Journal of Medical and Surgical Practice (JMSP)
Vol. 06, Issue 03 July-September 2020

Extreme Neonatal Hyperbilirubinemia; Risk Factors of Short Term Neurological Outcome

Dr. Adil K. Zghair*

Children Welfare Teaching Hospital, Medical City Directorate. Baghdad- Iraq

***Corresponding Author , contact email:** aliadil9595@yahoo.com*

Original Article

ABSTRACT

Background: *Significant neonatal hyperbilirubinemia is the most common clinical condition in the newborn requiring evaluation and management. Bilirubin encephalopathy is a neurologic syndrome resulting from the deposition of unconjugated bilirubin in the basal ganglia and brainstem nuclei.*

Aim of study: *To assess the risk factors that may increase the possibility of early neurological complications or death at a short-term outcome*

Patients & Methods*: An observational study was completed for 72 jaundiced neonates with TSB equal or more than 25mg/dl, 34 weeks of gestation or more, body weight equal or more than 2.2 kilogram, admitted from 1st Dec. 2018 to 1st Dec. 2019 to the Children Welfare Teaching Hospital, Medical city, Baghdad, Iraq. BIND score was used to categorize the patient to normal, subtle, moderate and severe acute bilirubin encephalopathy.*

Results*: Fifty cases (69.4%) were males and 22 (30.6%) cases were females, 12 cases (16.7%) with body weight > 2.5 kg and 60 cases (83.3%) ≥2.5 kg. Sepsis was the cause of hyperbilirubinemia in 4 cases (5.6%), Rh incompatibility in 17 cases (23.6%), idiopathic cause in 14 cases (19.4%), ABO incompatibility in 27 cases (37.5%), combined ABO and Rh in 10 cases (13.9%). Mean TSB on admission was (28.1) with a range (25-42). Eleven cases (15.3%) had moderate ABE on admission, 6 cases (54.5%) had BE on discharge, 8 cases (11.1%) had severe ABE on admission, all (100%) patients developed BE on discharge, 1 case (1.3%) died. The BIND score ≥ 4 had an adverse outcome anticipation of BE of (73.4%)*

Conclusions: *Low birth weight, hemolytic diseases and sepsis greatly increase the probability of severe hyperbilirubinemia and subsequent ABE at admission and BE at discharge.*

Keywords: *Neonatal Hyperbilirubinemia, pathophysiology, epidemiology, Risk Factors, Neurological Outcome*

Article information: Received: May 2020, Revised and Accepted July 2020, Published online August 2020

How to cite this article*:*

ZghairA.K, Extreme Neonatal Hyperbilirubinemia; Risk Factors of Short Term Neurological Outcome. Journal of Medical and Surgical Practice (JMSP)2020; 6 (3): 27-37

1.INTRODUCTION

Neonatal jaundice (The term "jaundice" comes from the root jaune, the French word for "yellow") or neonatal hyperbilirubinemia or neonatal icterus (from the Greek word ἴκτερος attributive adjective: icteric) is yellowing of the sclera and skin of a newborn infant. A bilirubin level of more than 85 μmol/l (5 mg/dL) leads to a jaundiced appearance in neonates (1). Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. Jaundice is observed during the 1st week of life in approximately 60% of term infants and 80% of preterm infants (2), Neonatal hyperbilirubinemia is the most common clinical condition in the newborn requiring evaluation and management and remains a frequent reason for hospital readmission during the first week of postnatal life (3). Premature babies have much higher incidence of neonatal jaundice requiring therapeutic intervention more commonly than term newborns (4).because of the potential toxicity of bilirubin; newborn infants must be monitored for early identification of severe hyperbilirubinemia and, prevention of acute bilirubin encephalopathy or kernicterus (5).

