Relationship Between Unbound Bilirubin Levels and Acute Bilirubin Encephalopathy in Exchange Transfusion Neonates

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ABSTRACT

BACKGROUND: Evidence regarding the relationship between unbound bilirubin levels and acute bilirubin encephalopathy was limited. Therefore, this study set out to investigate whether the unbound bilirubin level was independently related to acute bilirubin encephalopathy in children who underwent exchange transfusion after adjusting for other covariates.

METHODS: A total of 46 neonates who underwent exchange transfusion were involved in The First People's Hospital Of Changde City in China from 2016-1-1 to 2018-12-31. The target independent variable and the dependent variable were unbound bilirubin levels measured at baseline and acute bilirubin encephalopathy respectively. Covariates involved in this study included sex, age, birth weight, blood glucose, red blood cell, hemolysis, receive phototherapy before exchange transfusion.

RESULTS: The average gestational age of 46 selected participants was 38.6 ± 1.3 weeks old, the average age was 146.5 ± 86.9 hours old, 52.17% of them were male. Result of fully-adjusted binary logistic regression showed unbound bilirubin levels were positively associated with risk of acute bilirubin encephalopathy after adjusting confounders (Odds ratio = 1.41, 95% confidence intervals 1.05-1.91, P value <0.05).

CONCLUSION: Unbound bilirubin levels are associated with neonatal acute bilirubin encephalopathy. The mechanism of unbound bilirubin levels leading to neonatal acute bilirubin encephalopathy needs to be further explored.

KEY WORDS: neonatal, acute bilirubin encephalopathy, exchange transfusion, unbound bilirubin.

INTRODUCTION

Neonatal jaundice is one of the most common clinical diagnoses and is due to elevated unbound bilirubin (UB) and/or conjugated bilirubin (1). When the serum bilirubin at or near exchange transfusion (ET) threshold based on postnatal age and cause of the condition (typically total serum bilirubin (TSB) ≥ 20 mg/dL or 342 µmol/L) or any elevated bilirubin levels associated with signs of acute bilirubin encephalopathy (ABE), those are defined as severe neonatal hyperbilirubinaemia (SNH) (2,3,4). Neonatal jaundice affects 60%–80% of newborns, SNH portends significant risks of avoidable mortality and severe long-term neurodevelopmental sequelae in several low-income and middle-income countries and also some high-income countries (2,5,6,7). Twenty-four million were at risk for neonatal hyperbilirubinemia related adverse outcomes. Kernicterus with Rh disease ranged from 38 to 25/100,000 live births for Eastern Europe/Central Asian, sub-Saharan African, South Asian, and Latin American regions, respectively. Most survivors with kernicterus had one or more impairments (7). One study with a total of 1920 newborns showed a high incidence of SNH (25 per 1000 newborns) among in-hospital neonates (8). An estimate of the incidence of SNH in Canada would be 1 in 2480 live births (9). Seven incidence studies conducted internationally between 1988 and 2005 identified an estimated incidence of SNH was between 7.1 and 45 per 100 000 births and the rate of ABE was between 0.4 and 2.7 per 100000 births (10).

The detailed definition of ABE is described as follows: Acute features include lethargy, irritability, abnormal muscle tone and posture, temporary cessation of breathing (apnoea) and convulsions (1,11,12). It has previously been observed that phototherapy and ET are the mainstays of treatment to prevent kernicterus or bilirubin-related mortality. ET usually becomes a priority when phototherapy proves ineffective in averting the risk of bilirubin neurotoxicity or when the neurological signs of ABE are evident. Most practice guidelines recommend ET based on prescribed age-specific thresholds for TSB, and/or

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clinical signs of ABE (3,12,13). One study showed that ET was effective in decreasing the TSB (14). Wusthoff et al. consider that a linear relationship does not exist between neonatal TSB and the risk of Bilirubin-induced neurologic dysfunction (BIND); rather, other measures of hyperbilirubinemia, such as UB or the bilirubin-albumin binding capacity, may be more relevant (15). Since UB can cross the blood-brain barrier, the level of plasma-free bilirubin is considered to be a more reliable index of the risk of neurotoxicity and acute auditory impairment than TSB (16,17,18). Measurement of UB can also be an important marker of the risk of hyperbilirubinemia. A study by Morioka et al. suggested that chronic high UB levels may help identify early low-birth weight infants at risk of developing kernicterus (19). Sanjiv findings add to the growing evidence for the usefulness of UB in the evaluation of BIND (20).

