Intensive phototherapy *vs.* exchange transfusion for the treatment of neonatal hyperbilirubinemia: a multicenter retrospective cohort study

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Abstract

Background: Intensive phototherapy (IPT) and exchange transfusion (ET) are the main treatments for extreme hyperbilirubinemia. However, there is no reliable evidence on determining the thresholds for these treatments. This multicenter study compared the effectiveness and complications of IPT and ET in the treatment of extreme hyperbilirubinemia.

Methods: This retrospective cohort study was conducted in seven centers from January 2015 to January 2018. Patients with extreme hyperbilirubinemia that met the criteria of ET were included. Patients were divided into three subgroups (low-, medium-, and high-risk) according to gestational week and risk factors. Propensity score matching (PSM) was performed to balance the data before treatment. Study outcomes included the development of bilirubin encephalopathy, duration of hospitalization, expenses, and complications. Mortality, auditory complications, seizures, enamel dysplasia, ocular motility disorders, athetosis, motor, and language development were evaluated during follow-up at age of 3 years.

Results: A total of 1164 patients were included in this study. After PSM, 296 patients in the IPT only group and 296 patients in the IPT plus ET group were further divided into the low-, medium-, and high-risk subgroups with 188, 364, and 40 matched patients, respectively. No significant differences were found between the IPT only and IPT plus ET groups in terms of morbidity, complications, and sequelae. Hospitalization duration and expenses were lower in the low- and medium-risk subgroups in the IPT only group.

Conclusions: In this study, our results suggest that IPT is a safe and effective treatment for extreme hyperbilirubinemia. The indication of ET for patients with hyperbilirubinemia could be stricter. However, it is necessary to have a contingency plan for emergency ET as soon as IPT is commenced especially for infants with risk factors. If IPT can be guaranteed and proved to be therapeutic, ET should be avoided as much as possible.

Keywords: Neonatal hyperbilirubinemia; Exchange transfusion; Intensive phototherapy

Introduction

Neonatal hyperbilirubinemia, which presents as jaundice, is the most common clinical condition that affects newborns. Hyperbilirubinemia affects approximately 60% of full-term and 80% of preterm neonates.[1] Approximately, 10% of newborns are likely to develop clinically significant hyperbilirubinemia that requires close monitoring and treatment.[2] Extreme hyperbilirubinemia is defined as having a bilirubin concentration that is at the exchange transfusion (ET) threshold or showing signs of bilirubin encephalopathy (BE).[2] Extreme hyperbilirubinemia can lead to BE, which is associated with risks of neonatal mortality, cerebral palsy, auditory complications, and long-term neurodevelopmental impairments.[3] In the early neonatal period (0–6 days), neonatal hyperbilirubinemia accounts for 1309 deaths per 100,000 live births. It

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is also the seventh most common cause of neonatal death.[4]

Intensive phototherapy (IPT) and ET are the main treatments for hyperbilirubinemia. Evidence has shown that phototherapy is effective and can reduce the need for ET.[5] However, there is no reliable evidence on the optimal thresholds for phototherapy or ET in neonates with hyperbilirubinemia.[6] Most guidelines state that the ET threshold curve is adapted from the American Academy of Pediatrics (AAP).[7] However, the threshold suggested by the AAP is backed by the consensus of a committee and not by evidence from clinical research. In clinical practice, some patients with extreme hyperbilirubinemia, especially in developing countries, are treated with IPT instead of ET based on the consent of their parents. Although the bilirubin levels of these patients may be higher than the ET threshold according to the AAP guideline, they can be effectively reduced to a normal level using IPT.

We conducted a multicenter study to compare the effectiveness and complications of IPT and ET for the treatment of extreme hyperbilirubinemia using propensity score matching (PSM). Propensity score methods are becoming increasingly popular for reducing potential confounding factors in observational studies that compare the effectiveness of healthcare interventions.[8] In this study, we compared the effectiveness and complications of IPT and ET and evaluated the ET threshold to provide evidence for the treatment of extreme hyperbilirubinemia.

Methods

Ethics approval

This study was approved by the institutional Ethics Review Board of West China Second Hospital, Sichuan University (No. 2021013).

Patients and study design

We conducted a retrospective cohort study in seven centers from January 2015 to January 2018. Six of the seven centers were tertiary centers, whereas one was a secondary center. The inclusion criteria were as follows: (1) patients with gestational age >35 weeks and (2) patients with extreme hyperbilirubinemia that met the criteria for ET according to the expert consensus of the Chinese Pediatric Society in 2014.[9] The threshold curve for ET was the same as that outlined in the AAP guideline.[7] The exclusion criteria were as follows: (1) patients with hypoxic-ischemic brain injury, hypoglycemic brain injury, intracranial infection, congenital genetic metabolic diseases, chromosome abnormalities, and severe congenital malformations, such as severe congenital heart disease, digestive tract malformation, congenital biliary atresia, etc.; (2) patients with incomplete data; and (3) patients lost to follow-up.