Pathophysiology

When red blood cells undergo hemolysis, hemoglobin is released within the reticuloendothelial system(6).Approximately 75% of bilirubin is derived from hemoglobin but degradation of myoglobin, cytochrome and catalase can also contributes. Because of its intermolecular hydrogen bonds, it's almost insoluble in water (7). Bilirubin, after formation, is released into the circulation, where it is reversibly bound to albumin. 1 g of albumin binds 8.5 mg of bilirubin in a newborn (8). Albumin in the circulation provides a vast bilirubin binding source, so that unbound bilirubin in plasma is generally low. Albumin transports bilirubin to its specific metabolic pathway in the liver, where bilirubin uptake is rapid. Intracellular transport of bilirubin from the hepatic plasma membrane to the endoplasmic reticulum, where conjugation occurs, cytosolic proteins (Y or ligandin Z or fatty-acid- binding protein) account for most of the intracellular bilirubin binding capacity.

The conversion of bilirubin to mono- and di-glucuronide conjugates occurs in the endoplasmic reticulum. A stepwise addition of D glucuronic acid from UDP-D- glucuronic acid to bilirubin, takes place with the help of the enzyme UDP-glucuronate-bilirubin glucuronyltransferase. The addition of glucuronide makes conjugated bilirubin(more stable, nontoxic, water soluble) capable of canalicular transport into the bile and excreted in the intestine (9). Hepatic uridine diphosphoglucuronosyl transferase(UDGT) increases dramatically in the first few weeks after birth.

At 30 to 40 weeks' gestation, UDGT values are approximately 1%of adult values, rising to adult concentrations by 14 weeks of age. (10).

Bilirubin encephalopathy

Bilirubin encephalopathy is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei (2). The clinical spectrum of signs of bilirubin neurotoxicity relates to the bilirubin-induced damage to specific brain areas. Specific brain stem nuclei (auditory, vestibular and oculomotor), cerebellar Purkinje cells, basal ganglia (i.e., globus pallidus and subthalamus) and the hippocampus are particularly vulnerable to bilirubin neurotoxicity (11). The terms bilirubin encephalopathy and kernicterus represent clinical and pathologic abnormalities respectively resulting from bilirubin toxicity in the central nervous system; to avoid confusion and encourage greater consistency in the literature, the American academy of pediatrics (APP) recommended that the term acute bilirubin encephalopathy (ABE) be used to describe the acute manifestations of bilirubin toxicity seen in the first week after birth and the term kernicterus be reserved for chronic and permanent clinical sequel of bilirubin toxicity(12).

Bilirubin induced neuropathy dysfunction (BIND)

Recently, a numeric scoring system for quantifying the degree of ABE has been outlined; it is detailed in (Table i) (13), this scoring system of bilirubin-induced neurologic dysfunction may prove to be a useful clinical tool in identifying infants with intermediate to advanced ABE, conditions that pose significant risk for CBE and are an indication for the urgent application of bilirubin reduction strategies. Indeed, preliminary observations suggest this numeric approach may be quite reliable in characterizing the severity of ABE (14) and may prove helpful in managing infants with hazardous hyperbilirubinemia. Notably, the AAP recommends immediate exchange transfusion in any infant who is jaundiced and manifests signs of intermediate to advanced stages of ABE (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry), even if the TSB is falling (15). Scores of 1–3 are consistent with subtle signs of acute bilirubin encephalopathy in infants with hyperbilirubinemia. Scores of 4–6 represent moderate acute bilirubin encephalopathy and are likely reversible with urgent and prompt bilirubin reduction strategies. Scores of 7–9 represent advanced acute bilirubin encephalopathy; urgent, prompt, and individualized intervention are recommended to prevent further brain damage, minimize severity of sequelae, and possibly reverse acute damage (16).

2. PATIENTS and METHODS

An observational study, based on comprehensive prospective medical records was completed for 72 jaundiced neonates, more than 34 weeks gestation. We examined the early outcomes of newborns with severe neonatal hyperbilirubinemia admitted to the neonatal care unit (NCU) of children welfare teaching hospital, medical city complex in Baghdad, Iraq. The observation was limited to a 12-month period from December 1st, 2018 to December 1st, 2019. The study was approved by the ethics committee of the Pediatrics Department, children welfare teaching hospital, Medical city, Baghdad. Inclusion criteria included infants with severe hyperbilirubinemia (TSB more than 25mg/dl) (2) on admission with gestational age 34 weeks or more (late preterm and term) (2) documented by ultra sound and weight of 2.2 kg (median weight for 34 weeks gestation) (2) and more. Neonate with TSB less than 25 mg/dl and gestational age less than 34 weeks with weight less than 2.2kg were excluded from this study. In this study, the total serum bilirubin (TSB) was done at the emergency department on admission regardless of whether being conjugated or unconjugated. The TSBs were repeated at the NCU to decide which type of treatment (phototherapy or phototherapy and exchange transfusion) to be started. Laboratory tests included blood group and Rh (mother and baby), comb's test, urea and electrolytes and when clinical signs of sepsis were suspected; lumbar puncture and blood culture were done at admission.

