EVALUATION OF PATTERNS OF NEONATAL BILIRUBIN ENCEPHALOPATHY USING BILIRUBIN INDUCED NEUROLOGIC DYSFUNCTION {BIND SCORE} RELATED TO GESTATIONAL AGE AND BODY WEIGHT

By

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ABSTRACT

Introduction: *Jaundice is the most common condition that requires medical attention in newborns. Kernicterus means "yellow kern," with kern indicating the most commonly affected region of the brain. Identifying neonates with intermediate to advanced acute bilirubin encephalopathy {ABE}.*

Aim of work: *Early detection of neonatal encephalopathy using BIND score.*

Patients and methods: *This prospective study was carried out in NICU of Sayed Galal University Hospitals on 100 neonates; divided into two groups: first group of 50 full-term neonates and second group of 50 preterm neonates. Serum bilirubin was determined.*

Results of the study*: The full-term group consisted of 36 males (72%) and 14 females (28%) with mean age ± SD of 7.5 ± 2.4 days (range, 5-14 days), while the preterm group consisted of 34 males (68%) and 16 females (32%) with mean age ± SD of 5.2 ± 1.4 days (range, 3-9 days). Statistically, there was a high significant difference between full-term and preterm groups regarding age, but there was a non-significant difference regarding sex. Also, there were non-significant differences between full-term and preterm groups regarding natal history including mode of delivery and complicated delivery. There were statistically high significant differences between full-term and preterm groups regarding weight, respiratory rate and heart rate, a significant difference regarding head circumference and non-significant differences regarding length and capillary refill. There were statistically high significant differences between full-term and preterm groups regarding hemoglobin concentration, red blood cell count, white blood cell count and total serum bilirubin and non-significant differences regarding platelet concentration, direct serum bilirubin, ABO and RH. There was statistically a high significant relation between BIND score and consultant diagnosis.*

Conclusion: *The use of the BIND score among consultant pediatricians and their resident doctors is reliable for identifying neonates with the clinical diagnosis of neonatal bilirubin encephalopathy.*

Recommendations: *We recommend development of Bilirubin-Induced Neurological Dysfunction (BIND score), because it is useful in evaluation of neonatal jaundice as it is fast, cheap and more trusted than other scores. Also, use of this score prevents complications which have long-term, tragic consequences for the neonates, their families and their communities.*

Key words: *neonatal jaundice, kernicterus, neonatal bilirubin encephalopathy, bilirubin-induced neurologic dysfunction.*

INTRODUCTION

Jaundice is the most common condition that requires medical attention in newborns. The yellow coloration of the skin and sclera in newborns with jaundice is the result of accumulation of unconjugated bilirubin. In most infants, unconjugated hyperbilirubinemia reflects a normal transitional phenomenon. However, in some infants, serum bilirubin levels may rise excessively, which can be a cause for concern because unconjugated bilirubin is neurotoxic and can cause death in newborns and lifelong neurologic sequelae in infants who survive (kernicterus) **(Huang et al., 2011).**

The term kernicterus literally means "yellow kern," with kern indicating the most commonly affected region of the brain (ie, the nuclear region). Historically, the term refers to an anatomic diagnosis made at autopsy based on a characteristic pattern of staining found in babies who had marked hyperbilirubinemia before they died. Hervieux first described the condition in 1847, and Schmorl first used the term kernicterus as early as 1903. Regions most commonly affected include the basal ganglia; hippocampus; geniculate bodies; and cranial nerve nuclei, such as the oculomotor, vestibular, and cochlear. The cerebellum can also be affected. Bilirubin-induced neurologic dysfunction (BIND) refers to the clinical signs associated with bilirubin toxicity (ie, hypotonia followed by hypertonia and/or opisthotonus or retrocollis) and is typically divided into acute and chronic phases. The 2 terms are commonly used interchangeably, but this use is not technically accurate because one refers to clinical manifestations and the other to an anatomic diagnosis **(Brooks et al., 2011).**