According to the AAP guideline, ET is recommended if the total serum bilirubin (TSB) level of a patient does not decrease and is still higher than the ET threshold after 4–6 hours of IPT. In addition, ET is recommended for patients with clinical manifestations of acute BE. The written consent of a parent is required before ET can be performed. If the parents refuse, IPT should be continued. The ET threshold used in this study was based on the risk factors and gestational age recommended by AAP.[7] All the included patients were categorized into an IPT or IPT plus ET group according to the treatment they received. The patients in each group were further divided into the low-risk group (gestational age ≥38 weeks and no risk factors), medium-risk group (gestational age ≥38 weeks with risk factors or 35–37 weeks gestational age without risk factors), and high-risk group (35–37 weeks gestational age with risk factors) according to the AAP guidelines. Risk factors included isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase deficiency, asphyxia, significant lethargy, temperature instability, sepsis, and acidosis.[7]

Treatment

Phototherapy instruments and phototherapy boxes with light-emitting diodes (LEDs) (450–480 nm) were used for continuous phototherapy. The irradiance delivered by the IPT instrument was $>30\ \mu W \cdot cm^{-2} \cdot nm^{-1}$. The distance from the light source to the baby was 40 cm. Patients were placed in the supine position with protection for the eyes and perineum. TSB measurements were repeated 4–6 hours after IPT was initiated. When the TSB level dropped to 50 μmol/L (approximately 3 mg/dL), that is, below the ET threshold, the treatment was stepped down to conventional phototherapy. The irradiance delivered by the conventional phototherapy instrument was $8–10\ \mu W \cdot cm^{-2} \cdot nm^{-1}$. TSB was measured every 4–6 hours after conventional phototherapy was initiated. When the TSB level dropped to 50 μmol/L below the IPT threshold, conventional phototherapy was stopped.[9]

Automatic peripheral arteriovenous ET with a speed of $50–80\ mL \cdot kg^{-1} \cdot h^{-1}$ was used for ET. The volume to be exchanged was twice the patient's total blood volume (150–160 mL/kg). Reconstituted packed red blood cells and fresh frozen plasma in a ratio of 3:1 were used. TSB levels were measured before and after ET. IPT was continued immediately after ET.

Outcome and follow-up

The primary outcome of this study was the development of BE at discharge, including BE diagnosis before, during, and after treatment. The diagnosis of BE was mainly based on typical clinical nervous system manifestations. Brain magnetic resonance imaging and the auditory brainstem response test can facilitate the diagnosis of BE. The secondary outcomes of this study included hospital readmission within 2 weeks, duration of hospitalization, expenses, and complications. Complications of both ET and IPT included gastrointestinal hemorrhage, sepsis, fever, bronze infant syndrome, diarrhea, and eruptions.

Follow-up was conducted at age of 3 years for all patients using the online medical follow-up system of West China Second Hospital by telephone or text message. Mortality, auditory complications, seizures, enamel dysplasia, ocular motility disorders, were evaluated using questionnaires.

Motor and language development were evaluated using the Chinese version of the Gesell Development Diagnosis Scale.[10] The follow-up questionnaire is outlined in the supplementary material, http://links.lww.com/CM9/A913.

PSM and statistical analysis

The propensity score was calculated by fitting a logistic regression model. The covariates included age, sex, gestational age, birth weight, weight on admission, age at onset, feeding type (breast milk, formula, or mixed feeding), mode of delivery (vaginal or cesarean), TSB level, albumin use, and signs of BE on admission. Once the propensity score had been estimated for each patient, patients treated with ET plus IPT and only IPT were matched on the propensity score. Nearest-neighbor matching within a specified caliper width was used. With this method, the first randomly selected patient in ET group was matched to the patient in IPT only group with the closest propensity score within a specified range (the caliper width). If multiple patients in IPT only group are equally close to this patient in ET group, then one of the patients in IPT only group is randomly selected for matching to this patient treated in ET group. This process is repeated until all possible matches have been formed. If for a given patient in the ET group, no available patient in IPT only group lies within the specified caliper width, then that patient in ET group is excluded from the matched sample. Similarly, unmatched patients in IPT only group are excluded from the matched sample.[8] In our study, propensity scores were used to match patients treated with ET to patients treated with IPT within a caliper of 0.2 standard deviations of the logit function of the propensity scores. Patients in IPT plus ET group and IPT only group were matched at a ratio of 1:1. The covariate imbalance was compared before and after matching the comparison groups. The descriptive characteristics of the study population and propensity-score-matched subpopulations are presented as means and standard deviations for continuous data and as numbers and percentages for categorical data. PSM was conducted using the R software version 4.0.2 (R Core Team, Vienna, Austria).