However, findings from previous studies regarding the relationship between UB levels and ABE were limited, especially in cases of SNH. In view of the fact that the bilirubin in neonatal cases of ET has reached a certain level, this dissertation aims to investigate whether UB levels are independently related to ABE in neonatus who underwent ET.

Materials and methods

We non-selectively and consecutively collected data for all neonates on admission from the Neonatology department, The First People's Hospital Of Changde City, Hunan, China. The data in the database is anonymous for the purpose of protecting participants' privacy. Data is stored in the hospital' electronic medical record system. The study complied with the ethical principles of the Declaration of Helsinki and was approved by the local Ethics Committee.

This study is a retrospective study, the target independent variable is UB levels obtained before ET. The dependent variable is the occurrence of ABE. Inclusion criteria include Children who were admitted to the neonatology department of the First People's Hospital of Changde from January 2016 to December 2018.

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Inclusion criteria: 1) infants hospitalized in neonatology department of our hospital; 2) diagnosed with neonatal hyperbilirubinemia; 3) undergone ET. An ET is always done with informed parental consent. A written informed consent is obtained from the parent/s before initiating the procedure of ET. Benefits and risks of the procedure as well as the risks of not doing the procedure in an infant with SNH are explained in understandable verbal and written communication.

The study data were initially collected for a total of 5317 hospitalized neonates from the Neonatology department. A total of 1776 late-preterm and term infants (33.4%) were enrolled with a diagnosis of neonatal hyperbilirubinemia, out of which 46 (2.59%) underwent ET, ET was performed according to the AAP criteria (3). Standard and experienced treatment was given to every patient according to the cause of the SNH after the initial investigations. 36 (78.3%) of them received multiple phototherapy before ET, 13 (28.3%) of them got intravenous immunoglobulins before ET. While prepare for ET and during ET, multiple phototherapy was continuous. Following ET continuous multiple phototherapy. The entire clinical practice for every participant was performed according to NICE neonatal Jaundice Clinical Guidelines 2010 (12).

We obtained UB levels at baseline before ET and recorded as a continuous variable. The UB and TSB levels were tested by Beckman Coulter Chemistry Analyzer AU5800, measurement method was Vanadate Oxidation Method. We extracted the following data for each patient receiving ET: age, birth weight, blood glucose, white blood cell, weight, sex, diagnosis as ABE or not, and hemorrhage, hemolysis, and infection etc (table 1). In details hemorrhage includes scalp hematoma, intracranial hemorrhage showed by magnetic resonance imaging, and abdominal haemorrhage showed by ultrasonography, hemolysis includes ABO haemolytic, RhD haemolytic, Autoimmune haemolytic and Glucose-6-phosphate Dehydrogenase defificiency, while infection includes sepsis, pulmonary infection, intracranial infection and umbilical

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infection.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (normal distribution) or medium (min, max) (Skewed distribution). Categorical variables were expressed in frequency or as a percentage. We used χ2 (categorical variables), Student T test (normal distribution) to test for differences among different ABE groups (ABE（yes/no）). Multivariate Logistic regression analysis was used to analyze the relationship between UB and ABE in ET neonates, and three models were constructed to illustrate the stability of this relationship: model 1, no covariates were adjusted; model 2, only adjusted for sociodemographic data (such as sex and age) and birthweight; model 3, model 2+other covariates presented in table 2. Since blood glucose, red blood cell, and receive phototherapy before ET got a statistically significant among two ABE groups (table 1), multivariate regression analysis adjusting for those covariates effects on ABE would be necessary. Some reports suggested hemolytic was assocaited with ABE or ET（11,21,22,23), so we adjust for those covariates in table 2. All the analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, MA). P values less than 0.05 (two-sided) were considered statistically significant.

RESULTS

Baseline characteristics of selected participants

The total neonatal admissions for the three year period was 5317 out of which 1776 (33.4%) were admitted for Neonatal hyperbilirubinemia. Phototherapy and ET were used as per AAP guidelines (3). A total of 46 participants were selected for the final data analysis after screening by inclusion and exclusion criteria (see Figure 1 for a flow chart). We showed baseline characteristics of these selected participants in

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table 1 according to diagnosis of ABE (12). In general, the average age of the 46 selected participants was

146.5 ± 86.9 hours old，and about 52.17% of them were male. 9 of them were with hemorrhage(19.6%) ,

28 with hemolysis (60.9%) which includes ABO haemolytic (n=8) ,RhD haemolytic (n=2), Autoimmune

haemolytic (n=2) and Glucose-6-phosphate Dehydrogenase defificiency(n=16), 19 with infection (41.3%).

