Research Article

Severe Neonatal Hyperbilirubinemia And Acute Bilirubin Encephalopathy

Basil Hanoudi, *C.A.B.P*,[1] ***Protty MB*** *M.B.Ch.B, MRCP*,[2] ***Hadeel Awad,*** *M.B.Ch.B*[3]

[1] Department of Pediatrics College of Medicine/ Al-Mustansiriya University/ Baghdad

[2] Cardiff university school of medicine/ Cardiff/ Wales/ UK

[3] Central child teaching hospital/ Baghdad

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Address for Correspondence:
Basil Hanoudi, C.A.B.P, Department of Pediatrics College of Medicine/ Al-Mustansiriya University/ Baghdad

Abstract

Introduction: Neonatal jaundice is a common condition with 60% of newborns being clinically affected in the first days of life. Severe hyperbilirubinemia makes infants at considerable risk of potentially dangerous bilirubin encephalopathy with subsequent kernicterus.

Aim of study : To evaluate importance of clinical and laboratory factors affecting occurrence of acute bilirubin encephalopathy in neonates with severe neonatal hyperbilirubinemia.

Patients and methods: A cross sectional study was conducted in the central child teaching hospital/ neonatal ward/ Baghdad/ Iraq, over the period of 9.5 months(from 1st of October 2015 to 15th of July 2016), including neonates presented with severe hyperbilirubinemia, whom required phototherapy ± exchange transfusion. Neonates were less than 14 days of life, and were term and near term. Full history and physical examination was conducted, and features of acute bilirubin encephalopathy by using the BIND score were assessed.
Relevant laboratory tests were performed.

Results: A 120 neonates with severe hyperbilirubinemia were studied. Mean age of admission was 7.4±2.97 days. Males:female ratio was 2.16:1, mean gestational age was 37.5±1.1 weeks. Term neonates were 100, while preterms were 20. Hemolytic diseases were commonest causes of jaundice (Rh isoimmunization and ABO incompatibility), then followed by sepsis. Fifty one neonates were affected with acute bilirubin encephalopathy according to BIND score.
Neonates of BIND positive group were significantly younger (P <0.01), yet gender and weight were indifferent. Also neonates of BIND positive group were significantly
near terms (P 0.00), low body weight (P 0.024), caesarean delivered (P 0.04), and those needed exchange transfusion (P 0.00). Laboratory investigation in BIND positive group showed significantly higher total serum bilirubin, higher bilirubin/albumin ratio, and lower albumin (P <0.01, <0.01, <0.01 respectively).
ROC analysis identified a total serum bilirubin cut off value of 19.5mg/dl, and bilirubin/albumin ratio was 6.337mg/g, with bilirubin/albumin ratio was more sensitive than total serum bilirubin as a predictor of acute bilirubin encephalopathy.

Conclusion and Recommendations; Near term, low weight, and caesarean section deliveries carry risk for acute bilirubin encephalopathy. Bilirubin cut off value of 19.5mg/dl is critical in evaluating neonatal jaundice, while initial bilirubin/albumin ratio is a predictor of acute bilirubin encephalopathy in severe hyperbilirubinemia.
So we recommend early checkup of serum bilirubin and albumin of neonates with jaundice. Also, encourage term deliveries, and early feeding in cesarean deliveries, and encourage public educational programs about risks of developing neurological dysfunction in newborns with neonatal jaundice and the importance of early seeking medical advice.

Key words: Acute bilirubin encephalopathy, neonatal jaundice, BIND score, bilirubin/albumin ratio, hyperbilirubinemia

INTRODUCTION

Neonatal jaundice is one of most the common conditions with more than half of all newborns being affected in the first 3 - 5 postnatal days.[1] It is normally a benign transitional phenomenon after birth expressing a dynamic balance between bilirubin production and elimination. The combination of increased bilirubin production and impaired elimination makes infants at considerable risk for developing potentially dangerous hyperbilirubinemia with subsequent kernicterus. [2]

Bilirubin neurotoxicity may occur if levels of bilirubin become excessive, and this pathologic state makes jaundiced newborn vulnerable in presence of certain risk factors such as; prematurity, perinatal-neonatal complications, hemolysis, altered bilirubin-albumin binding, severity and duration of hyperbilirubinemia, and individual vulnerability of infants, to develop bilirubin-induced neurologic dysfunction.[3,4,5]

The syndrome of bilirubin-induced neurologic dysfunction represents a spectrum of neurologic manifestations in vulnerable infants after exposure to high bilirubin levels. So early detection of this state can eliminate long standing and irreversible brain damage.[3]

Aim of study

To evaluate importance of clinical and laboratory factors affecting occurrence of acute bilirubin encephalopathy in neonates with severe neonatal hyperbilirubinemia.