Patients were statistically extracted from each group after PSM. McNemar's and Wilcoxon matched-pairs signed-ranks tests were used for the comparisons of the categorical and continuous variables of the matched groups, respectively. Multivariable logistic analysis was performed in all patients to explore whether there are differences in efficacy and safety among different interventions after adjusting for other factors. A P value < 0.05 was considered significant. Statistical analyses were performed using SPSS software (version 24.0; SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of the study population

A total of 1556 patients with extreme hyperbilirubinemia met the criteria for ET; 121 patients were excluded because their data were incomplete, and 271 (17.4%) patients were lost to follow-up. Of the remaining 1164 patients, 699 were in the IPT only group and 465 in the IPT plus ET group. With regard to the subgroups, 279 patients in the IPT only group and 111 patients in the IPT plus ET group were in the low-risk subgroup; 349 patients in the IPT only group and 305 patients in the IPT plus ET group were in the medium-risk subgroup; and 71 patients in the IPT only group and 49 patients in the IPT plus ET group were in the high-risk subgroup. After PSM, 296 patients in each group were further categorized into the subgroups: 94 patients in the low-risk subgroup, 182 in the medium-risk subgroup, and 20 in the high-risk subgroup. Figure 1 presents a flowchart of the selection process for the study groups.

The demographic and clinical characteristics of the total patients are summarized in Supplementary Table 1, http://links.lww.com/CM9/A913. In the low-risk subgroup, patients who underwent ET had higher TSB levels and higher incidence of BE on admission than patients who underwent IPT. In the medium-risk subgroup, patients who underwent ET had lower age and age of onset, higher gestational age, higher birth weight, and higher prevalence of BE at admission than those who underwent IPT; they also had different feeding patterns. In the high-risk subgroup, patients who underwent ET had lower birth weight and admission weight, more albumin use, higher TSB level, and higher incidence of BE on admission than patients who underwent IPT. After PSM, no differences were found in the basic demographic characteristics of the infants between the IPT only and IPT plus ET groups [Table 1].

We also compared the basic demographic and clinical data between all patients and patients with complete follow-up data in IPT only group and IPT plus ET group, respectively. The result [Supplementary Table 2, http://links.lww.com/CM9/A913] showed that there was no significant difference.

Clinical results of patients in the low-risk subgroup

The clinical results of the total patients are summarized in Supplementary Table 3, http://links.lww.com/CM9/A913. After PSM, all patients in the low-risk subgroup survived. The morbidity rates of BE for patients in the IPT only and IPT plus ET groups were 8.5% (8/94) and 16.0% (15/94), respectively; no significant differences were noted between the two groups ($P = 0.118$). Moreover, no significant differences were observed between the IPT only and IPT plus ET groups regarding hospital readmission 2 weeks after discharge. The mean duration of hospitalization for patients in the IPT only and IPT plus ET groups were 4 days and 6 days ($P < 0.001$), respectively. The hospitalization expenses of the patients in the IPT plus ET group were 2.15 times higher than those of patients in the IPT group ($P < 0.001$).

Regarding complications, two patients developed gastrointestinal hemorrhage in each group (the IPT only and the IPT plus ET group). The patients in the IPT plus ET group had higher incidence of fever than those in the IPT only group (5.3% [5/94] *vs.* 2.1% [2/94], $P = 0.453$). No significant differences were noted between the IPT and IPT plus ET groups regarding any of the complications mentioned.