No statistically significant differences were detected in gestational age, birth weight, white blood cell,

weight, sex, hemorrhage, hemolysis, infection among ABE group or no-ABE group (all p values > 0.05).

Statistically significant differences were detected in age, blood glucose, red blood cell, hemoglobin, TSB_1

(TSB at starting ET), UB, TSB_2 (TSB at end of the ET), receive phototherapy before ET among ABE

group or no-ABE group (P values<0.05) (table 1).

Results of unadjusted and adjusted binary logistic regression

In this study, we constructed three models to analyze the independent effects of UB levels on ABE

(multivariate binary logistic regression). The effect sizes (Odds ratio) and 95% confidence intervals were

listed in Table 2. In the unadjusted model (model 1), the model-based effect size can be explained as the

difference in 1 mg/dL of UB levels associated with risk of ABE. In the minimum-adjusted model (model 2:

adjust I model adjust for: sex, age, birth weight), Odds ratio (OR) is 1.34, 95% confidence intervals (CI) is

1.11 to 1.63 (p <0.05), In the fully-adjusted model (model 3) (adjusted all covariates presented in table 2,

include sex, age, birth weight, blood glucose, red blood cell, hemolysis and receive phototherapy before

ET), the effect size (OR:1.41, 95% CI 1.05, 1.91) is also stable.

DISCUSSION

Bhutani et al. estimate the current risk of chronic kernicterus is about one in seven in infants with

TSB >30mg/dL (24). One study suggested that TSB (above 25 mg/dL) was a poor predictor of ABE when risk

factors were existent (25). Another study reported that increasing UB levels are associated with higher mortality

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or poor neurodevelopmental outcomes in spite of any clinical condition. An increase in TSB levels is directly related to an increased risk of unstable infant (not stable infant) death or poor neurodysplasia (26). UB is still one of the main reasons of neonatal morbidity and hospitalization. Sometimes UB can ascend to a severely high level and cause brain injury (27). The measurement of UB is important for assessing the risk of bilirubin neurotoxicity and for proper interference in high-risk neonates with hyperbilirubinemia (28). Lower concentration of UB can cause cell apoptosis, while high concentration of UB can lead to neuron necrosis. Bilirubin toxicity is more likely to affect the basal ganglia and various brain stem nuclei. Superfluous release of glutamate, mitochondrial energy exhaustion, discharge of pro-inflammatory cytokines and Increased intracellular calcium levels constitute the mechanism of bilirubin-induced neurotoxicity (29,30). Moderate to severe UB was associated with high levels of oxidative stress.Oxidative stress changes may predict adverse outcomes early. Low bilirubin levels can also cause high DNA damage, suggesting that UB may have genotoxic effects (27). Findings from in vivo and in vitro experiments seem to suggest a decreased number of myelinated axons, decreased thickness of myelin sheaths, and less compact axons with more debris in brains exposed to UB (31). UB into the brain can cause neurological dysfunction. Acute features which is known as ABE. In our data 46 infants received ET: the UB median value was 450.1 ± 105.4 µmol/L, of which 18 with ABE. Ebbesen et al. (32) identified 32 near-term and term infants in whom the TSB values exceeded the indications for ET, 11 with evidence of ABE. The correlation between levels of circulating bilirubin and the occurrence of ABE is poor. Some factors which probably influence the passage of bilirubin into the brain include preterm birth, sepsis, hypoxia, seizures, acidosis and hypoalbuminaemia, may increase the risk of ABE (12). UB may be deposited in the basal ganglia, the auditory passage and the movable core muscle. This deposition and accompanying damage leads to the typical symptoms of kernicterus. In full-term infants, when the bilirubin level exceeds 20 mg/dL, the risk of kernicterus is

increased (17). In premature infants, the damage threshold of bilirubin can reach 14 mg/dL. As UB serum levels increase, the risk increases (17). Brito et al. reporting on a preterm neonate with kernicterus, suggested that UB increases the density of blood vessels in the hippocampus and striatum related to the nucleus macula and triggers the immune response of VEGF and VEGFR-2, and albumin infiltrates into the brain parenchyma (33). When the bilirubin-binding ability of the blood is enhanced or when other alternative substances compete for the bilirubin-binding site on albumin, UB enters cerebrum. Gestational age, infection or sepsis, haemolysis and particularly Rh isoimmunization, which are associated with neuronal susceptibility, are other important risk factors for kernicterus (11). In our data, there is no significant difference in infection, hemolysis and gestational age in ABE and no-ABE group, which may be related to the small sample size (Table 1).

