeding jaundice plays a prominent role in infants for whom there is no other etiologic causes for hyperbilirubinemia, which is consistent with the report by Bjerre JV[16].

None of our infants had abnormal neurological signs at discharge. Possibilities are that neurological signs from bilirubin toxicity may be transient, and that early aggressive treatment is effective in lowering bilirubin level as a result of the Jaundice Fast-track System. Although our study was not designed to assess the incidence of long-term neurological disease, follow-up study is warranted to estimate the effect of bilirubin toxicity and its associated morbidity.

The authors' results raise concern that every effort should be made to identify an infant at risk of developing severe hyperbilirubinemia before they are discharged. Health care personnel should follow the guidelines that promote and support successful breastfeeding by providing appropriate support and advice, including how to assess the adequacy of intake in the breastfed infant, and providing appropriate follow-up based on the time of discharge and the risk assessment.

The main limitation in this research was the low number of infants who underwent exchange transfusion. A larger study is needed to determine the differences between the two groups.

Conclusion

One of the greatest, but preventable, challenges in our department continues to be infants who are readmitted with severe hyperbilirubinemia. To prevent these infants from bilirubin toxicity, it must be assessed as a medical emergency with immediate attention to lowering the bilirubin level by early aggressive and effective treatment. The present study has demonstrated that initiating phototherapy within an hour of admission is highly effective in preventing bilirubin encephalopathy. The physician's early recognition of the risk factors for exchange transfusion is crucial.

Acknowledgement

The authors wish to thank all pediatric residents and clinical staff members at Thammasat University Hospital who cared for these infants. The infants and their family members who took part in the present study are highly appreciated for their contribution. Doctor Chayanton Pathumanon and Saowarat Kaewjaiyen for their assistance in statistical analysis.

Potential conflicts of interest

None.

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ผลการรักษาด้วยการส่องไฟอย่างเร่งด่วนในทารกที่มีภาวะตัวเหลืองรุนแรงที่โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ

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วัตถุประสงค์: ศึกษาสาเหตุของภาวะตัวเหลืองรุนแรง ปัจจัยที่มีผลต่อการเปลี่ยนถ่ายเลือด และผลการรักษาในทารกแรกเกิดที่กลับมา readmit ภายในสัปดาห์แรกของชีวิตที่โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ ด้วยปัญหาตัวเหลืองรุนแรงและเข้ารับการรักษาในโครงการส่องไฟอย่างเร่งด่วน (Jaundice Fast-track System)

วัสดุและวิธีการ: ผู้นิพนธ์ได้ทำการศึกษาย้อนหลังในทารกแรกเกิดที่กลับมา readmit ภายในสัปดาห์แรกของชีวิต ที่โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ ด้วยปัญหาตัวเหลืองรุนแรง และเข้ารับการรักษาในโครงการการส่องไฟอย่างเร่งด่วน (Jaundice Fast-track System) ระหว่างวันที่ 1 ตุลาคม พ.ศ. 2554 ถึง วันที่ 30 กันยายน พ.ศ. 2556

ผลการศึกษา: ทารก 76 ราย มี 1 ราย ที่มีอาการทางระบบประสาทขณะ readmit ทารกทุกรายได้รับการรักษาด้วย intensive phototherapy ทารก 8 ราย (ร้อยละ 10.5) ต้องการการรักษาด้วยการเปลี่ยนถ่ายเลือด สาเหตุของภาวะตัวเหลืองพบว่า breastfeeding jaundice เป็นสาเหตุที่พบมากที่สุด (ร้อยละ 47) รองลงมาได้แก่ cephalhematoma blood group incompatibility และ G6PD deficiency ร้อยละ 10.5 ร้อยละ 10.5 และร้อยละ 7.8 ตามลำดับ ทารกกลุ่มที่ได้รับการเปลี่ยนถ่ายเลือดมีค่า mean peak MB สูงกว่ากลุ่มที่ได้รับการส่องไฟอย่างมีนัยสำคัญทางสถิติ (25.0±2.9 mg/dL vs. 21.2±1.8 mg/dL, $p<0.001$) ไม่พบการติดเชื้อในกระแสโลหิต (sepsis) ขณะ readmit ในทารกกลุ่มที่ได้รับการรักษาด้วยการส่องไฟ แต่พบ 3 ราย ในทารกกลุ่มที่ต้องรับการเปลี่ยนถ่ายเลือด ทารกที่ได้รับการวินิจฉัยว่าเป็น cephalhematoma ไม่มีรายใดที่ต้องรักษาด้วยการเปลี่ยนถ่ายเลือด และพบ length of stay นานกว่าในทารกกลุ่มที่ต้องรับการเปลี่ยนถ่ายเลือด (9 (2-15) days vs. 2 (1-12) days, $p<0.001$) ไม่พบความแตกต่างของ age at readmission และ time to phototherapy ในทารกทั้งสองกลุ่ม ทารกทุกรายมีอาการทางระบบประสาทปกติก่อนจำหน่ายออกจากโรงพยาบาล ปัจจัยที่พบว่าเพิ่มโอกาสการเปลี่ยนถ่ายเลือดคือ ค่า peak MB ที่สูงกว่าหรือเท่ากับ 24 mg/dL โดยมีค่า odds ratio เท่ากับ 26.6 (95% CI = 4.6, 153.7)

สรุป: แพทย์ควรทราบถึงปัจจัยที่เพิ่มโอกาสการเปลี่ยนถ่ายเลือดในทารกที่กลับมา readmit ด้วยปัญหาตัวเหลืองรุนแรง และควรให้การรักษาด้วยการส่องไฟอย่างเร่งด่วนและถ่ายเปลี่ยนเลือดเมื่อมีข้อบ่งชี้