History was obtained from the care givers of neonates using a questionnaire form, The neonates` information included the gender, age at admission, age of start of jaundice, mode of delivery, type of feeding (breast, bottle or mixed), 31 history of familial neonatal jaundice, cause of hyperbilirubinemia: ABO incompatibility, Rh incompatibility, combined ABO and Rh incompatibility ,cephalhaematoma ,polycythemia, others, sepsis [A diagnosis of sepsis required clinical signs of sepsis associated with (1) a positive blood culture result and/or (2) an elevated C-reactive protein level, total leukocyte count of >25 000 or 0.2, or a band count of >10%]. G6PD was not included in this study because immediately after a hemolytic episode, reticulocytes and young RBCs predominate, these young cells have significantly higher enzyme activity than do older cells and the result will be negative (2).

Statistical analysis

The data has been analyzed with computer software SPSS version 23, frequency distribution tables and graphs .Chi square and Fisher's exact tests were done, Binary logistic regression used to estimate the Odds of the significant risk factors. Confidence level of 95% with P value equal to or

less than 0.05 was considered statistically significant and a P value of less than 0.01 considered as of high statistical significance.

3. RESULTS

The mean age of admission in days was (5.7±2.3) ranging from (2-15) days and mean age of starting of jaundice was (2.4±0.9) ranging from (1-5) days, the mean body weight in kilograms was (2.95±0.42) ranging from (2.2-4) kg and the mean gestational age in weeks was (37.3±1.5) ranging from (34-42) weeks. The mean total serum bilirubin at admission in mg/dl was (28.1±2.5) ranging from (25-42) (**Table 1**).

Thirty-three cases (45.8%) had 0 BIND score at admission, none of them had evidence of BE at discharge,20 cases (27.8%) had BIND score from 1-3(subtle), 19 cases (95.5%) discharged with no evidence of BE and 1 case (5%) discharged with BE, this case had Rh hemolytic disease progressed from subtle signs on admission to frank BE at discharge. BIND score of 4-6 (moderate ABE) was in 11 cases (15.3%), 5 cases (45.5%) discharged well and 6 case (54.5%) had BE at discharge. BIND score from 7-9 (severe ABE) was in 8 cases (11.1%), 1 case (12.5%) that proved sepsis as the cause of hyperbilirubinemia developed BE and died and other the 7 cases (87.5%) discharged with BE (Table.3). The short term outcome includes 57 cases (79.2%) discharged well and 15 cases (20.8%) discharged with signs of BE. The BIND score was a good outcome predictor with score equal or more than 4 as 14 cases out of 19 cases(73.4%) with moderate and severe BIND score had adverse outcome at discharge. (**Table 2**).

The risk factors (continuous variables) for the 15 cases (20.8%) that were discharged with BE to the 57 cases (79.2%) that discharged well without BE: included age on admission in days, cases with BE had mean of (6.33±3.51) and (5.54 ± 1.91) in cases without, P value is not statistically significant (0.247), regarding age at starting of jaundice in days, BE occur in cases with mean of (2.33±1.17) and (2.35±0.83) in cases without, P value is not statistically significant (0.947) (Table 5). For Gestational age in weeks, BE occur in cases with a mean of (36.67±0.97) and a mean of (37.44±1.59) in cases without, P value is not statistically significant (0.079), regarding TSB at admission in mg/dl, cases with BE had mean of (29.53±4.38) and (27.72±1.61) in cases without, p value is statistically significant (0.012), (**Table 3**).