Identifying neonates with intermediate to advanced acute

bilirubin encephalopathy {ABE} ABE defines an encephalopathic state induced by hazardous hyperbilirubinemia during the first days of postnatal life and is characterized by a constellation of abnormal clinical signs typically progressive in their severity. In term (37week's gestation) and late preterm (34-37 week's gestation) infants, the initial phase of ABE is characterized by stupor (lethargy), hypotonia, and poor sucking These nonspecific signs are seen in numerous clinical contexts, but in a hyperbilirubinemic infant, they should raise the possibility of early ABE. Clinical signs of intermediate to advanced stages of ABE are increasingly more specific to bilirubin-induced **(Escobar et al., 2005)**

The aim of the work is early detection of neonatal encephalopathy using BIND score.

PATIENT AND METHODS

A prospective study was carried out in NICU of Sayed Galal University Hospitals during a period of 6 months from July2017 to January2018.

Well-informed verbal and written consents were obtained from parents or caregivers. The study was approved by the Ethics Committee of the Faculty of Medicine, Al-Azhar University.

Our studied cases were selected by simple random method from all N.B attending NICU in Sayed galal university hospital

Inclusion criteria:

1. Newborn < 28 days old
2. Hyperbilirubinemia:

(a) > 20 mg/dl in full term.

(b) > 15mg/dl in preterm**.**

Exclusion criteria:

- Age > 28 days old
- Neonates with any abnormal neurological signs suggesting neurological disease (hypoxic ischemic encephalopathy, muscle disease, …etc.).

Methods:

All neonates were subjected to the following:

1. Thorough history taking including

(a) Full history taken with particular emphasis on pre-natal, natal and postnatal gestational age, sex (male/female) weight, family history of other sibling admitted to NICU with jaundice, history about time of apperance of jaundice and its exetension .

(b) Family history

(c) Maternal drugs or disease and mode of delivery.

2. Thorough clinical examination including:

Gestational age, Apgar score and physical assessment.

3. Bilirubin-Induced Neurological Dysfunction (BIND) score on admission:

Clinical bilirubin-induced neurological dysfunction (BIND) score of onset, severity, and progression of acute bilirubin encephalopathy, as elicited by history and physical examination		
Acute bilirubin encephalopathy	Bilirubin-induced neurological dysfunction score	Clinical signs
Mental status		
None	0	Normal
Subtle	1	Sleepy but able to be aroused; decreased feeding
Moderate	2	Lethargy, poor suck, and/or irritable/jittery with strong suck
Advanced	3	Semicoma, apnea, unable to feed, seizures, coma
Muscle tone		
None	0	Normal
Subtle	1	Persistent mild to moderate hypotonia
Moderate	2	Mild to moderate hypertonia alternating with hypotonia, beginning arching of neck and trunk on stimulation
Advanced	3	Persistent retrocollis and opisthotonos, bicycling or twitching of hands and feet
Cry pattern		
None	0	Normal
Subtle	1	High-pitched when aroused
Moderate	2	Shrill, difficult to console
Advanced	3	Inconsolable crying or weak or absent cry
Total BIND (acute bilirubin encephalopathy score)		
Notes: 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 **(Johnson et al., 2009)**.		

4. Laboratory investigations:

- Complete blood picture
- Blood grouping for mother and babies.
- Reticulocyte count
- Total and direct bilirubin before and after phototherapy.
- Coombs test direct and indirect
- Other investigation in special cases

5. Cases complicated with bilirubin encephalopathy were managed by:

Effective phototherapy:

The use of phototherapy, akin to pharmacotherapy, is usually prophylactic with a goal of containing the rate-of-rise of bilirubin. The most effective phototherapy is administered using blue light in the wavelength range of 430 to 490 nm. The effectiveness of irradiance delivered may be modulated by an infant's hematocrit.