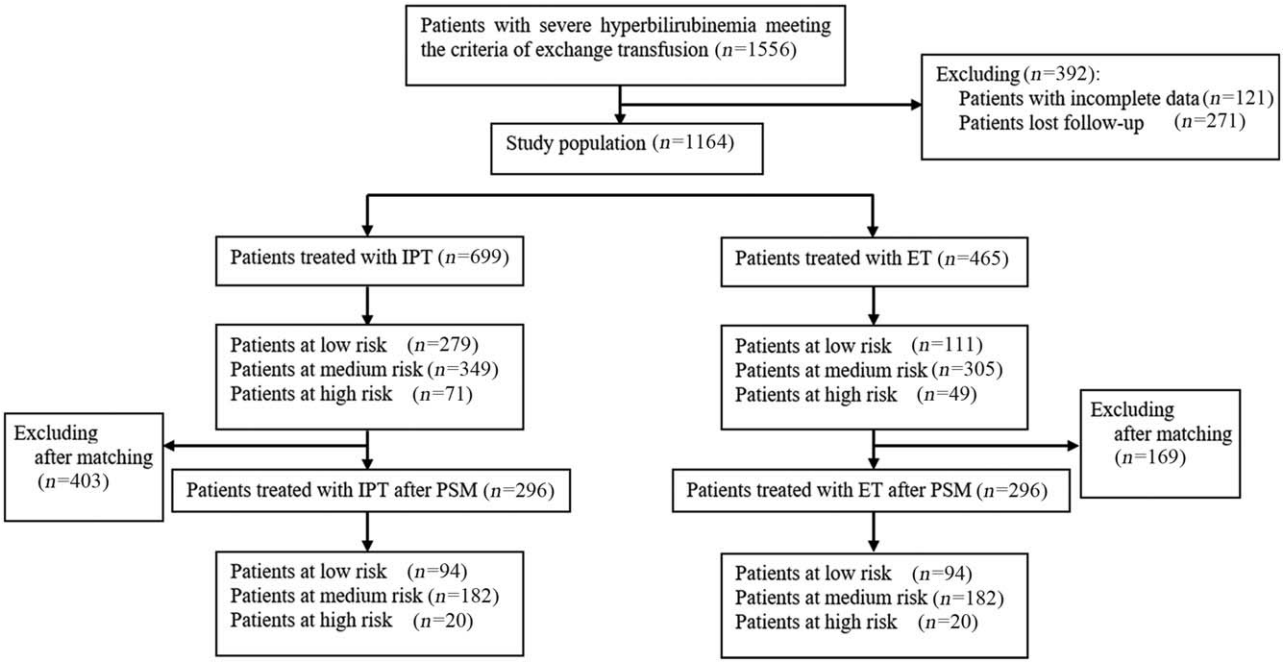

Figure 1: Flowchart of the selection process of the study groups.

Table 1: Basic demographic characteristics and clinical data of patients after propensity score match.

	Low risk			Medium risk			High risk		
Parameters	IPT only	IPT plus ET	*P* value	IPT only	IPT plus ET	*P* value	IPT only	IPT plus ET	*P* value
N	94	94		182	182		20	20	
Age (days)	7.29 ± 3.70	7.50 ± 3.67	0.706	5.48 ± 2.89	5.20 ± 3.79	0.432	6.57 ± 3.28	5.74 ± 3.65	0.459
Male	58 (61.7)	55 (58.5)	0.766	101 (55.5)	101 (55.5)	>0.999	13 (65.0)	12 (60.0)	>0.999
Gestational age (weeks)	39.05 ± 0.82	39.20 ± 0.94	0.244	38.48 ± 1.41	38.51 ± 1.49	0.845	36.61 ± 0.92	36.64 ± 0.99	0.909
Birthweight (g)	3326.97 ± 356.57	3372.02 ± 444.79	0.445	3193.94 ± 439.65	3173.38 ± 470.98	0.667	2963.00 ± 437.19	2832.00 ± 425.29	0.343
Weight at admission (g)	3123.88 ± 374.29	3215.90 ± 440.66	0.125	3053.21 ± 437.04	3022.88 ± 477.75	0.528	2786.50 ± 444.21	2646.50 ± 360.21	0.281
Age of onset (days)	3.42 ± 2.04	3.53 ± 2.30	0.723	2.85 ± 1.95	2.77 ± 2.52	0.719	2.86 ± 1.35	2.96 ± 2.22	0.864
Feeding types			0.927			0.798			0.921
Breast milk	62 (66.0)	63 (67.0)		100 (54.9)	105 (57.7)		9 (45.0)	10 (50.0)	
Formula feeds	4 (4.3)	3 (3.2)		27 (14.8)	23 (12.6)		5 (25.0)	4 (20.0)	
Mixed feeds	28 (29.8)	28 (29.8)		55 (30.2)	54 (29.7)		6 (30.0)	6 (30.0)	
Mode of delivery			0.870			0.445			0.751
Vaginal	67 (71.3)	69 (73.4)		112 (61.5)	120 (65.9)		10 (50.0)	12 (60.0)	
Cesarean	27 (28.7)	25 (26.6)		70 (38.5)	62 (34.1)		10 (50.0)	8 (40.0)	
Albumin for treatment	75 (79.8)	78 (83.0)	0.708	161 (88.5)	158 (86.8)	0.750	17 (85.0)	17 (85.0)	>0.999
TSB (μmol/L)	491.12 ± 58.34	489.37 ± 60.83	0.841	440.55 ± 63.47	448.02 ± 93.37	0.372	423.34 ± 50.77	429.34 ± 102.31	0.815
BE at admission	6 (6.4)	10 (10.6)	0.433	21 (11.5)	31 (17.0)	0.178	1 (5.0)	1 (5.0)	>0.999

Data are presented as *n* (%) or mean ± standard deviation. BE: Bilirubin encephalopathy; ET: Exchange transfusion; IPT: Intensive phototherapy; TSB: Total serum bilirubin.

