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CORROBORATION OF BILIRUBIN INDUCED NEUROLOGICAL DYSFUNCTION (BIND) SCORING CRITERIA AMONG HYPERBILIRUBINEMIA NEONATES - A PROSPECTIVE COHORT STUDY.

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Abstract:
Background: Untreated unconjugated hyperbilirubinemia is potentially neurotoxic characterized by bilirubin induced neurological dysfunction (BIND), kernicterus and subsequently chorio-athetoid cerebral palsy. BIND scoring criteria is not adopted as standard for hyperbilirubinemia neonates' assessment in most NICUs' till date.
Aims: To determine Incidence of BIND and to assess the correlation of risk factors for BIND in neonates with hyperbilirubinemia.
Methods: This prospective observational study was conducted in Level III A NICU of BLDE (DU) Shri B M Patil Medical College Hospital and Research Center from January 2020 to December 2021. Inclusion Criteria: All neonates with gestational age >35 weeks presenting with hyperbilirubinemia were enrolled. Serum Bilirubin level estimation was done if neonate was icteric on clinical examination. BIND scoring was assessed in all neonates with significant hyperbilirubinemia as per AAP guidelines. In all BIND positive babies AABR was performed.
Results – Out of 173 neonates enrolled into the study, 80(46.2%) were females and 93 (53.8%) were males. The Mean age at admission was 70.3 ± 31 hours. The mean birth weight was 2665.8 grams ±268.6 grams and mean weight at admission was 2183.1 grams ±259. 125 (72.3%) neonates were term and 48 (27.7%) neonates were preterm. ABO incompatibility (38%) was most common maternal risk factor. Inadequate breast feeding (64.7%) was most common neonatal risk factor. History of previous sibling receiving phototherapy was 22 (12.7%). Mean duration of history of jaundice 10.4 hours± 7.9 hours. Mean total bilirubin was 14.1mg/dl ± 3.2 mg/dl with maximum being 27mg/dl. Mean BIND score was1± 0.7. Using BIND scoring criteria, 48% had subtle acute bilirubin encephalopathy. All BIND positive neonates passed AABR.
Conclusion – The incidence of bilirubin induced neurological dysfunction was 48% (Subtle BIND) in neonates with significant hyperbilirubinemia. The amalgamation of the BIND scoring system in all hyperbilirubinemia neonates' checklist at the time of admission is recommended.

Keywords: Bilirubin Induced Neurological Dysfunction, Acute bilirubin encephalopathy, Neonatal Jaundice, Automated auditory brainstem response.

INTRODUCTION: Neonatal hyperbilirubinemia is one of the leading causes of hospital readmission after birth. Around 60% of term and 80% of preterm neonates develop jaundice in the 1st week of life. Bilirubin induced neurological dysfunction (BIND) refers to clinical signs and symptoms associated with bilirubin neurotoxicity. Extreme form of BIND is Kernicterus.[1] BIND refers to individuals with subtle neurodevelopment disabilities without classical findings of kernicterus that appear to be due to bilirubin neurotoxicity.[2] South Asia is reported to be the leading contributors to an estimated 1.1 million neonates with severe hyperbilirubinemia total bilirubin level (TB) >20 mg/dL worldwide[3,4]. 3% of neonates admitted to a hospital have signs and symptoms of BIND.[5]

Kernicterus leads to devastating disability including athetoid cerebral palsy, speech and hearing impairment representing the severe manifestations of BIND. A higher BIND score would be indicative of worsening signs and symptoms of acute neurotoxicity. The earliest signs and symptoms of ABE are non specific therefore may be easily missed. Moderate signs of ABE have been considered as a definitive signs of kernicterus.[6]

During the early phases, prompt and effective treatment could prevent chronic kernicterus squeal in neonates with significant hyperbilirubinemia. Hence this study was done to determine incidence of BIND in neonates with hyperbilirubinemia and to assess the correlation of risk factors for BIND in neonates with hyperbilirubinemia.

