Exchange Transfusion and its Morbidity in Ten-Year Period at King Chulalongkorn Hospital

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The objectives of this study were to consider the rate of exchange transfusion (ET) in the newborns at King Chulalongkorn Hospital, Bangkok, from 1994 to 2003, and to evaluate its morbidity and mortality.

One hundred and sixty five neonates underwent 183 episodes of ET. In-housed fullterm had ET performed at a younger age than the readmitted/referred infants (72.2 ± 30.9 vs 150.2 ± 90.7 hours, $p < 0.001$), and the in-housed preterm neonates (85.4 ± 36.7 hours, $p < 0.05$). They also had lower mean TsB than those of the readmitted/referred infants when ET was initiated (21.8 ± 2.1 vs.26.0 ± 5.1 mg/dL, $p < 0.001$). Preterm needed phototherapy after ET longer than fullterm neonates (5.3 ± 3.2 vs 3.3 ± 1.7 days, $p < 0.001$). ABO incompatibility (21.3%), G6PD deficiency (13.4%), both conditions (6.7%), and others (22.2%) were identified as causes of hyperbilirubinemia. Unknown causes accounted for 36.4%. There was no mortality in the present study. Overall rate of morbidity was 15.3% of which 67 percent was infection associated conditions. Preterm suffered additional complications of anemia, apnea and cardiac arrest. Sick infants (31.3%) were more likely to develop complications than healthy ones (6.8%). In the healthy group, preterm were more likely to develop morbidity than fullterm neonates ($p = 0.0016$), while no significant difference was identified between them in the sick group ($p = 0.8$).

ET causes high morbidity, therefore, it should be initiated only when the benefit of preventing kernicterus outweighs the complications associated with the procedure.

Keywords: *Neonatal hyperbilrubinemia, Kernicterus, Exchange transfusion, Morbidity, Mortality*

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Neonatal hyperbilirubinemia is known to cause bilirubin encephalopathy or kernicterus if total serum bilirubin (TsB) level rises to a certain level[1,2]. Identification of infants at risk[3,4] and screening of bilirubin levels at various ages have been proposed[5,6]. Phototherapy and exchange transfusion (ET) are used to lower TsB. The level at which treatment should be initiated has been subjected to change[7]. Treatment is usually started with phototherapy. When the bilirubin continues rising, instead of declining, to the level that kernicterus is considered a threat, then exchange transfusion is considered. Morbidity and mortality have been reported in association with the procedure[8,9].

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The objectives of this study were to consider the rate of ET in the past 10 years and to evaluate the morbidity and mortality associated with the procedure.

Material and Method

The medical records of infants ≤ 28 days old with the codes of ET and neonatal jaundice in King Chulalongkorn Hospital, Bangkok, from January 1994 to December 2003 were retrospectively reviewed. ABO incompatibility was defined as an infant's blood type A or B with type O mother, regardless of the Coomb's test. Rh or minor blood group incompatibility was defined as different maternal-infant antigens and positive direct Coomb's test. An infant was considered healthy if jaundice was the only problem, as opposed to sick if there was an ongoing illness that required treatment prior to or at the same time ET was done. The morbidity and mortality caused by each ET was defined as complications which occurred

within 7 days of the procedure. All episodes of complication were recorded to identify the effect of maturity (fullterm or preterm) and ongoing illness towards morbidity and mortality, using Chi-square test or Fisher exact test (Epi Info 3.2). Data from fullterm (> 37 weeks of gestational age) and preterm (≤ 37 weeks gestational age) as well as referred/readmitted vs in-housed, were determined separately. Percentage, mean, standard deviation and Wilcoxon W test were then analyzed.