PATIENTS AND METHODS

A cross sectional study was conducted in the child central teaching hospital/ neonatal ward/ Baghdad/ Iraq, over the period of 9.5 months (from 1st of October 2015 to 15th of July 2016). The study group included neonates presented with severe hyperbilirubinemia, whom required phototherapy ± exchange transfusion. Neonates were less than 14 days of life, and were term and near term (near term are those born at 34 to <37 weeks of gestational,[6] with gestational age ≥ 34 weeks, (as assessed by Ballard scoring, maternal ultrasound during pregnancy, or the mother's last menstrual period).[7]

Inclusion criteria; admitted to the neonatal ward with total serum bilirubin (TSB) ≥17 mg/dl, and direct TSB is less than 20%.[4]

Exclusion criteria; neonates with hydrops fetalis, congenital nephrotic syndrome, birth asphyxia, and incompletely reported cases.

Information of study group neonates, admitted to the neonatal ward at day time, fulfilling the criteria of the study was collected via proper questionnaire setting, including the history (gender, age, mode of delivery, last menstrual period, admission weight, positive family history of neonatal jaundice in a sibling).

Physical examination of neonates was done to assess gestational age, wellbeing of neonate, and the features of acute bilirubin encephalopathy (ABE). The neurologic evaluation was performed within 12 hours of admission by using the bilirubin-induced neurologic dysfunction protocol (BIND score) based on clinical signs characteristic of ABE.[8] The examiner was blinded to the admission TSB value. The BIND score is used to evaluate changes in mental state, muscle tone, and cry.[9] A scoring system was implemented to assess signs of acute bilirubin induced neurological dysfunction by onset, severity and progression of acute bilirubin encephalopathy (ABE) in infants with severe hyperbilirubinemia as elicited by history and physical examination.

Table 1: Clinical BIND score

Clinical signs	BIND score	ABE Severity
Mental status		
Normal	0	None
Sleepy but arousable; decreased feeding	1	Subtle
Lethargy, poor suck and/or irritable/jittery with strong suck	2	Moderate
Semi-coma, apnea, unable to feed, seizures, coma	3	Advanced
Muscle tone		
Normal	0	None
Persistent mild to moderate hypotonia	1	Subtle
Mild to moderate hypertonia alternating with hypotonia, beginning arching of neck and trunk on stimulation	2	Moderate
Persistent retrocollis and opisthotonos—bicycling or twitching of hands and feet	3	Advanced
Cry pattern		
Normal	0	None
High pitched when aroused	1	Subtle
Shrill, difficult to console	2	Moderate
Inconsolable crying or cry weak or absent	3	Advanced
Total BIND score		

Abbreviations: BIND, bilirubin-induced neurological dysfunction; ABE, acute bilirubin encephalopathy; TSB, total serum bilirubin.

Score of 1–3: subtle signs of ABE

Score of 4–6: moderate ABE and likely to be reversible with urgent bilirubin reduction strategies

Score of 7–9: represent advanced ABE: urgent intervention to prevent further brain damage, minimize severity of sequelae and may reverse damage.

Laboratory tests include; neonatal serum albumin, and TSB levels were determined at time of admission through venous blood sample aspirated under aseptic technique, using 2 ml of blood in non heparinized tube (plain tube). Albumin assessment was via bromocresol-green-colorimetric test kit and measured by spectrophotometry (CECIL) at 630 nm wave length, and results were in mg/dl with normal range of (36-52mg/dl). The TSB was measured via (bilirubin meter), results were in mg/dl, and the ratio of bilirubin to albumin was calculated.

Other investigations of the neonates were as needed and include; C-reactive protein, urine culture, blood culture [diagnosis of sepsis required clinical signs; temperature instability, metabolic acidosis mottled skin, irritability, lethargy, apnea, seizures, feeding intolerance, associated with a positive blood culture result and/or an elevated C-reactive protein level, or total leukocyte count of >25 000 or <5000], complete blood counts, G_6PD assay evaluated by methemoglubinem reduction test, PCV, neonatal and maternal blood group, and Rh factor.