Methods: A hospital based prospective observational study was conducted in Level III A NICU of BLDE (DU) Shri B M Patil Medical College Hospital and Research Center from January 2020 to December 2021. Inclusion Criteria: All neonates with gestational age >35 weeks presenting with hyperbilirubinemia were enrolled. Exclusion criteria: Neonates with birth asphyxia, hypoglycemia, hypothermia, sepsis, obvious central nervous system malformation like hydrocephalous, conjugated hyperbilirubinemia were excluded. Serum Bilirubin level estimation was done if neonate was icteric on clinical examination. BIND scoring was assessed in all neonates with significant hyperbilirubinemia as per AAP guidelines. In all BIND positive babies AABR was performed.

Statistical analysis

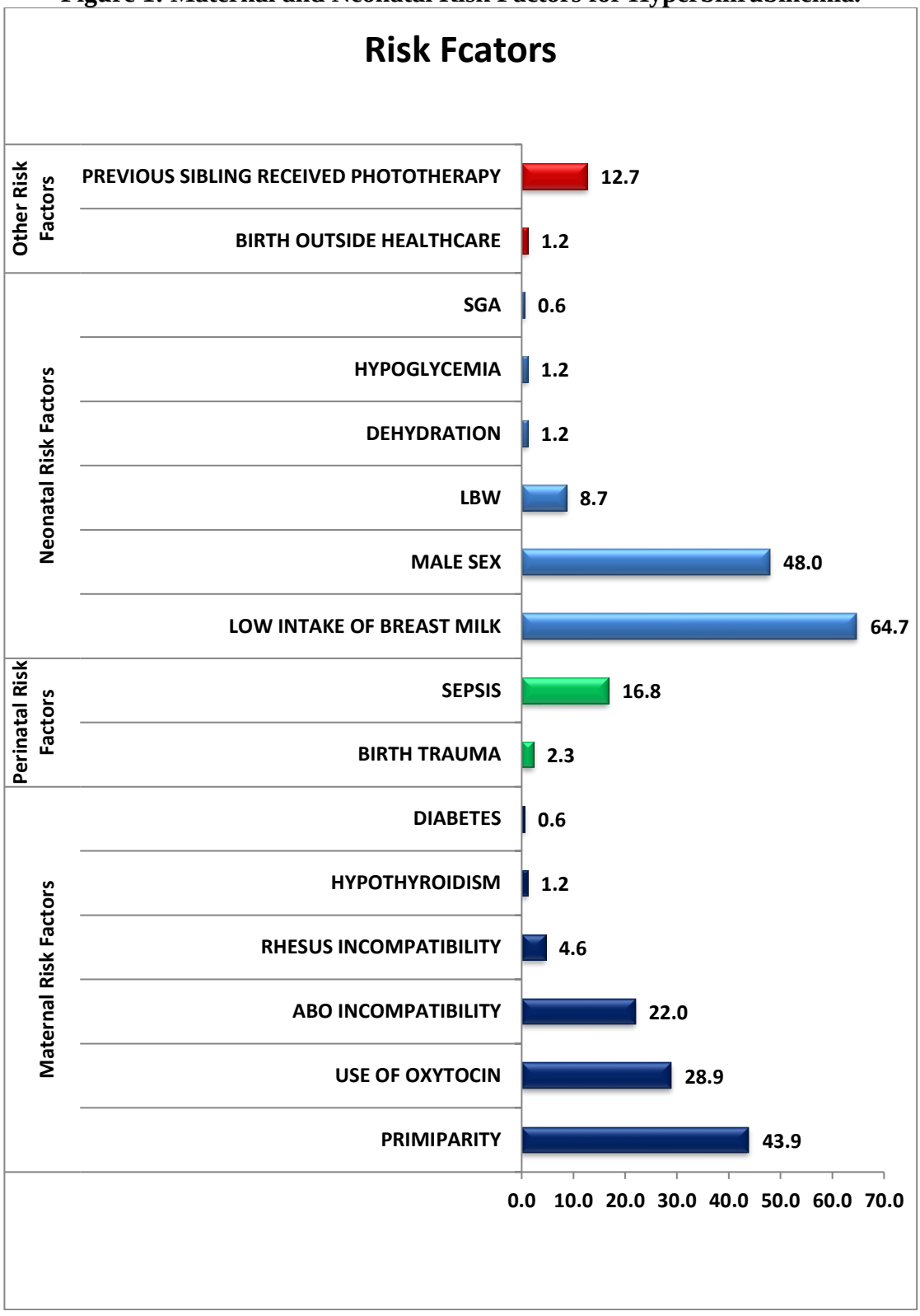
All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables. The difference of the means of analysis variables between two independent groups was tested by unpaired t test. If the p-value was < 0.05, then the results were considered to be statistically significant. Data were analyzed using SPSS software v.23 (IBM Statistics, Chicago, USA).