Regarding the follow-up outcomes, 1 (1.1%) patient in the IPT only group and 3 (3.2%) patients in the IPT plus ET group had seizures; however, no significant difference was noted between the groups ($P = 0.50$). Patients in the IPT plus ET group had higher incidence of delayed language or motor development than those in the IPT only group, but no significant difference was found between the groups [Table 2].

Clinical results of the patients in the medium-risk subgroup

After PSM, the mortality rates in the IPT only and IPT plus ET groups were both 0.5% (1/182). The morbidity rates of BE in the IPT only and IPT plus ET groups were 14.8% (27/182) and 22.5% (41/182), respectively ($P = 0.03$). The mean duration of hospitalization for the IPT only group was less than that of the IPT plus ET group ($P < 0.001$). The hospitalization expenses of the IPT plus ET group were 2.05 times higher than those of the IPT group ($P < 0.001$).

Regarding complications, IPT plus ET group (11.5%) had higher incidence of fever than IPT group (4.9%). No significant differences were found between the two groups.

In terms of sequelae at age of 3 years, 2 (1.1%) patients in each group had auditory complications. In addition, 6 (3.3%) patients in the IPT only group and 5 (2.7%) in the IPT plus ET group had delayed language development. Six

Table 2: Comparison of early clinical results, complications, and follow-up of patients after propensity score match.

Parameters	Low risk			Medium risk			High risk		
	IPT only	IPT plus ET	*P* value	IPT only	IPT plus ET	*P* value	IPT only	IPT plus ET	*P* value
N	94	94		182	182		20	20	
BE	8 (8.5)	15 (16.0)	0.118	27 (14.8)	41 (22.5)	0.030	2 (10.0)	1 (5.0)	>0.999
Hospital admission in 2 weeks after discharge	0 (0)	1 (1.1)	>0.999	3 (1.6)	1 (0.5)	0.625	2 (10.0)	0 (0)	0.500
Length of stay (days)	4.0 (2.0)	6.0 (2.0)	<0.001	4.0 (3.0)	7.0 (4.0)	<0.001	4.0 (5.0)	7.0 (4.5)	0.152
Hospitalization expenses (CNY)	5573.6 ± 2906.7	11,996.2 ± 4889.9	<0.001	6902.8 ± 6094.7	14,165.0 ± 5661.7	<0.001	6260.6 ± 9536.9	13,149.0 ± 5004.2	0.052
Complications									
Gastrointestinal hemorrhage	2 (2.1)	2 (2.1)	>0.999	0 (0)	4 (2.2)	0.125	1 (5.0)	0 (0)	>0.999
Sepsis	0 (0)	1 (1.1)	>0.999	2 (1.1)	3 (1.6)	>0.999	1 (5.0)	0 (0)	>0.999
Fever	2 (2.1)	5 (5.3)	0.453	9 (4.9)	21 (11.5)	0.031	3 (15.0)	0 (0)	0.250
Bronze infant syndrome	0 (0)	0 (0)	-	1 (0.5)	3 (1.6)	0.625	0 (0)	0 (0)	–
Diarrhea	0 (0)	2 (2.1)	0.500	2 (1.1)	0 (0)	0.500	0 (0)	0 (0)	–
Eruptions	0 (0)	2 (2.1)	0.500	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Follow-up									
Mortality	0 (0)	0 (0)	–	1 (0.5)	1 (0.5)	>0.999	1 (5.0)	0 (0)	>0.999
Auditory complications	0 (0)	0 (0)	–	2 (1.1)	2 (1.1)	>0.999	1 (5.0)	2 (10.0)	>0.999
Seizures	1 (1.1)	3 (3.2)	0.500	1 (0.5)	0 (0)	>0.999	0 (0)	0 (0)	–
Enamel dysplasia	0 (0)	0 (0)	–	0 (0)	0 (0)	–	0 (0)	2 (10.0)	0.500
Athetosis	0 (0)	0 (0)	–	1 (0.5)	0 (0)	>0.999	0 (0)	0 (0)	–
Delayed language development	2 (2.1)	6 (6.4)	0.219	6 (3.3)	5 (2.7)	>0.999	1 (5.0)	1 (5.0)	>0.999
Delayed motor development	2 (2.1)	6 (6.4)	0.219	6 (3.3)	6 (3.3)	>0.999	3 (15.0)	1 (5.0)	0.625

Data are presented as *n* (%) or mean ± standard deviation. BE: Bilirubin encephalopathy; CNY: Chinese Yuan; ET: Exchange transfusion; IPT: Intensive phototherapy.