Results

During 1994-2003, 165 hyperbilirubinemic newborn infants, for whom phototherapy had failed to keep TsB from reaching the levels recommended by AAP[7] and clinical practice guideline of the unit[10], underwent two-blood-volumed exchange transfusions. Twenty eight (28) infants were readmitted from home after being discharged from the normal newborn nursery or referred from other hospitals (23 fullterm and 5 preterm infants), and 137 infants were in the neonatal ward during their postnatal period (97 fullterm and 40 preterm infants). Repeated ET from 1-4 times totaled the episodes to 183 (Table 1). In-housed fullterm infants had ET performed at a younger age than the referred/readmitted ones (72.2 ± 30.9 vs 150.2 ± 90.7 hours, $p < 0.001$), and the in-housed preterm neonates (85.4 ± 36.7 hours, $p < 0.05$) (Table 1). TsB levels at which ET was initiated were significantly lower in the in-housed fullterm neonates compared with those of the referred/ readmitted ones (21.8 ± 2.1 vs 26.0 ± 5.1 mg/dL, $p < 0.001$). Comparison was not done in the preterm group due to the small number of the referred/readmitted infants. Comparing preterm and fullterm infants, preterm needed phototherapy after ET for a longer period than fullterm infants to lower their TsB to the safety levels (5.3 ± 3.2 vs 3.3 ± 1.7 days, $p < 0.001$).

The causes of neonatal hyperbilirubinemia that necessitated ET included ABO incompatibility (21.3%), G6PD deficiency (13.4%), both conditions (6.7%), prematurity (8.4%), others (13.8%), and unidentified causes (36.4%) (Table 2). Thirty five (35) of the total 46 cases of ABO incompatibility had Coomb's tests done, and 15 of them were Coomb's positive.

There was no death attributed to the procedure. Morbidity was identified in 9 fullterm and 14 preterm neonates who suffered a total of 28 adverse conditions from 183 procedures (15.3%) (Table 3). Infection associated problems, such as omphalitis, septicemia, etc. accounted for 67% of these cases. Additional serious complications such as anemia, apnea and cardiac arrest occurred in the preterm only (Table 3). All morbidity were observed within 1-3 days after ET, except necrotizing enterocolitis (NEC) which was diagnosed in day 4-5 following the procedure. Three fullterm and 2 preterm infants who were referred from other hospitals were noted to have lethargy, hypotonia, absent or decreased Moro's reflex and not sucking well. Their maximum TsB levels were 27-29 mg/dL. All neurological abnormalities disappeared after ET was done. Oral feeding was resumed and their hospital courses were similar to the others. Follow up data was not available but there was no infant admitted for the treatment of kernicterus during this 10 year period.

Fifteen of 48 infants (31.3%) who had ongoing illness at the time of ET developed adverse conditions, while the rate in healthy newborns was only 6.8% (8 in 117, Table 4). Stratifying the data in healthy and sick infants, a healthy preterm was more likely to develop morbidity than a fullterm infant

Table 1. Demographic data, ages and serum bilirubin levels at the time of exchange transfusion

	Referred/readmitted		In-housed	
	Fullterm	Preterm	Fullterm	Preterm
Number (n = 165)	23	5	97	40
Male:Female	13:10	5:0	51:46	19:21
Body weight (gram)	2,891±402 (2,400-3,700)	2,108±694 (1,180-2,700)	3,063±457 (1,690-4,390)	1,741±642 (760-3,050)
Gestational age (week)	39.8±0.7 (38-41)	34.2±2.4 (30-36)	39.7±0.7 (38-41)	33.4±3.0 (27-37)
Number of exchange transfusion (n = 183)	25	5	102	51
Age at the time of exchange transfusion (hr)	150.2±90.7 (33-384)	148.8±46.2 (96-216)	72.2±30.9 (19-216)	85.4±36.7 (25-216)
Bilirubin level when exchange transfusion was initiated (mg/dL)	26.0±5.1 (21-35)	22.2±5.8 (16-28)	21.8±2.1 (15-30)	16.5±4.2 (7-27)

Table 2. Causes of hyperbilirubinemia that necessitated exchange transfusion

Causes	n = 165	%
ABO incompatibility	35	21.3
G6PD deficiency	22	13.4
Prematurity	14	8.4
ABO incompatibility with G6PD deficiency	11	6.7
Polycythemia	6	3.6
Breast feeding	6	3.6
Rh incompatibility	5	3.0
Cephalhematoma	4	2.4
Minor blood group incompatibility	2	1.2
Unidentified causes	60	36.4

