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Original article

Outcome of Neonatal Hyperbilirubinemia and Its Effect on the Neurological System in Full Term and Preterm Babies

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Abstract

Background: Bilirubin-induced neurologic dysfunction (BIND) is the term applied to the spectrum of neurologic abnormalities associated with hyperbilirubinemia. **This study aimed to** study the outcome of neonatal hyperbilirubinemia and its effect on the neurological system in full term and preterm babies. **Methods:** This cross sectional study was conducted on 112 patients with indirect hyperbilirubinemia (75 full terms and 37 preterms). All the studied patients were subjected to full history taking, complete clinical assessment, laboratory investigations and BIND score. Follow up was done at 3 months by detailed neurological assessment. **Results**: The preterm group had a significantly higher frequency of adverse outcome (62.2%) compared to the full term group (25.3%), p<0.001. The mortality rate was significantly higher in the preterm group (32.4%) compared to the full term group (5.3%). The BIND score was significantly higher in the preterm group (29.7%) compared to the full term group (20%), p=0.022. Neonates with adverse outcome had statistically higher BIND scores (7.5±1.3) compared to neonates with normal outcome (4.2±1.6), p<0.001. BIND score correlated positively with the total bilirubin, and negatively with weight and Apgar score. ROC analysis was done to assess the performance of BIND score to predict adverse outcomes in the studied neonates. At a cutoff point > 5, the sensitivity was 90.5% and specificity was 77.1%. **Conclusion:** BIND score can predict adverse outcomes in infants with neonatal hyperbilirubinemia, which would be more useful for the clinicians to take a more prompt and aggressive intervention on those with a high risk of adverse outcomes.

Keywords: Neonatal; Hyperbilirubinemia; Neurological; Full term; Preterm

Introduction

Neonatal hyperbilirubinemia is a common clinical problem encountered during the neonatal period, especially in the first week of life (1)**.** Nearly 8% to 11% of neonates develop hyperbilirubinemia. When the total serum bilirubin (TSB) rises above the 95th percentile for age (high-risk zone)

during the first week of life, it will be considered as hyperbilirubinemia (2)**.**

In most infants, unconjugated hyperbilirubinemia reflects a normal transitional phenomenon. However, in some infants, entry of unconjugated bilirubin into the brain can cause both short-term and long-term neurological dysfunctions (bilirubin encephalopathy). In this case, unconjugated hyperbilirubinemia is potentially harmful for the central nervous system and may cause severe and permanent neurological sequelae that is defined as bilirubin-induced neurological dysfunction (BIND) (3)**.**

Bilirubin-induced neurologic dysfunction (BIND) is the term applied to the spectrum of neurologic abnormalities associated with hyperbilirubinemia. It can be further divided into characteristic signs and symptoms that appear in the early stages (acute) and those that evolve over a prolonged period (chronic). The pathogenesis of BIND is multifactorial and includes interaction between the level of unconjugated bilirubin, free bilirubin, bilirubin bound to albumin, bilirubin passed through the brain-blood barrier and nerve damage (4)**.**

Kernicterus, or bilirubin encephalopathy, is a condition caused by bilirubin toxicity to the basal ganglia and various brain stem nuclei. Surviving infants usually develop a severe form of athetoid cerebral palsy, hearing loss, dental dysplasia, paralysis of upward gaze and, less often, intellectual and other handicaps (5)**.** It could be also presented in the form of subtle neurodevelopmental delay or learning disabilities without classical findings of kernicterus that, after careful evaluation, appears to be due to bilirubin neurotoxicity (6)**.**

Almost all preterm infants less than 35 weeks gestational age (GA) have elevated total serum/plasma bilirubin (TB) levels. When adjusted for gestational and postnatal ages, preterm infants are inherently at greater risk than more mature infants (those born term or late preterm) for developing bilirubin-induced neurologic dysfunction (BIND), which, if not treated in a timely and appropriate manner, can result in chronic neurologic sequelae (7,8)**.**

This study aimed to study the outcome of neonatal hyperbilirubinemia and its effect on the neurological system in full term and preterm babies.

Patients and methods

This cross sectional study was conducted on newborns admitted in the Neonatal Intensive Care Unit (NICU) of Benha University Hospitals with hyperbilirubinemia during the period from January 2022 to July 2022. During the study period, 155 patients of indirect hyperbilirubinemia were admitted to NICU, 16 patients were excluded due to severe congenital anomalies and 27 patients were excluded due to birth asphyxia and hemodynamic instability. Therefore, the final number of included patients was 112.