Exchange transfusions:

Exchange transfusion is recommended for any infant who shows signs of ABE (hypertonia, arching, retrocollis, opisthotonos, and high-pitched cry) although these signs are often subtle.

Medical treatments:

Treatment is undertaken often to improve dystonia, which can manifest as irritability in infants.

Supportive treatments:

Some of the most encouraging treatments for moderate to severe neonatal encephalopathy are supportive, including gastrostomy tubes and Nisson fundoplication to treat gastroesophageal reflux, and sometimes feeding or gastrostomy tubes to supplement feeding.

RESULTS

Table (1): Age and gender distribution among the studied groups.

	Full-term (n = 50)	**Preterm (n = 50)**	**t**	**p**
Post natal Age (days)				
Mean ± SD	7.5 ± 2.4	5.2 ± 1.4	5.7	< 0.001
Range	5-14	3-9		(HS)
Sex				
Male	36 (72%)	34 (68%)	X^2 =	0.66
Female	14 (28%)	16 (32%)	0.19	(NS)

This table shows highly significant difference between F.T and P.T regarding post natal age of hyperbilirubenmia,while no significant relation between F.T and P.T regarding sex.

Table (2): Perinatal data, natal history and postnatal history

	Full-term (n = 50)		Preterm (n = 50)		X^2	p
	No	%	No	%		
Perinatal data						
Maternal diseases	22	44	16	32	1.53	0.21 (NS)
Drug intake	20	40	16	32	0.69	0.4 (NS)
Radiation	0	0	0	0	0	1 (NS)
Natal history						
Mode of delivery						
CS	34	68	35	70	0.05	0.8
VD	16	32	15	30		(NS)
Complicated delivery						
Prolonged	0	0	0	0	0	1
Obstructed	0	0	0	0		(NS)
Postnatal history						
Apgar						
Mean ± SD	3.5 ± 0.6		3.5 ± 0.7		0.1	0.7
Range	2-5		3-5			(NS)
RD	0 (0%)		0 (0%)		1	1 (NS)
MAS	0 (0%)		0 (0%)		1	1 (NS)
Examination						
Yellowish colour	50 (100%)		50 (100%)		0	1 (NS)
Activity						
Active	18 (36%)		26 (52%)		2.6	0.1
Sleepy	32 (64%)		24 (48%)			(NS)

Table (2) showed that there were non-significant differences between full-term and preterm groups regarding perinatal data (including maternal diseases, drug intake and radiation), natal history (including mode of delivery and complicated delivery) and postnatal history including Apgar score, respiratory distress, meconium aspiration syndrome, examination and activity ($p > 0.05$).

Table (3): Laboratory findings in studied groups

	Full-term (n = 50)	**Preterm (n = 50)**	**t**	**p**
Hb				
Mean ± SD	12.9 ± .4	15.4 ± 0.8	10.8	< 0.001
Range	10.6-15.5	13.9-17		(HS)
RBCs				
Mean ± SD	3.9 ± 0.2	4.96 ± 0.4	17.1	< 0.001
Range	3.4-4.25	3.9-5.5		(HS)
WBCs				
Mean ± SD	12 ± 2	10.4 ± 1.4	4.5	< 0.001
Range	7.8-19.4	8.5-12.5		(HS)
Platelets				
Mean ± SD	269.8±68.7	246.9 ± 51	1.89	0.06
Range	119-458	180-350		(NS)
TSB				
Mean ± SD	22.8 ± 3.1	18.5 ± 0.7	9.5	< 0.001
Range	19.3-30	16.5-19.9		(HS)
DSB				
Mean ± SD	0.6 ± 0.6	0.5 ± 0.3	1.1	0.23
Range	0.2-3.14	0.23-1.7		(NS)
ABO				
A	20 (40%)	28 (56%)		
B	12 (24%)	14 (28%)	X^2 =	0.06
AB	14 (28%)	8 (16%)	7.12	(NS)
O	4 (8%)	0 (0%)		
RH				
-ve	0 (0%)	0 (0%)	0	1
+ve	50 (100%)	50 (100%)		(NS)

Table (3) showed that there were statistically high significant differences between full-term and preterm groups regarding hemoglobin concentration, red blood cell count, white blood cell count and total serum bilirubin ($p < 0.001$) and non-significant differences regarding platelet concentration, direct serum bilirubin, ABO and RH ($p > 0.05$).