Table 3. Morbidity associated with exchange transfusion

Morbidity	Fullterm (n = 9)	Preterm (n = 14)	Total (%)
Omphalitis/infected wound	3	6	9 (32.2)
Septicemia	1	3	4 (14.3)
NEC	1	1	2 (7.1)
Pneumonia	2	0	2 (7.1)
Diarrhea	2	0	2 (7.1)
Anemia	0	7	7 (25)
Apnea	0	1	1 (3.6)
Cardiac arrest	0	1	1 (3.6)
Total	9	19	28 (100)

(NEC: necrotizing enterocolitis)

(p = 0.0016), while there was no difference between them in the sick group (p = 0.8) (Table 4).

Discussion

In the neonatal unit, in-housed infants are monitored for jaundice, and treated when TsB reach the levels considered to be a threat to their brains, according to AAP practice parameter and later the clinical practice guideline developed by the staff of the unit. For the referred/readmitted infants, time has elapsed before an abnormality is noticed and action taken. Thus ET is usually performed at a later age and at higher TsB level than the previous group.

Premature infants are considered to be vulnerable to bilirubin encephalopathy or kernicterus. To prevent any bilirubin related neurodevelopmental abnormalities, several guidelines have been provided for intervention in various circumstances[11]. All suggest treatment of preterm at lowered TsB levels[7,11] which is also the practice followed in the present study. Repeated ET is, therefore, more frequent in preterm (56 procedures in 45 infants) than in fullterm (127 in 120 infants) (Table 1) in order to keep TsB from rising above the recommended levels. Preterm has a more protracted course of hyperbilirubinemia than fullterm neonates[12], as shown in the present study that they required phototherapy for a longer period of time. Many factors may be responsible for the slow decline of TsB, such as hepatic and gastrointestinal immaturity and delayed enteral feeding which enhances enterohepatic circulation[12].

In the present study, ABO incompatibility and G6PD deficiency accounted for 38.8% of the identified causes of hyperbilirubinemia. No definite causes were discovered in one third of the cases (60 cases, 36.4%). Breast milk can be the sole cause of hyperbilirubinemia. Newman, et al showed that 7 of 11 neonates whose TsB were 30.7-45.5 mg/dL were exclusively breast fed[13]. Six infants (3.6%) in the present study had breastfeeding as the only risk factor for their hyperbilirubinemia. All were fullterm or nearterm neonates readmitted at more than 5-7 days old. Although there is no recommendation for breast milk jaundice to be treated with ET, all these infants presented with high TsB between 27-32 mg/dL and ET was performed immediately before other investigations disclosed no specific causes.

There was no mortality related to ET in the present study. The most serious complication was a cardiac arrest in a very low birthweight preterm infant

Table 4. Morbidity associated with exchange transfusion in healthy and sick fullterm and preterm infants

	Morbidity (case)	Without morbidity (case)	Total (case)
Fullterm	3	97	100
Preterm	5	12	17
Total (case)	8	109	117

A. Healthy infants

p = 0.0016 (Chi-square, Fisher exact test)

	Morbidity (case)	Without morbidity (case)	Total (case)
Fullterm	6	14	20
Preterm	9	19	28
Total (case)	15	33	48

B. Sick infants

p = 0.8 (Chi-square, Fisher exact test)

who also suffered from apnea of prematurity. Resuscitation was successful but he developed septicemia following the second ET. The rate of morbidity was as high as 15.3%, which was similar to the 16% rate of combined death, permanent serious sequelae and serious prolonged complications studied by Jackson[8]. Infection associated conditions in both fullterm and preterm infants necessitated aseptic technique to be strictly observed during the procedure and prompt initiation of treatment should signs and symptoms appear. Anemia and apnea were identified in the preterm only. ET might not be solely responsible for these latter conditions, since preterm infants required frequent blood tests that could cause anemia of which presenting symptom is apnea.

Kernicterus in the healthy fullterm and near-term infants is rare[14]. There was no kernicterus in the present study. Five infants might be considered to enter phase 1 of acute form of clinical kernicterus with the manifestations of poor sucking, stupor and hypotonia[15], but the abnormalities disappeared after ET.