Inclusion criteria:

- Neonates with hyperbilirubinemia reached level of phototherapy or exchange transfusion according to

the American Academy of Pediatrics guidelines. (9)

- Age: from 0 to 28 day
- Full term and preterm babies
- Both sexes were included

Exclusion criteria:

- Direct hyperbilirubinemia
- Perinatal asphyxia
- Severe birth defects or congenital anomalies.
- Hemodynamic instability

Written consents were obtained from all the participants' parents. The study was approved by the ethics committee of Benha Faculty of Medicine

All the studied patients were subjected to full history taking, complete clinical assessment and laboratory investigations as complete blood count, ABO and Rh grouping, serum bilirubin total and direct to be repeated according to the case and reticulocytic count.

Modified bilirubin-induced neurological dysfunction (BIND) score was applied on admission for the patients who presented with neurological manifestations and was used to assess the severity of acute bilirubin encephalopathy (ABE) through examining the mental state, muscle tone, and cry pattern (10).

Follow up was done at 3 months by detailed neurological assessment including muscle tone of the trunk and upper and lower limbs, reflexes including deep tendon reflexes, primitive neonatal reflexes (Moro, suckling, and tonic neck reflexes), extrapyramidal reflexes (cremasteric and abdominal reflexes) and neurodevelopmental assessment (head control, social smile, response to sound, and eye contact). Babies who depicted any abnormal motor examination were subjected to brain stem auditory evoked response (BAER) and magnetic resonance imaging (MRI).

Statistical analysis:

The collected data were revised, coded and tabulated using Statistical Package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Shapiro test was done to test the normality of data distribution. Mean ± SD was used for parametric numerical data and median and range for non-parametric numerical data. Frequency and percentage were used for non-numerical data. Student T Test was used to assess the statistical significance of the differences between two study group means. Chi-Square test was used to examine the relationship between two qualitative variables. Fisher's exact test: was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells.

Correlation analysis was used to assess the strength of association between two quantitative variables. The correlation coefficient defines the strength and direction of the linear relationship between two variables. The ROC curve (receiver operating characteristic) provides a useful way to evaluate the sensitivity and

specificity for quantitative diagnostic measures that categorize cases into one of two groups. The optimum cut off point was defined as that which maximized the AUC value. The area under the ROC curve (AUC) results were considered excellent for AUC values between 0.9-1, good for AUC values between 0.8-0.9, fair for AUC values between 0.7-0.8, poor for AUC values between 0.6-0.7 and failed for AUC values between 0.5-0.6. Probability of results; all reported p values were two-tailed and p <0.05 was considered to be significant

Results

This study included 112 neonates (75 full terms and 37 preterms) admitted to Neonatal Intensive Care Unit (NICU) of Benha University Hospitals with hyperbilirubinemia during the period from January 2022 to July 2022. The gestational age was significantly higher in the full term group than in the preterm group, while there were no statistical differences between the groups regarding sex or residence (Table 1).

The preterm group had significantly lower hemoglobin levels compared to the full term group while there were no significant differences between the groups regarding WBCs, platelets, reticulocyte and RBC counts as well as the total and direct bilirubin levels (Table 2).

The most common cause of jaundice in full term babies was physiological jaundice (66.7%), followed by ABO incompatibility while in the preterm group, the most common cause was prematurity (70.3%), followed by sepsis (21.6%), p<0.001. Regarding treatment of jaundice, 72.3% of the patients were treated by phototherapy, 17.9% by intensive phototherapy and 9.8% by exchange transfusion with no significant differences between the groups. Regarding associated comorbidities, in the full term group, 8% of the patients had sepsis, 5.3% had TTN and 86.7% had no comorbidities, while in the preterm group; 40.5% had RDS, 40.5% had low birth weight, 19% had sepsis, with significant differences between the groups. There was no significant difference between the full term and preterm groups regarding the occurrence of kernicterus (10.7% and 19% respectively), p=0.22 (Table 3).

The preterm group had a statistically significant higher frequency of adverse outcomes as death and developmental delay compared to the full term group (Table 4). Neonates with adverse outcome had statistically significant higher BIND scores compared to neonates with normal outcome, in preterm and full term neonates (Table 5). Bind score correlated positively with total bilirubin, and correlated negatively with weight and Apgar score, but it had no statistical correlation with gestational age, capillary refill time, respiratory rate, heart rate, random blood sugar, hemoglobin level, WBCs and platelets counts, direct bilirubin and reticulocyte count (Table 6).