Statistical analysis of database was performed using SPSS version 20, and P value was statistically significant if below (0.05) using Fisher exact test.[10] The Youden's J Statistic (Youden's index) is used in conjunction with Receiver Operating Characteristic (ROC) analysis. The index is defined for all points of an ROC curve for selecting the optimum cut-off point. The index is represented graphically as the height above the chance line, and it is also equivalent to the area under the curve subtended by a single operating point.[11]

RESULTS

The study group of neonates with severe hyperbilirubinemia requiring phototherapy ± exchange transfusion was 120 neonates, aged 1-14 days. Mean age of admission was 7.4±2.97 days.

Males were 82(68.3%), and females were 38(31.7%), male: female ratio was 2.16:1; mean gestational age was 37.5±1.1 weeks. Term neonates were 100 (≥37 weeks), while preterms were 20 (34 to <37 weeks), mean weight of neonates was 2.9±0.6 Kg. Of the total sample; 85 had been delivered by vaginal delivery, and 35 were delivered by caesarean section.

Regarding causes of jaundice in the study group; hemolytic diseases (Rh isoimmunization and ABO incompatibility) were the commonest cause then followed by sepsis, as seen in figure 1

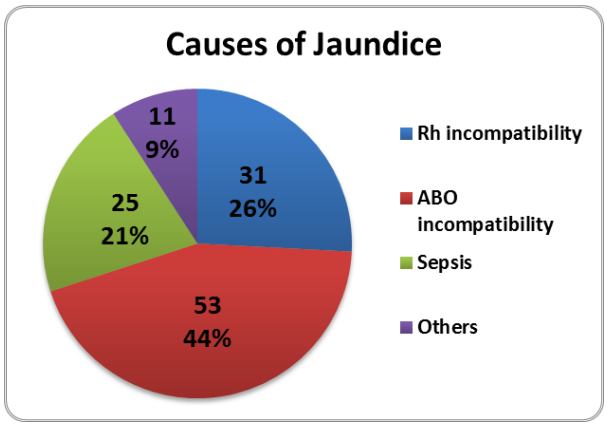

Figure 1: Causes of Jaundice in the study group

Laboratory data of sepsis detection by different tests showed; blood culture was most positive in infection screen, followed by CRP test and urine culture.

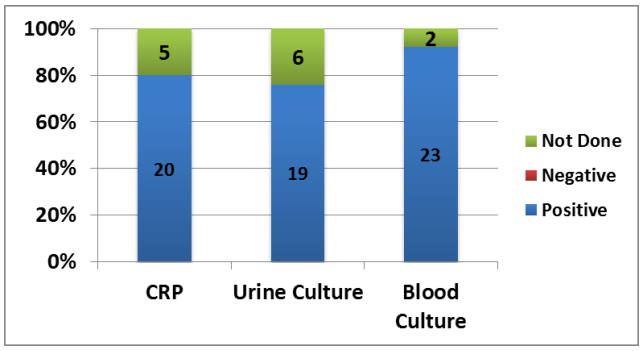

Figure 2: Markers of infection in neonates with sepsis

Distribution of severity of ABE according to severity in BIND positive group 51(42.5%) of neonates, while BIND negative were 69(57.5|%), as seen in figure 3

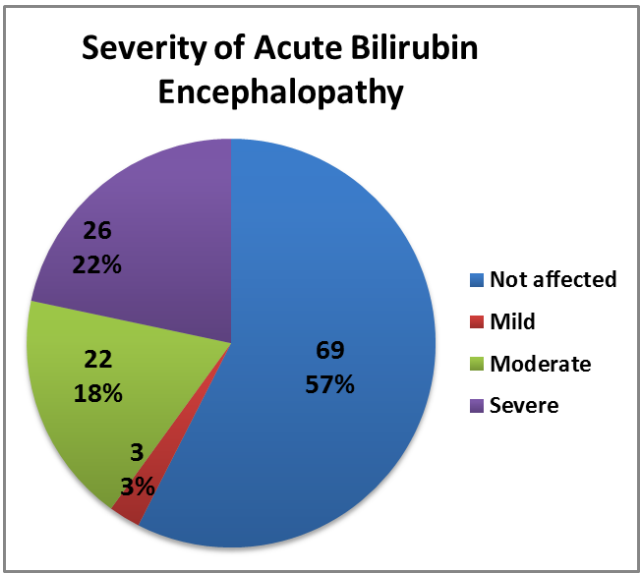

Figure 3: Severity of acute bilirubin encephalopathy as estimated by BIND score.