(3.3%) patients in each group showed delayed motor development. No significant differences were found between the IPT only and IPT plus ET groups regarding any of the sequelae mentioned above [Table 2].

Clinical results of the patients in the high-risk group

After PSM, the mortality rate of the IPT only group was 5% (1/20) and that of the IPT plus ET group was 0% (0/20) [$P > 0.999$; Table 2]. Moreover, 2 (2/20, 10.0%) patients in the IPT only group and 1 (1/20, 5.0%) in the IPT plus ET group had BE ($P > 0.999$). The mean duration of hospitalization of the IPT only and IPT plus ET groups was 4 days and 7 days, respectively ($P = 0.152$). The hospitalization expenses of the IPT plus ET group were 2.1 times higher than that of the IPT only group ($P = 0.052$). No significant differences were found between the IPT only and IPT plus ET groups regarding any of these results.

Moreover, no significant differences were noted in the incidence rates of auditory complications, enamel dysplasia, delayed language development, and delayed motor development between the two groups [Table 2].

Fitting the curves of the ET threshold

No significant differences were observed between the mortality, BE morbidity, complications, and sequelae of the low-risk, medium-risk, and high-risk patients in the IPT and ET groups. In addition, the hospitalization duration and expenses of the low-risk and medium-risk patients were lower in the IPT only group than in the IPT plus ET group. To accurately judge the threshold for ET in the clinic, we used the age (day) and the mean TSB level of the matched patients to fit an ET threshold curve for the low-, medium-, and high-risk subgroups.

For low-risk patients, the relationship between age and TSB level fit a logarithmic function curve well (TSB = 57.6 ln [days] + 372.4, $R^2 = 0.8577$, $P < 0.001$; Figure 2A). Comparison of the ET threshold curve with that suggested by the AAP guideline showed that the ET threshold based on our study result is higher than that outlined in the AAP guidelines. For example, the ET threshold was 24.3 μmol/L higher on day 4. Similarly, the threshold was higher on other days after birth. The ET threshold still showed an increasing tendency even after day 4, which is different from that outlined in the AAP guideline.

For patients in the medium-risk group, the relationship between age and TSB level fit a logarithmic function curve well (TSB = 45.8 ln [days] + 358.2, $R^2 = 0.8216$, $P < 0.001$; Figure 2B). Comparison of the ET threshold curve with that suggested by the AAP guideline showed that the ET threshold based on our study is higher than that outlined in the AAP guideline. For example, the ET threshold was 45.5 μmol/L higher on day 4. Similarly, the threshold was higher on other days after birth. The ET threshold still showed an increasing tendency even after day 4, which is different from that shown in the AAP guideline.

For high-risk patients, the relationship between age and TSB level fit a logarithmic function curve (TSB = 56.1 ln [days] + 327.6, $R^2 = 0.5697$, $P = 0.012$; Figure 2C). Comparison of the ET threshold curve with that suggested by the AAP guideline showed that the ET threshold based on our study is higher than that in the AAP guideline. For example, the ET threshold was 82.4 μmol/L higher on day 4. Similarly, the threshold was higher on other days after birth. The ET threshold still showed an increasing tendency even after day 4, which is different from that shown in the AAP guideline.

Sensitivity analysis on data of different levels of hospitals

The study was conducted in seven centers including six tertiary centers and a secondary center. The sensitivity analysis was performed on the data quality of different levels of hospitals. The results are shown in Supplementary