ROC analysis was done to assess the performance of BIND score to predict adverse outcome in the studied neonates; AUC was 0.935 (95% confidence interval: 0.889-0.980), p<0.001. At a cutoff point $\geq$ 6, the sensitivity was 90.5% and specificity was 77.1% (Figure 1).

Table 1: Sociodemographic data of the studied groups

Sociodemographic data		Full term		Preterm		Total		Test	P value
		N=75	%	N=37	%	N=112	%		
Sex	**Males**	48	64.0%	21	56.8%	69	61.6%	X^2=0.55	0.45
	Females	27	36.0%	16	43.2%	43	38.4%		
Gestational age (weeks)	**Mean±SD**	38.3±1.1		33±2.1		36.5±2.9		t=17.4	**<0.001***
	Range	37-41		30-36		30-41			
Residence	**Urban**	30	40.0%	16	43.2%	46	41.1%	X^2=0.11	0.74
	Rural	45	60.0%	21	56.8%	66	58.9%		

t: Student t-test; X^2: Chi square test; *: significant

Table 2: Laboratory investigations of the studied groups

Laboratory investigations		Full term	Preterm	Total	Test	P value
		N=75	N=37	N=112		
Hemoglobin (gm/dl)	**Mean±SD**	18.3±2.1	15.6±1.1	17.5±2.2	t=7.5	**<0.001***
	Range	15.3-22	14.5-17.2	14.5-22		
WBCs (10^3/l)	**Mean±SD**	11.8 ±1.7	11.5±2.1	11.7±1.9	t=1.1	0.34
	Range	9.4-15.5	9-16.1	9-16.1		
Platelets (10^3/l)	**Mean±SD**	238 ±63	255±57	247±60	t=2.1	0.11
	Range	165-355	170-318	165-355		
Reticulocyte count (%)	**Mean±SD**	6.5 ±1.8	6.7±2.1	6.6±1.9	t=0.6	0.57
	Range	2.5-9.6	2.6-9	2.5-9.6		
RBS (mg/dl)	**Mean±SD**	76.7 ±7	72.3±6.5	75.1±6.9	t=2.4	0.07
	Range	65-90	65-82	65-90		
Total bilirubin (mg/dl)	**Mean±SD**	19.9 ±3.2	18.8±2.9	19.6±3.1	t=1.7	0.11
	Range	16.6-25.6	15.6-24.3	15.6-25.6		
Direct bilirubin (mg/dl)	**Mean±SD**	0.96 ±0.5	1.1±0.3	1±0.4	t=1.9	0.09
	Range	0.7-2.6	0.9-1.4	0.7-2.6		

t: Student t-test; *: significant, WBCs: white blood cells, RBS: random blood sugar

Table 3: Causes of jaundice, comorbidities and treatment in the studied groups

Causes, comorbidities and treatment of jaundice		Full term		Preterm		Total		Test	P value
		N=75	%	N=37	%	N=112	%		
Cause of jaundice	Physiological	50	66.7%	0	0.0%	50	44.6%	X^2=86.3	**<0.001***
	ABO incompatibility	9	12.0%	1	2.7%	10	8.9%		
	Rh incompatibility	2	2.7%	2	5.4%	4	3.6%		
	Sepsis	7	9.3%	8	21.6%	15	13.4%		
	Prematurity	0	0.0%	26	70.3%	26	23.2%		
	IDM	7	9.3%	0	0.0%	7	6.3%		
Treatment of jaundice	Phototherapy	57	76.0%	24	64.9%	81	72.3%	X2=5.1	0.076
	Intensive phototherapy	14	18.7%	6	16.2%	20	17.9%		
	Exchange transfusion	4	5.3%	7	18.9%	11	9.8%		
	None	65	86.7%	0	0.0%	65	58.0%		
Other comorbidities	RDS	0	0.0%	15	40.5%	15	13.4%	X^2=97.5	**<0.001***
	Sepsis	6	8.0%	7	19%	13	11.6%		
	Prematurity	0	0.0%	15	40.5%	15	13.4%		
	TTN	4	5.3%	0	0.0%	4	3.6%		
Kernicterus	No	67	89.3%	30	81.1%	97	86.6%	X^2=1.4	0.22
	Yes	8	10.7%	7	19%	15	13.4%		