The clinical features of neonates in table 3 shows; a significantly more near terms in BIND positive cases (P 0.00), more low body weight in BIND positive cases (P 0.024),

more caesarean deliveries in BIND positive cases (P 0.04), age at 1st presentation was older in BIND negative cases (P 0.001), and more BIND positive cases in those needed exchange transfusion (P 0.00).

Table 2: Clinical Features of neonates in the study group

Variable		Total (120) No. (%)	BIND positive(51) No.(%)	BIND negative(69) No.(%)	P value
Gestational age (Weeks)	34 to <37	20 (16.7%)	17 (33.3%)	3 (4.3%)	0.00
	≥ 37	100 (83.3%)	34 (66.7%)	66 (95.7%)	
Gender	Male	82 (68.3%)	33 (64.7%)	49 (71.0%)	0.46
	Females	38 (31.7%)	18 (35.3%)	20 (29.0%)	
Weight (Kg)	<2.5Kg	18(15.0%)	12(23.5%)	6(8.7%)	0.024
	≥2.5Kg	102(85.0%)	39(76.5%)	63(91.3%)	
Type of delivery	Vaginal	85 (70.8%)	31 (60.8%)	54 (78.3%)	0.04
	Caesarean	35 (29.2%)	20 (39.2%)	15 (21.7%)	
Age 1st presented (Days)	3 day	23(19.1%)	16(31.4%)	7(10.2%)	0.18
	4 – 7 day	56(46.7%)	28(54.9%)	28(40.5%)	1.0
	8 – 14 day	41(34.2%)	7(13.7%)	34(49.3%)	0.001
Family history of NNJ	Positive	36 (30.0%)	19 (37.3%)	17 (24.6%)	0.14
	Negative	84 (70.0%)	32 (62.7%)	52 (75.4%)	
Need exchange transfusion	Positive	38 (31.7%)	33 (64.7%)	5 (7.2%)	0.00
	Negative	82 (68.3%)	18 (35.3%)	64 (92.8%)	
No. of exchange transfusion	One	34 (28.3%)	29 (56.9%)	5 (7.2%)	0.41
	Two	4 (3.3%)	4 (7.8%)	0 (0.0%)	
Causes of jaundice: Rh Incompatibility	Yes	31 (25.8%)	14 (27.5%)	17 (24.6%)	0.73
	No	89 (74.2%)	37 (72.5%)	52 (75.4%)	
ABO Incompatibility	Yes	53 (44.2%)	23 (45.1%)	30 (43.5%)	0.86
	No	67 (55.8%)	28 (54.9%)	39 (56.5%)	
Sepsis	Yes	25 (20.8%)	12 (23.5%)	13 (18.8%)	0.53
	No	95 (79.2%)	39 (76.5%)	56 (81.2%)	
Other	Yes	11 (9.2%)	2 (3.9%)	9 (13.0%)	0.09
	No	109 (90.8%)	49 (96.1%)	60 (87.0%)	

Findings of laboratory investigation in BIND positive group of severely jaundiced neonates showed, TSB, and bilirubin/albumin ratio were significantly higher, while serum albumin was significantly lower (P <0.01, <0.01, <0.01 respectively), as seen in table 3

Table 3: Distribution according to laboratory investigations

Laboratory findings	All (120) Mean(±S/D)	BIND positive (51) Mean(±S/D)	BIND negative (69) Mean(±S/D)	p-value
PCV(mg/dl)	48.6 (7.6)	45.7 (7.5)	49.4 (0.4)	0.17
TSB(mg/dl)	21.2 (3.4)	23.0 (0.0)	19.4 (0.2)	<0.01
Albumin(g/dl)	3.6 (1.2)	3.9 (1.7)	4.5 (0.0)	<0.01
B/A ratio(mg/g)	7.2 (3.7)	7.0 (3.9)	4.4 (0.0)	<0.01

ROC analysis identified a TSB cut off value of 19.5mg/dl, with a sensitivity of 100% and specificity of 86%. Also, according to the ROC curve, B/A ratio cut off value for predicting acute BIND was 6.337mg/g, with a sensitivity of 100% and specificity of 96%, as calculated by Youden's J Statistic (11), and 0.8 g/dL for albumin. The area under the curve for B/A is higher than for TSB, so more valuable as a predictor of ABE than TSB.