Our research include three years with 5317 neonatal admissions, out of which 1776 (33.4%) were admitted for neonatal hyperbilirubinemia. In one study with a similar incidence rate. The study reported that peak TSB was one of the predictors of ABE, while peak TSB, ABO incompatibility and ABE were predictors of ET (23). Risk evaluation of kernicterus based on TSB levels alone has often proved insufficient, the TSB levels of starting ET is also a lack of uniformity even when the clinical signs/symptoms of ABE and haemolytic disease is taken into account. ET is an effective interventions for BIND in newborns with SNH; However, it also carries some risks and needs to start after careful assessment of the risk of kernicterus (4). TSB or UB in terms of sensitivity and specificity in determining risk of ABE, there are not yet enough published data to define precisely. However, the existing laboratory and clinical data shows that UB is superior to TSB in discriminating risk for bilirubin toxicity in SNH (34).

Emerging evidence suggests that UB may be a better predictor of BIND than TSB in premature and term infants (28,35,36). Our findings indicate UB level is positively associated with ABE after adjusting

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for other covariates (OR: 1.41, 95%CI 1.05, 1.91), with gender, age, birth weight and blood glucose etc included as covariates (Table 2). This result suggests a positive correlation on the independent association between UB levels and ABE. Similar findings were reported in a study: there was a significant association of peak UB (but not peak TSB or peak bilirubin albumin molar ratio) with chronic auditory toxicity (37). Similar findings were also reported in the study of a sample of 44 participants with SNH, Sanjiv et al. suggested that UB is a more sensitive and specific predictor of auditory neuropathy spectrum disorder than TSB or bilirubin albumin molar ratio (20). A prospective study in India found that birth asphyxia, serum bilirubin levels and UB levels were statistically significantly associated with the development of kernicterus with multiple logistic regression analyses (38). One study reported that the probability of bilateral refer automated auditory brainstem response results increases significantly with increasing UB concentrations but not with increasing TSB concentrations (39).

Our studies take into account the effect of age, gender, birth weight, blood glucose, red blood cell, hemolysis and receive phototherapy before ET on the UB levels and ABE relationships when adjusting covariates. Previous studies have confirmed that these variables may be related to UB levels or ABE. Our results show that statistically significant differences were detected in age, blood glucose, red blood cell, UB, receive phototherapy before ET among ABE group or no-ABE group (P values<0.05) with the occurrence of ABE. However, in the fully-adjusted model (model 3) (adjusted all covariates presented in table 2) for each additional mg/dL of UB levels, results are still stable.

The clinical value of this study is as follows: To the best of our knowledge, it is the first observation of the independent association between UB levels and ABE in Children who underwent ET; The findings of this study should be helpful for future research on the establishment of diagnostic or predictive models of ABE. There are some limitation in the present study including: 1) in this study, our research subjects are

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children who underwent ET. Therefore, there is a certain deficiency in the universality and extrapolation of research. 2) Because we exclude ABE neonatal who have not undergone ET, the findings of this study cannot be used for these people.

CONCLUSION

UB levels are independently associated with neonatal ABE in Children who underwent ET. The mechanism of UB levels leading to neonatal ABE needs to be further explored.

ABBREVIATIONS

UB: unbound bilirubin

ABE: acute bilirubin encephalopathy

ET: exchange transfusion

TSB: total serum bilirubin

SNH: severe neonatal hyperbilirubinaemia

BIND: Bilirubin-induced neurologic dysfunction

OR: Odds ratio

CI: confidence intervals

DECLARATIONS

Ethics approval and consent to participate: The study complied with the ethical principles of the Declaration of Helsinki and was approved by the Medical ethics committee of The First People's Hospital Of Changde City.