X^2: Chi square test; *: significant, IDM: infant of diabetic mother, RDS: respiratory distress syndrome, TTN: transient tachypnea of newborn

Table 4: Outcomes in the studied groups

Outcomes		Full term		Preterm		Total		Test	P value
		N=75	%	N=37	%	N=112	%		
Outcome	**Normal**	56	74.7%	14	37.8%	70	62.5%		
	Adverse outcome (death or Delayed development)	19	25.3%	23	62.2%	42	37.5%	X^2=14.3	**<0.001***
Death		4	5.3%	12	32.4%	16	14.3%	X^2=14.8	**<0.001***
Delayed development		15	20.0%	11	29.7%	26	23.2%		
• **Head control**		4	5.3%	3	8.1%	7	6.3%		
• **Social smile**		4	5.3%	3	8.1%	7	6.3%		
• **Respond to sound**		19	25.3%	7	18.9%	26	23.2%		
• **Eye contact**		12	16.0%	7	18.9%	1	0.9%		
• **Abnormal movement**		9	12.0%	3	8.1%	12	10.7%	X^2=27.8	**0.022***
• **Hypotonic**		2	2.7%	2	5.4%	4	3.6%		
• **Hypertonia**		3	4.0%	1	2.7%	4	3.6%		
• **Absent reflexes**		2	2.7%	2	5.4%	4	3.6%		
• **Exaggerated reflexes**		3	4.0%	1	2.7%	4	3.6%		

X^2: Chi square test; *: significant,

Table 5: BIND score in infants with normal and adverse outcomes

Groups		Outcome		Test	P value
		Normal	Adverse outcome		
		N=70	N=42		
Total	**Mean±SD**	4.2±1.6	7.5±1.3	t=11.1	**<0.001***
	Range	1-7	4-9		
Preterm	**Mean±SD**	4.6±1.2	7.7±1.4	t=7.2	**<0.001***
	Range	3-7	4-9		
Full term	**Mean±SD**	4.1±1.7	7.2±1.2	t=7.4	**<0.001***
	Range	1-7	5-8		

Discussion

The susceptibility to the neurotoxic effects of bilirubin varies according to cell type, brain maturity, and brain metabolism. Also, the concentration of bilirubin in the brain and the duration of exposure of the brain to bilirubin are important determinants of the neurotoxic effects of bilirubin, whereas the correlation between serum bilirubin concentration and bilirubin encephalopathy is poor in infants without hemolysis (4)**.**

In the current study, the preterm group had a significantly higher frequency of adverse outcomes (62.2%) compared to the full term group (25.3%), p<0.001. In the same way, the neurodevelopmental outcomes of preterm infants in Bangladesh, were studied and it was reported that of the 159 enrolled children, 65% survived, 16% died, and 19% were not available for follow-up. At a mean age of 31 months, developmental status of the 85 children followed-up for ≥12 months was normal in 32%; 45% had mild and 23% had serious neurodevelopmental impairments. Cognitive impairment was the most common deficit (60%) (11).

Our results agreed with others**,** who observed that the outcome data from 76 ABE patients included 51 normal outcomes and 25 adverse outcomes. Twelve severe ABE infants died during hospitalization (4 with ABO hemolysis, 3 with Rh hemolysis, 4 with sepsis, 1 with ABO hemolysis and sepsis), and 13 infants survived with poor outcomes (4 patients with hearing disabilities, 1 with cerebral palsy (CP), and 8 with both hearing disability and CP). Thus, morbidity of 33% (25/76) and mortality of 16% (12/76) were observed in ABE cases **(12).**

In the study done in 2010 on 426 neonates with neonatal jaundice, twelve (2.8%) individuals died with jaundice. Kernicterus developed in nine (2.1%) children, four of whom survived with neurological sequelae **(13)**. Later on, in 2020, it was found that the spectrum of bilirubin induced neurological dysfunction noted among their patients included 8/19 with classic kernicterus (6 had associated mild mental delay), 3/19 with isolated auditory impairment, 1/19 with severe motor and mild mental delay and 7/19 with mild motor delay **(14).**

However, it was reported in a previous study that, of the babies admitted with hyperbilirubinemia, 235/242 (97%) were discharged alive. Seven babies died, giving a mortality of 2.9%. Six of the babies had severe hyperbilirubinemia and one baby died due to severe anaemia. Of the 6 babies with severe hyperbilirubinemia, 1 had rhesus incompatibility and 2 had ABO incompatibility. The case fatality rate for the babies with severe hyperbilirubinemia was 20% (6/30). No preterm baby died **(15)**.