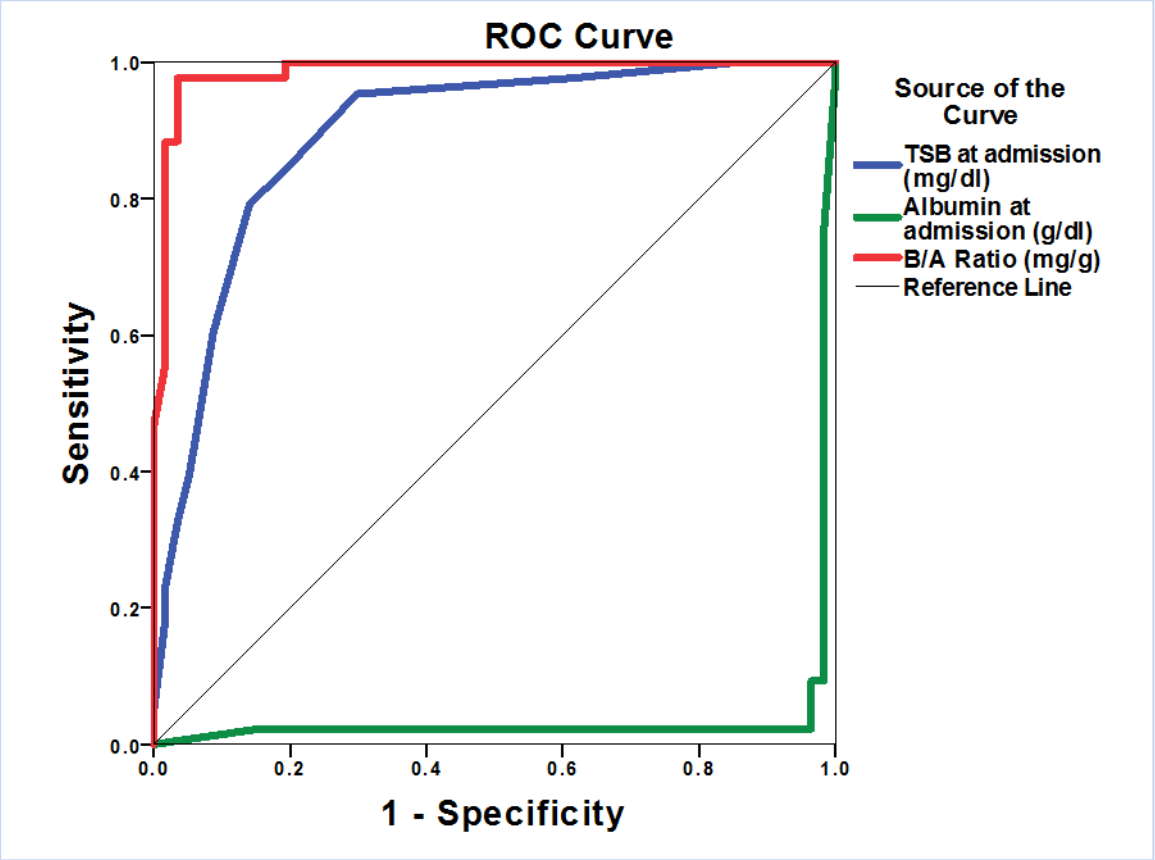

Figure 4: ROC Curve analysis according to total serum bilirubin (TSB), albumin**, and bilirubin/albumin ratio (B/A ratio). Cut-off values were 19.5mg/dL (TSB), 0.8 g/dL (albumin) and 6.337 (B/A ratio), as calculated by Youden's J Statistic.**

DISCUSSION

Neonatal jaundice is a common condition that needs medical attention in early life, and it is the leading cause of acute bilirubin encephalopathy (ABE), which is a recognized cause of bilirubin-induced neurological dysfunction. It has been demonstrated that the percentage of neonates who had BIND in the representative sample were 51(42.5%).