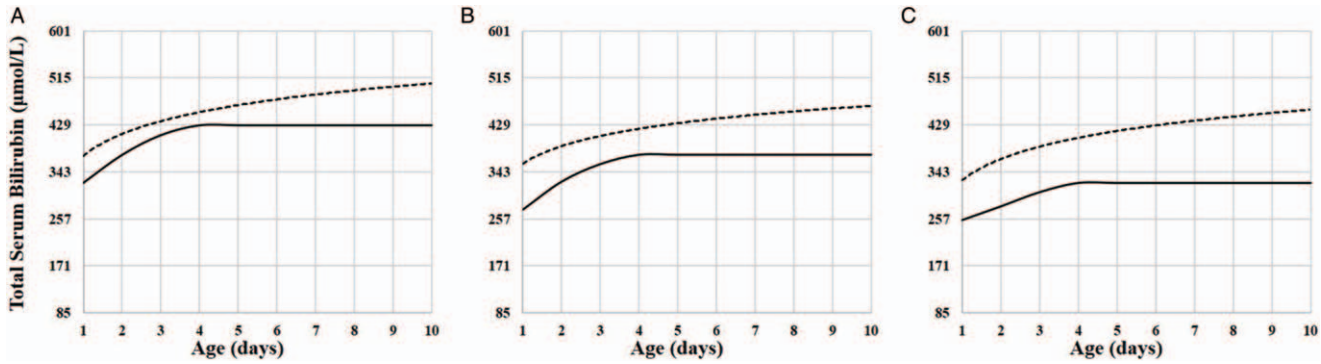

Figure 2: Relationship between age and TSB of matched patients fit logarithmic function curves. (A) Infants at lower risk, TSB = 57.6ln(days) + 372.4, $R^2 = 0.8577$, $P < 0.001$. (B) Infants at medium risk, TSB = 45.8ln(days) + 358.2, $R^2 = 0.8216$, $P < 0.001$. (C) Infants at high risk, TSB = 56.1ln(days) + 327.6, $R^2 = 0.5697$, $P = 0.012$. Dotted line shows fitting curve with matched patients (shows the threshold of ET according to the matched patients). Line shows threshold of exchange transfusion from AAP guideline. AAP: American Academy of Pediatrics; TSB: Total serum bilirubin.

Tables 4–6, http://links.lww.com/CM9/A913. We found no significant difference between all patients and patients from the tertiary centers.

Multivariable logistic analysis for all patients

The results of multivariable logistic analysis for all patients are shown in Supplementary Table 7, http://links.lww.com/CM9/A913. The table showed the results between different treatments after adjusting other factors, including age, gender, gestational age, birth weight, weight at admission, age of onset, feeding types, mode of delivery, risk group, TSB, and BE at admission. We found that there were no significant differences in efficacy and safety among different interventions after adjusting for other factors.

Clinical data of patients with BE

In our study, we compared the basic demographic and risk factors between patients with BE and without BE [Supplementary Table 8, http://links.lww.com/CM9/A913]. Patients with BE had higher incidence of isoimmune hemolytic disease (35.8% *vs.* 28.2%, $P = 0.049$), glucose-6-phosphate dehydrogenase (G6PD) deficiency (12.8% *vs.* 4.5%, $P < 0.001$), sepsis (21.8% *vs.* 8.6%, $P < 0.001$), significant lethargy (7.3% *vs.* 0.3%, $P < 0.001$), and temperature instability (6.7% *vs.* 1.5%, $P < 0.001$) than those without BE. In the medium-risk group, the patients with BE had higher incidence of G6PD deficiency (16% *vs.* 6%, $P = 0.001$), sepsis (22.7% *vs.* 11.8%, $P = 0.038$), significant lethargy (7.6% *vs.* 0, $P < 0.001$), and temperature instability (6.7% *vs.* 1.9%, $P = 0.008$) than those without BE. In high-risk group, the patients with BE had higher incidence of significant lethargy (14.8% *vs.* 3.2%, $P = 0.045$) than those without BE.

Discussion

The management of extreme hyperbilirubinemia is a key factor in the prevention of neonatal death and neurological dysfunction. Injury to the nervous system is due to the high level of serum unconjugated bilirubin that crosses the blood–brain barrier into the central nervous system (CNS), resulting in neuronal injury in the basal ganglia, central and peripheral auditory and visual pathways, and the hippocampus and brainstem nucleus. Bilirubin in the CNS can lead to BE symptoms, such as lethargy and seizures, long-term neurological sequelae, such as motor dysfunction, hearing impairment, and oculomotor disorder, or death.[11,12] Therefore, immediate initiation of proper treatment, including phototherapy and ET, is very important in the clinic.