Sick infants seemed to suffer complications more than healthy ones (31.3% vs 6.8%) which was similar to the study of Jackson[8]. In the group of sick infants, there was no difference between fullterm and preterm in developing morbidity ($p = 0.8$). The ongoing illness was possibly severe enough to deteriorate their clinical conditions regardless of any additional procedure. In contrast, preterm infants in the healthy group were more likely to develop morbidity than fullterm ($p = 0.0016$). This was probably because the circulatory change during the procedure was an added burden to the already existing physiological instability of prematurity. The purpose of ET is to decrease TsB to a level that potential damage to the brain is unlikely although the specificity of the level is so far unknown. Bilirubin is not considered to be a single cause of kernicterus in prematurity. Duration of exposure to high TsB, rate of rising and free bilirubin have been suggested to be of importance to bilirubin encephalopathy[16]. Furthermore, the rate of ET has dramatically dropped recently that raises a concern about possible adverse consequences from inexperienced personnel performing the procedure[9]. With this uncertainty and high rate of morbidity, initiation of ET, especially in preterm infants, should be considered carefully. It should be individualized and take into consideration the risk, benefit and the specific condition of that particular patient.

The limitation of the present study is its retrospective nature and the small sample size of the sick infants. Generalization is therefore restricted to the population similar to this setting.

Conclusion

Despite being an effective method in decreasing TsB level after failing phototherapy, ET remains an invasive procedure with associated morbidity as high as 15%. There is no difference in developing morbidity between sick preterm and fullterm infants, but it is significantly greater in healthy preterm when compared to their fullterm counterpart. ET should be considered only when the benefit of decreasing TsB level to prevent kernicterus outweighs the complications associated with the procedure.

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Abbreviations

TsB: total serum bilirubin, ET: exchange transfusion

References

1. Maisels MJ. Jaundice. In: Avery GB, Fletcher MA, Mac Dounald MS, eds. Neonatology. Pathophysiology and management of the newborn 5th ed. Philadelphia: LW & W, 1999: 765-819.
2. Phaosavasdi S, Uerpairojkit B, Thamkhantho M, Prugsapong C, Karnjanapitak A. Medical ethics on the year of neonatal jaundice campaign. J Med Assoc Thai 2004; 87: 1539-41.
3. Stevenson DK, Fanaroff AA, Maisels MJ, Young BWY, Wong RJ, Vreman HJ, et al. Prediction of hyperbilirubinemia in near-term and term infants. Pediatrics 2001; 108: 31-9.
4. Phuapradit W, Chaturachinda K, Auntlamai S. Risk Factors for neonatal hyperbiliribinemia. J Med Assoc Thai 1993; 76: 424-8.
5. Sanpavat S, Nuchprayoon I. Noninvasive transcutaneous bilirubin as a screening test to identify the need for serum bilirubin assessment. J Med Assoc Thai 2004; 87: 1193-8.
6. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics 1999; 103: 6-14.
7. American Academy of Pediatrics, Provisional committee for quality improvement and subcommitte on hyperbilirubinemia. Practice parameter: Management of hyperbilirubinemia in the healthy term newborn. Pediatrics 1994; 94: 558-65.

8. Jackson JC. Adversed events associated with exchange transfusion in healthy and Ill newborns. Pediatrics 1997; 99: e7.
9. Patra K, Storfer-Isser A, Siner B, Moore J, Hack M. Adverse events associated with neonatal exchange transfusion in the 1990. J Pediatr 2004; 144: 626-31.
10. Sanpavat S. Neonatal Jaundice. In: Choteleosak V, Jongsrisawat B, Chatjatree P, Deerojvong J, Parbpal N, eds. Common pediatrics problems and treatment. Bangkok: Text and General Publication; 2002: 245-53.
11. Maisels MJ, Watchko JF. Treatment of jaundice in low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2003; 88: F459-63.
12. Watchko JF, Maisels MJ. Jaundice in low birthweight infants: Pathobiology and outcome. Arch Dis Child Fetal Neonatal Ed 2003; 88: F455-8.
13. Newman TB, Liljestrand P, Escobar GJ. Infants with bilirubin levels of 30 mg/dL or more in a large managed care organization. Pediatrics 2003; 111: 1303-11.
14. Ip S, Chung M, Kulig J, O'Brien R, Sege R, Glicken S, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics 2004; 144: e130-53.
15. Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. N Engl J Med 2001; 344: 581-90.
16. Watchko J, Oski FA. Kernicterus in preterm newborns: Past, present, and future. Pediatrics 1992; 90: 707-15.