Causes of Jaundice in the study population; hemolysis contributes to the majority of cases of severe hyperbilirubinemia. A finding similar to study of Bolajoko, [12] while Khuram,[13] stated almost equal hemolytic and infection causes of severe hyperbilirubinemia. Rasha Gamaleldin study,[14] showed ABO incompatibility is the commonest hemolytic cause, and ABO incompatibility with associated anemia had far less influence on ABE outcome than Rh incompatibility.

In our study, Rh incompatibility, ABO incompatibility, sepsis and G_6PD were the commonest causes of severe hyperbilirubinemia and ABE, yet they are not significantly different on BIND score (P 0.73, 0.86, 0.53, and 0.09 respectively).

Regarding the severity of BIND scoring; we found that 3% were mild, 18% were moderate and 22% had severe score; findings are similar to Rasha Gamaledin,[14] were 17.6% of newborns had moderate or severe ABE at admission, and it is lower than that obtained by Iman Iskander et al,[15] where 30% neonates had moderate and severe ABE, and kernicterus in 18%. Such discrepancy in frequency of BIND occurrence probably reflects the social insight of dealing with neonatal jaundice, and development of

severe hyperbilirubinemia due to delay in admission and seeking medical care.

The mean gestational age of study sample was 37.5 ±1.1days, with significantly higher age in those BIND negative group (P <0.01), 16.7% of them were 34 to <37 weeks of gestation, while 83.3% of them were ≥37 weeks of gestation. The BIND positive cases were significantly more in near term neonates (34 to <37 weeks) than terms, while more BIND negatives were found in terms (P 0.00). Findings similar to Vinod K. et al,[16] who found bilirubin neurotoxicity is more with decreasing gestational age of neonate. Also Sarici SU et al,[17] found near-term newborns of 35 to 37 weeks of gestation had significantly lower birth weights, higher TSB levels on days 5 - 7, and were 2.4 times more likely to have hyperbilirubinemia than those 38 - 42 weeks of gestation. Hyperbilirubinemia in preterms is more prevalent and its course is more protracted than in terms explained by exaggerated neonatal red cell, hepatic, and gastro-intestinal immaturity, and bilirubin conjugation immaturity.[18]

The frequency of severe hyperbilirubinemia was more common among male neonates (68.3%) in comparison to female neonates (31.7%). Severe hyperbilirubinemia was more in males in an Iraqi study in which (68.8%) were males, by Faris B. AL-Swaf et al.[19] While there were no significant impact of sex on BIND scores (P 0.46), this finding is similar to Ali Bulbul study,[20] and Seyedeh study (P 0.072).[21]

Neonates of light body weight (<2.5Kg) were significantly more BIND positive than heavier ones with BIND negative state (P 0.024). A finding similar to Shahin study regarding lighter BIND positive neonates with significant difference (P 0.05).[22] Also, Rasha Gamaleldin stated that Low admission weight (OR: 0.83 per 100 g) increased the risk for ABE.[14]

Regarding mode of delivery; vaginal delivery:caesarean delivery was 85:35, and BIND positive cases were significantly more common in caesarean delivery, while BIND negative cases were significantly more common in vaginal delivery (P 0.04). A fact could be explained by delayed feeding after C/S due to sick mother postoperatively, use of glucose water instead of breast milk in awaiting for initiation of breast feeding, and the more opportunity of separation of newborns from mothers after C/S. Seyedeh found unsuccessful breast feeding was a statistically significant risk factor for BIND (P 0.001).[21] Ali Bulbul found there was a significant association of vaginal delivery and supplementary feedings as significant risk factors for development of severe hyperbilirubinemia (P <0.001 and 0.04, respectively).[20] While Seyedeh found no effect of route of delivery on BIND (P 0.242).[21]

The age at first presentation was significantly older age group (8-14day) in those BIND negative neonates (P 0.001) as compared with younger ages, a finding explained by maturing blood brain barrier in older age group, thus making the harmful impact of severe hyperbilirubinemia less on brain. A finding is similar to Rasha, Ali Bulbul, and Seyedeh.[14, 20, 21]

Seventy percent of neonates had no family history of hyperbilirubinemia, with no significant difference in the history of hyperbilirubinemia in BIND positive and negative neonates (P 0.14), Seyedeh found family history of hyperbilirubinemia not significantly influencing BIND occurrence (P 0.424).[21]

There was need for exchange transfusion in 31.7% of neonates, which was significantly associated with increased risk of ABE (P 0.00), which actually reflects the severity of hyperbilirubinemia and probably the delay in seeking medical care, and admission, which is explained by local social and cultural taboos like using home phototherapy light source, herbs, date juice, garlic, …etc).