RESULTS

During the study period, a total of 173 hyperbilirubinemia neonates who met the inclusion criteria were enrolled into the study. 72.3 % of babies were term babies, and 27.7 % were late pre-term babies and 46.2% were females and 53.8% were males. 66.5 % neonates were delivered by normal vaginal delivery and 33.5% neonates by Caesarean section. The mean age at admission was 70.3 ± 31 hours. The mean birth weight was 2665.8 grams ±268.6 grams and mean weight at admission was 2183.1 grams ±259.

Among the maternal risk factors for neonatal hyperbilirubinemia, primiparity posed a major risk (43.9 %), followed by the use of oxytocin (28.9 %) and ABO incompatibility (22.0 %). Among the perinatal risk factors, 16.8 % neonates presented with sepsis and 2.3 % had birth trauma. Low intake of breast milk was a major neonatal risk factor (64.7%), followed by male sex (48%) and low birth weight (8.7%).Besides, 12.7 % infants had previous siblings who had received phototherapy. (Figure 1)

Figure 1: Maternal and Neonatal Risk Factors for Hyperbilirubinemia.



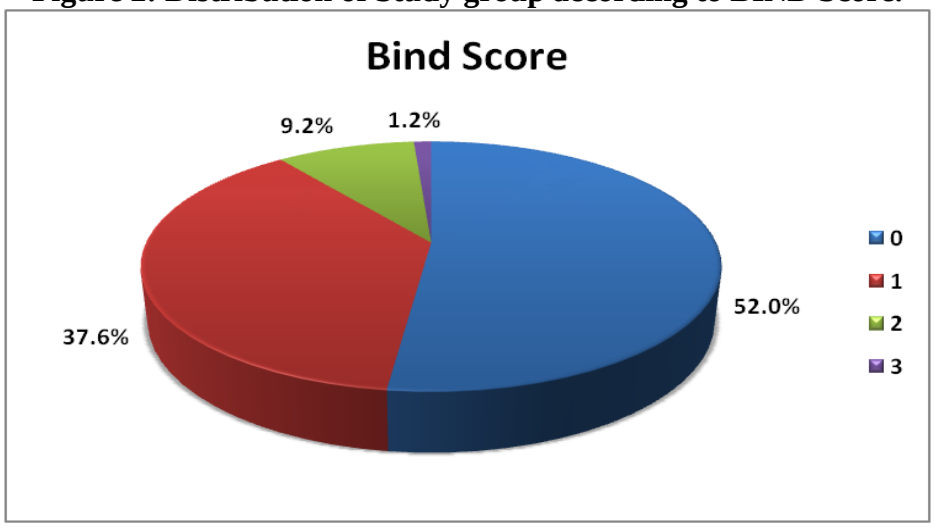
The initial total bilirubin value of the study group ranged between 7.1 mg/dL to 27 mg/dL with a mean of 14.1 mg/dL ± 3.2 mg/dL. The BIND score ranged 0 to 3, with a mean value of 1.6 ± 0.7. (Table 1).