Consent for publication：Not applicable

Availability of data and materials：Not applicable

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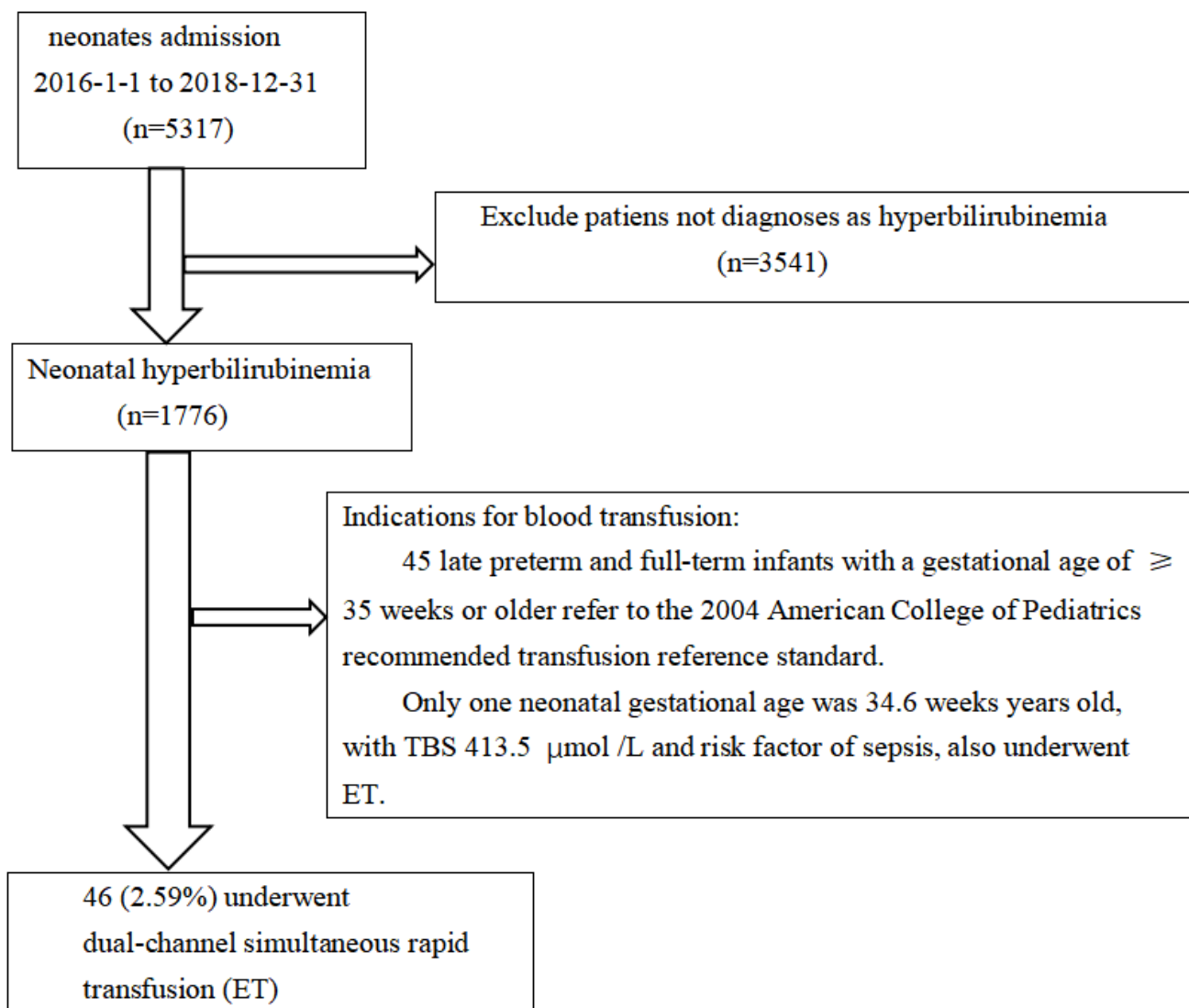
Figures

neonates admission
2016-1-1 to 2018-12-31
(n=5317)

Exclude patiens not diagnoses as hyperbilirubinemia
(n=3541)

Neonatal hyperbilirubinemia
(n=1776)

Indications for blood transfusion:
 45 late preterm and full-term infants with a gestational age of ≥ 35 weeks or older refer to the 2004 American College of Pediatrics recommended transfusion reference standard.
 Only one neonatal gestational age was 34.6 weeks years old, with TBS 413.5 μmol /L and risk factor of sepsis, also underwent ET.

46 (2.59%) underwent dual-channel simultaneous rapid transfusion (ET)

Figure 1

A total of 46 participants were selected for the final data analysis after screening by inclusion and exclusion criteria (see Figure 1 for a flow chart).