This study suggests that certain risk factors may increase the risk of BE, so we performed binary logistic regression model to measure the odd OR (odds ratio) in 95% CI (confidence interval) of

these risk factors: The weight at admission had odd ratio (9.87) range (1.51-93.19), the TSB had odd ratio (1.79) range (0.62-2.02), Sepsis had odd ratio (0.76) range (0.01-1.57), Rh incompatibility had odd ratio (15.1) range (4.2-101.7), other causes had odd ratio (0.42) range (0.26-0.96), ABO incompatibility had odd ratio (1.88) range (0.17-20.79) and combined ABO and Rh incompatibility had odd ratio (1.26) range (0.168-5.49),(**Table 4**).

Table 1. Descriptive statistics of the continuous variables within the sample (N=72)

Variable	Mean	SD	Lower	Upper
Age on admission (days)	5.7	2.3	2	15
Age at starting jaundice (days)	2.4	0.9	1	5
Weight (kg)	2.95	0.42	2.2	4
Gestational age (weeks)	37.3	1.5	34	41
TSB at admission (mg/dl)	28.1	2.5	25	42

SD: standard deviation of the mean

Table 2. BIND score as predictor of BE

BIND category	Total cases at admission	Short term outcome					
		Well		BE		Death	
		No.	%	No.	%	No.	%
0 (normal)	33	33	100.0	0	0.0	0	0.0
1-3 months	20	19	95.0	1	5.0	0	0.0
4-6 months	11	5	45.5	6	54.5	0	0.0
7-9 (Severe ABE)	8	0	0.0	7	87.5	1	12.5
Total	72	57	79.2	14	19.4	1	1.4

Table 3. Comparison of Short term outcomes according to continuous variables

Variable	BE (n 15) Mean ± SD	Well (n 57) Mean ± SD	*P. value*
Age on admission (days)	6.33 ± 3.51	5.54 ± 1.91	0.247 *NS*
Age at starting jaundice (days)	2.33 ± 1.17	2.35 ± 0.83	0.947 *NS*
Gestational age (weeks)	36.67 ± 0.97	37.44 ± 1.59	0.079 *NS*
TSB at admission (mg/dl)	29.53 ± 4.38	27.72 ± 1.61	0.012 *

*SD: standard deviation of the mean , NS : not statistically significant * statistically significant*

Table 4. Odd ratios of the risk factors of BE

Risk factor	OR (95% CI)	*P. value*
Weight	9.87 (1.51 – 93.19)	0.012*
TSB	1.79 (0.62 – 2.02)	0.013*
Sepsis	0.76 (0.01 – 1.57)	0.120 NS
Rh incompatibility	15.1 (4.2 – 101.7)	0.020*
others	0.42 (0.26 – 0.96)	0.195 NS
Rh & ABO incompatibility	1.26 (0.168 – 5.49)	0.043*
ABO incompatibility	1.88 (0.17 – 20.79)	0.031*

*OR: Odds ratio , NS : not statistically significant * statistically significant*

DISCUSSION

The incidence of ABE (according to BIND score) with severe hyperbilirubimia at admission and bilirubin encephalopathy at short term outcome recorded in the present study is intolerably high. This is because the disease, though preventable, results in permanent brain damage, high mortality and morbidity including deafness, cerebral palsy and mental retardation (1). Sepsis was the cause of jaundice in (5.6%), while in Manning et al (17) study (4%) and in Bulbul et al (18) (9.5%). Rh incompatibility was the cause in (23.6%) while in Bulbul et al (18) (5.1%) and in Manning et al (17)