Table 1: Descriptive Statistics of Bilirubin and BIND Score

Descriptive Statistics	Range(mg/dl)	Mean	SD
Highest Total Serum Bilirubin Value (TSB)	7.1-27	14.1	3.2
BIND Score	0-3	1.6	0.7

52% of neonates in the study group had a BIND score of 0 and were considered negative. 37.6 % neonates had a BIND score of 1, 9.2% had a BIND score of 2 and 1.2 % has a BIND score of 3 and were considered positive (Figure 2).

Figure 2: Distribution of Study group according to BIND Score.



The difference between the two groups (BIND positive and negative) was not statistically significant in any of the parameters observed such as Gestational age, Oxytocin administration to mother, Birth Weight, First total Bilirubin, ABO incompatibility except Rh incompatibility which showed statistically significant difference between two groups where P value was <0.05.(Table 2).

Table 2: Distribution of Parameters according to BIND Score

Parity	Bind Score Positive n= 83	Bind Score Negative n=90	P Value
SEX			0.467
Male	47	46	
Female	36	44	
PARITY			0.579
Primi	38	45	
Multi	45	45	
MODE OF DELIVERY			0.306
LSCS	31	27	
NVD	52	63	
GESTAIONAL AGE			0.313
Term	57	68	
Late preterm	26	22	
Age (In Hours)	71.23+26.42	69.39+34.84	0.698
Birth Weight (Grams)	2663.87+290.39	2667.51+248.55	0.929
First Total Bilirubin	14.31+3.91	13.89+2.37	0.399
ABO INCOMPATIBILITY			0.416
Positive	20	18	
Negative	63	72	
RH INCOMPATIBILITY			0.004
RH Positive	33	5	
RH Negative	50	85	
Oxytocin			0.422
Given	23	27	
Not Given	60	63	

DISCUSSION

Injury caused by deposition of free unconjugated bilirubin in the neurons leads to permanent injury in neonates. Neonatal hyperbilirubinemia is one of the most prevalent clinical problems observed during the 1st week of life affecting approximately 60% of term and 80% of preterm neonates. Pathophysiology of the jaundice is the same in term and preterm neonates, but premature babies are at a higher risk of developing hyperbilirubinemia and BIND. High bilirubin level may cause neurological impairment even in term neonates. Approximately 5-10% of them have clinically significant hyperbilirubinemia which may lead to bilirubin induced neurological dysfunction if untreated (Rennie, 2010).[7]

In our study, neonates who had multiparous mothers outnumbered neonates who had primiparous mothers (52 % vs 48 %) (Table 2). According to Rochjati[8], parity > 4 is one of the risk factors in pregnant women as it increases the risk of occurrence of complications of pregnancy, asphyxia and prematurity. Winkjosastro[9] (2008) also report that a high parity results in a baby that is born with low birth weight and consequently hyperbilirubinemia.

It is well documented that there is an increased risk for significant hyperbilirubinemia with decreasing gestational age. Late pre-term infants account for a large number of hospital readmissions for management of hyperbilirubinemia.[8] In our study, 72.3 % babies were term babies and 27.7% were late pre-term babies (Table 2).

In our study 66.5 % neonates were delivered by normal vaginal delivery and 33.5% neonates by Caesarean section (Table 3). A study by Jamir et al[10] reported that 84 % neonates were delivered by normal vaginal delivery where as Nepal D [11] et al reported 87.7 % neonates were delivered by spontaneous vaginal delivery, 8.2 % by caesarean section and 4.1 % by instrumental aid.

In our study, among the maternal risk factors for hyperbilirubinemia, primi parity posed a major risk (43.9 %), followed by the use of Oxytocin (28.9 %) and ABO incompatibility (22.0 %). Among the perinatal risk factors, 16.8 % neonates presented with sepsis and 2.3 % had birth trauma. Low intake of breast milk was a major neonatal risk factor (64.7%), followed by low birth weight (8.7%). Besides 12.7 % infants had previous siblings who had received phototherapy. Patel et al.[12] have reported the incidence of ABO incompatibility in their study to be 13.8% and of Rh incompatibility to be 1.37%. Similar to our study, Jamir[10] et al have reported that the most common etiological factor for neonatal jaundice was due to prematurity (8.7%) sepsis (5.3%), breast milk jaundice (4%), Rh isoimmunisation (2%), ABO incompatibility (1.3%) and hypothyroidism (1.3%).