Table (4): Correlation between BIND score and clinical diagnosis regarding gestational age

	Full-term (n = 50)	**Preterm (n = 50)**	**t**	**p**
Total score				
Mean ± SD	3.7 ± 1.96	5.3 ± 1.8	4.3	< 0.001 (HS)
Range	1-8	2-8		
Mild	18 (36%)	8 (16%)	X^2 = 18.7	< 0.001 (HS)
Moderate	26 (52%)	16 (32%)		
Advanced	6 (12%)	26 (52%)		

Table (4) showed that there was statistically a high significant relation between BIND score and clinical diagnosis ($p < 0.001$).

Table (5): Correlation between BIND score and clinical diagnosis

Bind score	**Clinical diagnosis**			**Kappa coefficient ± SD**	**p**
	Mild	**Moderate**	**Advanced**		
Subtle	26	10	0	0.76 ± 0.09	< 0.001 (HS)
Moderate	0	31	10		
Advanced	0	1	22		

Table (5) showed that there was statistically a high significant association between BIND score and consultant diagnosis ($p < 0.001$).

DISCUSSION

Deposition of indirect bilirubin in the neuron membrane leads to permanent neuronal injury. Neonatal jaundice is one of the most prevalent clinical problems observed during the first week of life affecting approximately 60% of term and 80% of preterm infants. Pathophysiological basis of the jaundice is the same in term and preterm neonates, but premature babies are at a higher risk of developing hyperbilirubinemia. High bilirubin level may cause neurological impairment even in term neonate. Approximately 5-10% of them have clinically significant hyperbilirubinemia (**Rennie, 2010**).

Premature babies have much higher incidence of neonatal jaundice requiring therapeutic intervention than term neonates. Hyperbilirubinemia was found to be the most common morbidity (65%) among 137 extremely low birth weight neonates born over a period of 7 years in AIIMS **(Gregory et al., 2012)**.

Elevated levels of unconjugated bilirubin can lead to bilirubin encephalopathy and subsequently kernicterus, with devastating permanent neurodevelopment handicaps. Conjugated hyperbilirubinemia indicates potentially serious hepatic disorders or systemic illnesses. Hence, appropriate management of neonatal hyperbilirubinemia is of paramount importance. Hyperbilirubinemia can be treated either by phototherapy or exchange transfusion or pharmacologic agents (**Kliegman, 2011**).

Trained medical professionals may miss the clinical signs and features of ABE, especially in the early stages, so that appropriate intervention for infants with reversible brain injury may be delayed. Thus, there is a need for a tool that clinicians can use to recognize the danger signs of ABE early enough when appropriate intervention is most likely to lead to limiting or reversing adverse neurodevelopmental outcomes **(Johnson et al., 2009)**.

The bilirubin-induced neurologic dysfunction (BIND) scoring algorithm was developed, assigning 1, 2 or 3 points to indicate mild, moderate, or severe abnormalities in an infant's mental status, muscle tone, or cry. Higher scores indicate worsening signs of acute neurotoxicity associated with excessive hyperbilirubinemia, providing a common descriptive framework for clinicians and researchers to estimate the severity of neonatal jaundice. The simplicity of the

BIND scoring system, similar to the Apgar score, makes it an attractive tool for clinical diagnosis of ABE in resource limited locations that lack ready access to MRI) and ABR testing **(Shapiro, 2005)**. However, the practicality and acceptance of this scoring algorithm in such settings has not been reported.