(6%), this disagreement may be due to large number of families have poor awareness about Rh incompatibility, indication and benefit of anti D, Anti D which is not always available and deliveries outside the hospitals including midwife interference. ABO incompatibility was the cause in (37.5%), Manning et al (17) showed (33%) and in Gamalelden et al (14) (23.7%). This increase in percentage due to poor education of many parents regarding their blood group, large number of cases with ABO incompatibility with high TSB requiring ET are referred to us from other hospital either due to lack of blood exchange set or under experienced staff. Combined ABO and Rh was the cause in (13.9%) that disagrees with Bulbul et al (18) (2.9%) and Gamalelden et al (14) (2.4%) because of the high number of Rh incompatibility cases in our study compared to other studies. Other causes of severe jaundice was found in (19.4%) in this study, Manning et al (17) showed (10%) of cases had other causes of jaundice, this disagreement due to difference in investigation facilities between Iraq and UK The mean age of admission in days was (5.7±2.3) with a range of (2-15) days, Age at which the jaundice started in days had a mean of (2.4±0.9) with a range (1-5) days, Bulbul et al (18) showed that the mean age of admission was (5.3) days with a range (1–28) and mean age of jaundice started was (3.5) with a range (1-26) days, families noticed the jaundice of the newborns on the third or fourth day of life and consult medical centers on the fifth day of life due to poor education about jaundice complications. Weight at admission in kilogram in this study showed a mean of (2.95±0.42) with a range (2.2-4). The mean gestational age in weeks in this study is (37.3±1.5) with a range (34-41) while Bulbul et al (18) had a mean gestational age of (38.6) weeks and a range of (35-42) weeks. The mean TSB at admission in mg/dl in this study is (28.1±2.5) and a range of (25-42). Iskander et al study in Egypt (19) had a mean of (28.2) with a range of (17-61) but Manning et al (38) had a mean serum bilirubin concentration of (32.2) mg/dl with range (28.3–44.5),this higher mean may be due to higher levels of TSB at admission in Manning study. BIND score as a predictor of BE in the 72 cases includes (45.8%) cases had BIND score of (0), none of them developed BE at discharge. Gamalelden et al (14) and Iskander et al (19) found (60%) and (66%) of cases respectively had (0) BIND score at admission. The difference is due to poor education of the parents, illiteracy, and false thought of the community regarding management of neonatal jaundice, bad situations regarding security and roads block that might cause late presentation of neonate to the hospital. Cases with BIND score 1-3(subtle) were (27.8%), Iskander et al (19) and Gamalelden et al (14) found (24.8%) and (22%) of cases respectively had subtle BIND score at admission. Cases with BIND score 4-6 (moderate ABE) were (15.3%), Iskander et al

(19) and Gamalelden et al (14) found (12.6%), (10%) of cases respectively had moderate ABE at admission. In this study (54.5%) of the cases with moderate ABE developed BE at discharge, this agrees with Gamalelden et al (14) that found (56%) of cases with moderate ABE at admission had BE at discharge. Cases with BIND score 7-9 (severe ABE) were (11.1%), in Khatami et al study in Iran (20) and Gamalelden et al (14) (12%) and (8%) of cases respectively had severe ABE at admission, in this study all cases (100%) with severe ABE developed signs of BE at discharge, Iskander et al (19) and Gamalelden et al (14) found (94%) and (95%) of cases respectively with severe ABE developed BE at discharge.

The causes of hyperbilirubinemia in this study have a high risk for development of BE at discharge as it is statistically significant with P value of (0.02), this result agrees with Gamalelden et al (14). Radmacher et al (21) study found that ABO and Rh incompatibility are not risk factor for BE and only sepsis is a risk factor, this is due to proportions of infants with ABO and Rh blood incompatibilities in the study did not differ significantly between the neonate with and without BE, suggesting that other factors such as G6PD, dehydration, and harmful cultural practices may play a more significant role in determining the course and severity of newborn jaundice in that area. Level of TSB at admission had a significant effect on short term outcome with P value of (0.012) which is comparable with Arnolda et al (22) and Gamalelden et al (14).

CONCLUSIONS

Low birth weight, hemolytic diseases and sepsis greatly increase the probability of severe hyperbilirubinemia and subsequent ABE at admission and BE at discharge.

Ethical Clearance

Ethical clearance and approval of the study are ascertain by the authors, all ethical issues and data collection were in accordance with the World Medical Association Declaration of Helsinki 2013 for ethical issues of researches. Verbal consent was obtained from parents of the cases. All official agreement were obtained from the ministry of health and environment/ scientific committee