Arun Babu[13] et al have reported that Rh incompatibility was an independent predictor of abnormal development in babies with neonatal jaundice similar to our study which showed statistically significant difference between BIND Positive and Negative study groups.

A meta-analysis of 13 studies by Olusanya[14] showed that ABO incompatibility (OR, 4.01; 95% CI:2.44-6.61), Rhesus hemolytic disease (OR, 20.63; 95% CI:3.95-107.65), G6PD deficiency (OR, 8.01; 95% CI:2.09-30.69), UGT1A1 polymorphisms (OR, 4.92; 95% CI:1.30-18.62), sepsis (OR, 9.15; 95% CI:2.78-30.10) placed infants at increased risk of severe hyperbilirubinemia or bilirubin induced neurologic dysfunctions.

In our study, the duration of having icterus ranged from 4 -76 hours and mean duration was 10.4 hours ± 7.9 hours (Table 3). Sharma et al.[15] also reported that early onset of jaundice within 24 hours was significantly associated with adverse neurodevelopmental outcomes (DQ≤70) at 3 and 12 months of age.

In our study, the initial total bilirubin value of the study group ranged between 7.1 mg/dL to 27 mg/dL with a mean of 14.1 mg/dL ± 3.2 mg/dL. The BIND score ranged between 0 to 3, with a mean value of 1 ± 0.7 (Table 1). Arun Babuet al.[13] reported that a peak serum bilirubin level of ≥ 22mg/dl was an independent predictor of abnormal development in babies with neonatal jaundice.

The BIND score is used to grade the severity and progression of bilirubin induced neurological dysfunction among term and late-term neonates. Lower values indicate normalcy. Higher values indicate increasing severity. In our study, a BIND score of 0 was considered negative, while a BIND score of 1 or more was deemed to be positive.

A major portion of neonates in the study group (52 %) had a BIND score of 0 and were considered negative. 37.6 % neonates had a BIND score of 1, 9.2 % had a BIND score of 2 and 1.2 % has a BIND score of 3 and were considered positive (Figure 2). So, the incidence of BIND was 48 % in our study.

In our study, the difference in the two study groups with respect to parity was not statistically significant (p=0.579) (Table 2). Our study is in line with a study by Astutik and Yuliawatib[16] who reported that there is no relationship between the maternal parity (p = 0,084; POR = 0,204 95% CI 0,040-1,031) and the incidence of jaundice. In contrast, a systematic review and meta-analysis by Olusanya et al[14] reported that primiparity (OR, 1.59; 95% CI:1.26-2.00) had increased risk of BIND. There was no significant difference between the BIND score positive and BIND score negative neonates with respect to their mothers and neonates having ABO incompatibility(p=0.16) in our study (Table 2).

Khurana et al[17] reported that late pre-term and term neonates with and without ABO incompatibility had similar bilirubin levels and no increased risk of significant hyperbilirubinemia. A Turkish study, Akgul et al[18] concluded that blood type has no effect on the severity of the hemolytic jaundice in ABO incompatibility whereas Kalakheti et al[19] reported that neonate with ABO incompatibility had two times higher chances of having hyperbilirubinemia than those babies with O '+ve' blood group.

Unnecessary interventions during delivery such as excessive use of oxytocin during labor, assisted deliveries and caesarean section are also considered as the risk factors[20,21.] In the present study, though the percentage of neonates who were delivered by caesarean section was more in the BIND positive group(37.3%) as compared to BIND negative groups(30%), this difference was not statistically significant (p=0.306) (Table 2). Similar to our study, Boskabadi et al.[18] found no significant relationship between the mode of delivery and the incidence of jaundice.