The TSB, serum albumin, and bilirubin/ albumin ratio (B/A) were all significantly different in BIND in neonates with severe hyperbilirubinemia. There is presently no method available for measuring free bilirubin accurately in plasma or serum. Adjunct measurements such as albumin concentration and B/A ratio may provide more prediction for bilirubin induced encephalopathy (Daood).[23] In present study, TSB and B/A ratio were significantly higher in patients with BIND positive than in others (P <0.01, <0.01respectively), and serum albumin was significantly lower in patients with BIND positive (P <0.01). The free bilirubin and not TSB is the principal of bilirubin neuro-toxicity and TSB level reflects the free bilirubin level (which is rarely measured). (Ritter DA).[24]

The free bilirubin can be used as a better indicator for therapeutic purposes to decrease BIND incidence. Experimental and clinical data suggest measurement of free bilirubin in neonates with hyperbilirubinemia will improve risk of assessment for neurotoxicity (Wennberg RP).[25] Ekta Patel stated that the free bilirubin, and not TSB, is the principal determinant of bilirubin neurotoxicity.[26] It seems that value of B/A ratio may be limited value because many factors may influence the intrinsic albumin–bilirubin binding constant in which it may be decreased by drugs (e.g.

ceftriaxone) or by plasma constituents (e.g. free fatty acids) that interfere with albumin– bilirubin binding (Hulzebos CV et al).[27]

In present study, the level of TSB and B/A ratio in the neonates with acute BIND were 23.0mg/dl and 7.0 ±3.9 mg/g respectively at admission. Ekta Patel found neonatal bilirubin and B/A ratio were significantly higher in patients with positive BIND ($p<0.05$) and B/A was (6.34 mg/g).[26] It seems that value of B/A ratio may be of limited value because many factors may influence the intrinsic albumin–bilirubin binding constant in which it may be decreased by drugs (e.g. ceftriaxone) or by plasma constituents (e.g. free fatty acids) that interfere with albumin– bilirubin binding (Hulzebos CV et al).[27]

ROC curve analysis according to total serum bilirubin (TSB), albumin, and bilirubin/albumin ratio (B/A ratio) showed the cut-off values were 19.5mg/dL (TSB), 0.8 g/dl (albumin) and 6.337 (B/A ratio), Shahin Behjati Ardakani et al study found B/A ratio in patients with positive BIND was significantly higher ($P<0.001$), and the ROC analysis identified TSB cut off value of 25 mg/dL with a sensitivity of 100% and specificity of 85%. And the B/A ratio cut off value for predicting acute BIND was 8 mg/g with sensitivity of 100% and specificity of 94%.[22]

The B/A ratio cut off value is similar to a study by Seyedeh, in which the area under the curve for B/A is higher than for TSB, making of B/A ratio a good predictor of ABE.[21] While in comparison with Iskander I, et al, in which the cutoff point is not superior to the TSB level for predicting acute BIND.[15] According to Iskander I, both TSB and B/A are strong predictors of neurotoxicity, but B/A does not improve prediction over TSB alone.

Conclusion:

- Near term, low weight, and caesarean section deliveries carry risk for acute bilirubin encephalopathy
- TSB cut off value of 19.5mg/dl is critical in evaluating neonatal jaundice.
- The initial TSB/Alb ratio is a predictor of acute bilirubin encephalopathy in severe hyperbilirubinemia

Recommendations:

- To measure serum bilirubin and albumin of neonates with neonatal jaundice, especially in the first days of life, and the TSB/Alb ratio as predictor of neurological dysfunction in severe cases.
- Encourage term deliveries, and early feeding in cesarean deliveries.
- Encourage public educational programs i.e. TV, about risks of developing neurological dysfunction in newborns with neonatal jaundice and the importance of early seeking medical advice.

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