In the current study, neonates with adverse outcome had statistically higher BIND scores (7.5±1.3) compared to neonates with normal outcome (4.2±1.6), p<0.001. Our results were comparable with others (11)**,** who observed a significantly higher value of BIND score (6.6 ± 1.4 vs. 4.4 ± 1.7, $P < 0.001$) in infants with adverse outcome as compared to those with normal outcome.

A group of researchers observed that on admission, 25 infants had moderate ABE (BIND 4–6). Among 22 of those 25 infants attending follow-up, 13 were healthy, 5 had isolated auditory neuropathy, and 4 had frank kernicterus. Severe ABE (BIND score 7–9 on admission) occurred in 33 infants. Two infants with BIND score of 7, lost to follow-up, were neurologically healthy at discharge but had bilateral (RR) automated auditory brainstem response (AABR). The remaining 31 infants (94%) had adverse outcomes compared with only 9 (41%) of 22 infants with moderate encephalopathy **(16)**

Similarly**,** it was reported that in the study done on 2011, no infants with BIND scores of 0 to 1 on admission (N = 166) developed later signs of bilirubin encephalopathy (BE). Fourteen of 25 patients with moderate ABE (BIND score of 4–6) and 18 of 19 with severe ABE (BIND score 7–9) had persistent evidence of BE at the time of death or discharge. A pretreatment BIND score was a very good predictor of outcome. BIND scores of ≥6 anticipated an adverse outcome in 22 of 25 patients (88%) **(17)**.

In the present study, BIND score correlates positively with total bilirubin, and correlates negatively with weight and Apgar score, while it had no significant correlation with gestational age, capillary refill time, respiratory rate, heart rate, random blood sugar, hemoglobin, WBCs count, platelets count, direct bilirubin or reticulocyte count. Similarly**, it was** reported that there was a positive correlation between BIND scores and TSB, the coefficient of determination was not very high (r2 = 0.54, *P* <0.005) **(18).**

In the current study, ROC analysis was done to assess the performance of BIND score to predict the adverse outcomes in the studied neonates; AUC was 0.935 (95% confidence interval: 0.889-0.980), p<0.001. At a cutoff point ≥ 5, the sensitivity was 90.5% and specificity was 77.1%. Our results were in agreement with the research that found that ROC analysis revealed a BIND score of 6 (AUC 0.839) with a sensitivity of 84.0%, a specificity of 77.1%, a positive predictive value of 65.9%, and a negative predictive value of 90.2% **(12)**.

It was reported that all infants with severe acute bilirubin encephalopathy (BIND scores 7-9) either died or suffered residual neurologic and auditory impairment. Of 24 patients with moderate encephalopathy (BIND 4-6), 15 (62.5%) resolved following aggressive intervention and were normal at follow-up. Three of 73 infants with mild encephalopathy (BIND scores 1-3) but severe jaundice (TSB ranging 33.5-38 mg/dL; 573-650 μmol/L) had residual neurologic and/or auditory impairment. A BIND score ≥4 had a specificity of 87.3% and a sensitivity of 97.4% for predicting poor neurologic outcomes (receiver operating characteristic analysis). BIND scores trended higher with severe hyperbilirubinemia (r2 = 0.54, P < .005), but 5/39 (13%) infants with total serum bilirubin (TSB) ≥36.5 mg/dL (624 μmol/L) had BIND scores ≤3, and normal outcomes at 3-5 months **(18)**.

Conclusion

Our results showed that the preterm group had a statistically significant higher frequency of adverse outcome compared to

full term group. Neonates with adverse outcome had statistically significant higher BIND scores compared to neonates with normal outcome, in preterm and full term neonates. As for the performance of BIND score to predict adverse outcomes in the studied neonates, AUC was 0.935, at a cutoff point $\geq$ 6, the sensitivity was 90.5% and specificity was 77.1%. BIND score would be useful for the clinicians to take a more prompt and aggressive intervention to those with a high risk of adverse outcomes to reverse bilirubin-induced neurological dysfunction during the early phases.

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