Phototherapy is a first-line therapy for neonatal hyperbilirubinemia, which can reduce the concentration of bilirubin in blood circulation. IPT is regarded as an emergency treatment for extreme neonatal jaundice.[13] It is generally believed that IPT can greatly reduce the need for ET in infants with or without hemolysis.[14,15] With the continuous updating and optimization of phototherapy equipment in recent years, more hospitals use LEDs for IPT. LED devices are more power-efficient, portable, and lighter, have a longer service life, generate less heat, and are more suitable for IPT than fluorescent lamps.[2,16] Significant adverse effects of phototherapy are rare.[17] Several studies have reported that patients developed bronze baby syndrome,[18,19] which was found not to be significantly different between the IPT only and IPT plus ET groups in the present study. Conventional phototherapy can lead to an imbalance between the thermal environment and water loss.[20,21] These shortages could be improved using LED, owing to its low heat output and lower likelihood to cause insensible water loss.[17]

ET is also an effective treatment for extreme hyperbilirubinemia. ET can quickly remove serum unconjugated bilirubin to prevent bilirubin neurotoxicity and occurrence of BE. However, ET has been reported to have more serious adverse effects, including infection, gestational hemorrhage, thrombocytopenia, hypocalcemia, hypotension, venous thrombosis, hypokalemia, and hypoglycemia.[22-24] Moreover, ET increases clinical blood consumption and the risk of transmission of blood-borne diseases.[2] Recently, studies have shown a progressive decline in the use of ET in the clinic, which might be associated with the widespread use of IPT, advances in prenatal and postnatal care, and use of intravenous immunoglobulin for hemolysis.[25]

In our previous study, we evaluated 12 clinical practice guidelines for the diagnosis and management of neonatal hyperbilirubinemia.[6] The qualities of the methodology strategies and recommendations for the treatment of hyperbilirubinemia in the guidelines were analyzed. Although the 12 guidelines indicated the threshold for ET, seven of them (Canadian Pediatric Society,[26] Chinese Pediatric Society,[9] Israel Neonatal Society,[27] Malaysia Health Technology Assessment Section,[28] Queensland Clinical Guidelines,[29] Spanish Association of Pediatrics,[30] and Turkish Pediatric Association[31]) stated that the ET threshold curve was reproduced from the AAP guidelines. However, the AAP guidelines indicate that the suggested threshold curve for ET is backed by the consensus of a committee and based on limited evidence.[7] Therefore, more evidence from research is needed to determine the threshold curve for ET.

Owing to the limited available evidence regarding the optimal ET threshold, we studied the effectiveness and complications of IPT and ET in treating extreme hyperbilirubinemia using propensity score methods. We found that IPT is an effective and safe method for treating hyperbilirubinemia. The use of IPT did not increase the morbidity of BE, complications, and neurological sequelae in our patients. Moreover, the patients in the IPT only group had less duration of hospitalization and expenses of patients in the low- and medium-risk subgroups. These findings suggested that some patients could be treated with IPT only instead of ET. The indication of ET could be stricter. However, after PSM, there are few children with BE at admission in this study. We suggested that patients with signs of BE may need more cautious and active treatment such as ET. Moreover, more research was needed on the topic of reducing the incidence of BE in clinical practice.

A study from Sweden reported that among infants with TSB levels of 510 μmol/L or higher, 28 of 67 (42%) patients had symptoms of BE.[32] The incidence was similar to that in our study (40.2%, 43/107). The incidence of BE in patients with severe hyperbilirubinemia is relatively high, and these patients should be treated timely and to avoid or reduce the occurrence of long-term neurological sequelae. In our study, we compared the basic demographic and risk factors between patients with BE and without BE. We found that patients with isoimmune hemolytic disease, G6PD deficiency, sepsis, significant lethargy, and temperature instability were more likely to develop BE. Therefore, we suggested that patients with these risk factors should be treated as soon as possible and have a contingency plan for emergency ET as IPT was commenced.

To the best of our knowledge, this is the first study in which IPT and ET were compared for the treatment of extreme hyperbilirubinemia using PSM. Data were collected from multiple centers, including seven hospitals, and >1000 patients were followed up for 3 years. Our findings are remarkable and helpful for clinical practice. However, this study has several limitations. First, the number of patients in the high-risk subgroup was only 40 after PSM. Therefore, the conclusions regarding high-risk patients need to be further verified using more large-scale studies. Second, as the gestational age of the included patients was >35 weeks, further research is necessary to assess patients with earlier gestational age and extremely low birth weights. Third, all patients included in this study were from China; thus, more evidence from studies of patients from other races and regions is needed.

Conclusions

In this multicenter study, we used propensity score methods to compare the effectiveness and treatment complications of IPT and ET in the treatment of extreme neonatal hyperbilirubinemia. In this study, our results suggest that IPT is a safe and effective treatment for extreme hyperbilirubinemia. The indication of ET for patients with hyperbilirubinemia could be stricter. However, it is necessary to have a contingency plan for emergency ET as soon as IPT is commenced especially for infants with risk factors. If IPT can be guaranteed and proved to be therapeutic, ET should be avoided as much as possible.

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Conflicts of interest

None.

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