Therefore, our study is intended to detect neonatal encephalopathy early using BIND score. To achieve our aim, this prospective study was carried out in NICU of Sayed Galal University Hospitals on 100 neonates; divided into two groups: first group of 50 full-term neonates and second group of 50 preterm neonates. Serum bilirubin was determined.

Our study showed that the full-term group consisted of 36 males (72%) and 14 females (28%) with mean age ± SD of 7.5 ± 2.4 days (range, 5-14 days), while the preterm group consisted of 34 males (68%) and 16 females (32%) with mean age ± SD of 5.2 ± 1.4 days (range, 3-9 days). Statistically, there was a high significant difference between full-term and preterm groups regarding age, but there was a non-significant difference regarding sex. Also, there were non-significant differences between full-term and preterm groups regarding natal history including mode of delivery and complicated delivery.

Our study showed also that there were statistically high significant differences between full-term and preterm groups regarding weight, respiratory rate and heart rate, a significant difference regarding head circumference and non-significant differences regarding length and capillary refill.

In our study, there were statistically high significant differences between full-term and preterm groups regarding hemoglobin concentration, red blood cell count, white blood cell count and total serum bilirubin and non-significant differences regarding platelet concentration, direct serum bilirubin, ABO and RH.

In the study by **Taheri et al. (2013)**, mean TSB in term neonates was 20.1±3.3 mg/dl. A prospective cohort study was conducted by **Mosayebi et al. (2016)** on 128 full-term breastfed hyperbilirubinemic neonates who were admitted to the children's medical center hospital requiring phototherapy. At enrollment, the mean ± standard deviation (SD) for gestational age at birth was 38.5 ± 0.6 weeks; birth weight 3163 ± 362 grams; neonatal age 5.7 ± 2.9 days; admission weight was 3002 ± 370 grams; admission

bilirubin level was 18.5 ± 2.9 mg/dL; admission hemoglobin was 15.7 ± 1.7 mg/dL; and the duration of phototherapy was 2.4 ± 0.6 days. Of the neonates, 64 (50%) were male, 81 (63%) were born by Cesarean section (C/S), and 66 (51%) had admission bilirubin 18 mg/dL. There were no significant differences in the demographics among the neonates with bilirubin 18 mg/dL and those with bilirubin < 18 mg/dL.

In the study done by **Radmacher et al. (2015)**, sixty-nine percent of infants were term (≥38 weeks), with a mean estimated gestational age of 37.7 (2.7) weeks, and 82.3% were born either at a clinic or in a hospital. The mean age at the time of BIND examination was 124 (74) hours; the mean infant weight at the time of examination was 2751 (725) grams. In infants with a clinical diagnosis of ABE, the mean postnatal age at examination was higher than in infants without ABE but not statistically significant. Additionally, gestational age at birth, birth weight, weight at examination and the proportions of infants with ABO and Rh blood incompatibilities did not differ significantly between the groups. The modified bilirubin induced neurologic dysfunction score for neonatal jaundice can be assigned reliably by both residents and experienced pediatricians in resource-limited settings as reflected in the algorithm's sensitivity and specificity. It may be useful for predicting the development and severity of acute bilirubin encephalopathy in neonates.

CONCLUSIONS

We have shown that the use of the BIND score among consultant pediatricians and their resident doctors is reliable for identifying neonates with the clinical diagnosis of neonatal bilirubin encephalopathy. Validation and further modification of this scoring system could provide a much needed tool for use to estimate the actual magnitude of neonatal bilirubin encephalopathy-related morbidity and mortality.

Such data would support the work of child health advocates to devise solutions to reduce or eliminate this preventable morbidity which has long-term, tragic consequences for the neonates, their families and their communities.

RECOMMENDATIONS

We recommend development of Bilirubin-Induced Neurological Dysfunction (BIND score), because it is useful in evaluation of neonatal jaundice as it is fast,

cheap and more trusted than other scores. Also, use of this score prevents complications which have long-term, tragic consequences for the neonates, their families and their communities.

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