Conflict of interest

None declared by the authors

***Funding*:** None, self-funded by the authors

REFERENCES

1. *Click R, Smith JD, Fowler L, et al. An osteopathic approach to reduction of readmissions for neonatal jaundice. OsteopathicFamily Physician 2012;5:17-23.*
2. *Ambalavanan N, Carlo WA. Jaundice and Hyperbilirubinemia in the Newborn.in: Kliegman RM, Stanton BF, St Games JW, et al. Nelsontextbook of pediatrics. 19thed. Philadelphia, PA: Saunders Elsevier;2011:1091-1103.*
3. *Maisels MJ, Kring E. Length of stay, jaundice, and hospital readmission. Pediatrics 1998;101(6):995–998.*
4. *Narang A, Kumar P, Kumar R. Neonatal jaundice in very low birth weight babies. Indian J Pediatr 2001;68:307-309.*
5. *Canadian Pediatric Society. Position Statement (FN2007-02). Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants (35 or more weeks 'gestation). Pediatr Child Health 2007;12:1B-12B.*
6. *Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. N Engl J Med 2001;344:581–590.*
7. *Sisson TR, Drummond GS, Samonte D, et al. Sn-protoporphyrin blocks the increase in serum bilirubin levels that develops postnatally in homozygous Gunn rats.J Exp Med. 1988;167(3):1247-1252*
8. *Clarence W. Gowen Jr. Fetal and Neonatal Medicine.in: kliegman R, Behram R, Jenson HB, et al.nelson essentials of pediatrics. 6thed. Philadelphia, PA: Saunders Elsevier;2011:244-252.*
9. *Bhutani VK, MaiselsMJ, Stark AR, et al. Management of jaundice and prevention of severe neonatal hyperbilirubinemia in infants >or=35 weeks gestation. Neonatology2008;94(1):63-67.*
10. *Watchko JF, Lin Z. exploring the genetic architecture of neonatal hyperbilirubinemia. Semin Fetal Neonatal Med. 2010; 15:169–175.*
11. *Wennberg R, Ahlfors C, Bhutani V, et al. Toward understanding kernicterus: achallenge to improve the management of jaundiced newborns. Pediatrics 2006; 117(2):474–485.*
12. *Maisels MJ, Jaundice, in: Macdonald M, Mullet M, Seshia M. Avery's neonatology pathophysiology of management of the newborn.6thed. Philadelphia: Lippincott –Williams of Wilkins. 2005: 768–846.*
13. *Johnson L, Brown AK, Bhutani V. BIND –a clinical scorefor bilirubin-induced neurologic dysfunction in newborns. Pediatrics1999;104:746–747.*
14. *Gamaleldin R, Iskander I, Seoud I, et al. Risk factors for neurotoxicity in newborns with severe neonatal hyperbilirubinemia. Pediatrics2011;128(4):e925–e931.*
15. *American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of*

hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics2004;114:297–316.

16. *Johnson L, Bhutani VK, Karp K, Sivieri EM, et al. Clinical report from the pilot USA kernicterus registry (1992 to2004). J Perinatol 2009;29:S25–S45.*
17. *Manning D, Todd P, Maxwell M, et al. Prospective surveillance study of severe hyperbilirubinaemia in the newborn in the UK and Ireland. Arch Dis Child Fetal Neonatal Ed 2007;92:F342-346.*
18. *Bulbul A, Cayonu N, Uslu S, et al. Evaluation of risk factors for development of severe hyperbilirubinemia in term and near term infants. Pak J Med Sci2014;30(5):1113–1118.*
19. *Iskander I, Gamaleldin R, El Houchi S, et al. Serum bilirubin and bilirubin/albumin ratio as predictors of bilirubin encephalopathy. Pediatrics2014;134(5):1330-1339.*
20. *Khatami SF, Parvaresh P. Acute Bilirubin Encephalopathy in Healthy Term Neonates Requiring Exchange Transfusion. Iranian Journal of Neonatology2012;1(3):8-12.*
21. *Radmacher P, Olusanya B, Slusher T, et al. A modified Bilirubin-induced neurologic dysfunction (BIND-M) algorithm is useful in evaluating severity of jaundice in a resource limitedsetting. BMC Pediatrics2015;15:28.*
22. *Arnolda G, Nwe HM, Trevisanuto D, et al. Risk factors for acute bilirubin encephalopathy on admission to two Myanmar national pediatric hospitals. Matern Health Neonatal Perinatol 2015; 15;1:22.*