ประสบการณ์ 10 ปี การถ่ายเลือดและภาวะแทรกซ้อนที่โรงพยาบาลจุฬาลงกรณ์

สุวิมล สรรพวัฒน์

การศึกษานี้เป็นการหาอัตราการถ่ายเปลี่ยนเลือด (ET) ที่ทำในทารกแรกเกิดในโรงพยาบาลจุฬาลงกรณ์ กรุงเทพฯ ระหว่าง พ.ศ. 2537 ถึง 2546 และศึกษาภาวะแทรกซ้อนที่เกิดขึ้น

ทารกจำนวน 165 คน ได้รับการรักษาด้วย ET รวม 183 ครั้ง ทารกคลอดครบกำหนดที่ยังพักอยู่ในหน่วยทารกแรกเกิดได้รับการรักษาเร็วกว่ากลุ่มที่รับใหม่/รับย้าย (อายุ 72.2 $\pm$ 30.9 ต่อ 150.2 $\pm$ 90.7 ชั่วโมง, $p < 0.001$) และเร็วกว่าทารกคลอดก่อนกำหนดที่ยังอยู่ในหน่วย (85.4 $\pm$ 36.7 ชั่วโมง, $p < 0.05$) ระดับบิลิรูบิน (TsB) ขณะทำ ET ของทารกคลอดครบกำหนดในหน่วย มีระดับต่ำกว่ากลุ่มที่รับใหม่/รับย้ายอย่างมีนัยสำคัญทางสถิติ (21.8 $\pm$ 2.1 ต่อ 26.0 $\pm$ 5.1 mg/dL, $p < 0.001$) หลังการถ่ายเปลี่ยนเลือด ทารกคลอดก่อนกำหนดต้องรักษาด้วยแสง (phototherapy) ต่อนานกว่าทารกคลอดครบกำหนด (5.3 $\pm$ 3.2 ต่อ 3.3 $\pm$ 1.7 วัน, $p < 0.001$) สาเหตุของภาวะตัวเหลืองในกลุ่มศึกษาคือ ABO incompatibility (21.3%), G6PD deficiency (13.4%) ทั้งสองภาวะ (6.7%) อื่นๆ (22.2%) และตรวจไม่พบสาเหตุ 36.4% ในการศึกษานี้ ไม่มีทารกเสียชีวิต อัตราการเกิดภาวะแทรกซ้อนเท่ากับร้อยละ 15.3 ซึ่งร้อยละ 67 เป็นภาวะที่เกิดร่วมกับการติดเชื้อ ภาวะซีด หยุดหายใจและหัวใจหยุดเต้นพบเฉพาะในทารกคลอดก่อนกำหนด ทารกที่ป่วยด้วยโรคอื่นในขณะทำ ET (31.3%) จะเกิดภาวะแทรกซ้อนมากกว่าทารกที่สุขภาพแข็งแรง (6.8%) ในการแยกวิเคราะห์กลุ่มทารกที่มีสุขภาพแข็งแรงขณะทำ ET ทารกคลอดก่อนกำหนดมีโอกาสเกิดภาวะแทรกซ้อนมากกว่าทารกครบกำหนด ($p = 0.0016$) แต่ไม่พบความแตกต่างกันถ้าทารกป่วยอยู่แล้วขณะทำหัตถการ ($p = 0.8$)

การถ่ายเปลี่ยนเลือดทำให้เกิดภาวะแทรกซ้อนได้มาก จึงควรตัดสินใจทำเมื่อประโยชน์จากการป้องกัน Kernicterus มากกว่าผลเสียที่เกิดจากการทำหัตถการเท่านั้น