However, in a study by Wijaya et al.[22], Ozdemirci et al.[23], Tamook et al[24], Gupta et al.[25] , caesarean section or Oxytocin induced deliveries were associated with an increased risk of neonatal jaundice. In the case of vaginal delivery, neonates are stressed before birth which causes them to induce conjugative enzymes before vaginal delivery, thereby leading to lower levels of unconjugated bilirubin. Also, newborns delivered by caesarean section are breast-fed relatively infrequently during the first 48 hours of life than those born by vaginal delivery, possibly leading to hyperbilirubinemia.

Though the percentage of late pre term neonates in the positive BIND group(31.3%) was more as compared to BIND negative group(24.4%), this difference in distribution was not statistically significant (p=0.313) (Table 2).

However, a Meta analysis by Olusanya[14] reported that low gestational age (OR, 1.71; 95% CI: 1.40-2.11) was a risk factor for BIND. A study by Aboelreesh et al.[26] reported that preterm neonates had a BIND score significantly higher than full term neonates (5.3 ± 1.8 vs 3.7 ± 1.96, p< 0.001). The study further revealed that 52% preterm neonates had advanced ABE based on the BIND score as compared to 12 % in the full term neonates, which was statistically significant (p<0.001).

Although oxytocin is widely accepted as a safe and effective initiator of uterine contractions, some studies have reported an association between oxytocic drugs and neonatal hyperbilirubinemia. Mechanisms that have been proposed to explain the higher incidence of neonatal hyperbilirubinemia and oxytocin administration are trauma to the fetal erythrocytes as a result of uterine activation, vasoconstrictive effect of Oxytocin on uterine blood vessels, alterations in erythrocyte deformability due to the anti-diuretic activity of Oxytocin and hyponatremia caused by the administration of large quantities of electrolyte-free diluents for Oxytocin infusion.[27]

In our study, Oxytocin was used to induce labour in 28.9 % cases (n=50). There was no significant relationship between the use and non-use of oxytocin and BIND score (p=0.422) (Table 3). Similar to our study, Alibakhshi A et al[27] also found no correlation of maternal oxytocin infusion and hyperbilirubinemia in neonates. In contrast, Garosi et al[28] reported that the mean total and direct bilirubin levels were higher in neonates delivered using Oxytocin (0.4±.1 and 17.99±0.4, respectively), compared to those without Oxytocin induction (0.383±0.1 and 16.2±0.28, respectively) (P=0.001).

There was a significant relationship between the Rh +ve/ Rh –ve group and BIND score ($p< 0.05$). (Table 2) A study by Patel et al.[12] reported that in Rh incompatibility group, 10% new-born developed kernicterus.

In our study, There was no significant relationship between the ABO +ve and ABO –ve group and BIND score ($p=0.416$). Akgul et al.[18] also reported that blood type has no effect on the severity of the hemolytic jaundice in ABO incompatibility. However, a study by Patel et al.[12] reported that in ABO incompatible group, 0.5 % new-born developed kernicterus.

The mean age of neonates who had a positive BIND score was 71.23 hours ± 26.42 hours, while that of neonates having a negative BIND score was 69.39 hours ± 34.84 hours. The difference between the two groups was not statistically significant ($p=0.698$) (Table 2).
Neonates who had a positive BIND score had a mean birth weight of 2663.87 grams ± 290.39 grams and neonates having negative BIND score had mean birth weight of 2667.51 grams ± 248.55 grams. The difference between the two groups was not statistically significant ($p=0.929$) (Table 2).Gamaleldin et al.[29] reported that low admission weight (OR: 0.83 per 100 g) increased the risk for bilirubin encephalopathy, especially when other risk factors were present. In an Indian study, Mala Kumar[30] et al reported that lower weight on admission (2254.68 g ± 417 g vs 2481.75 g ± 369 g; $p = 0.0195$), found to be a significant risk factor for the development of ABE.
The mean initial total bilirubin value of the neonate group who had a positive BIND score was more than that of the group who had a negative BIND score (14.31mg/dL ± 3.91 mg/dL vs. 13.89 mg/dL ± 2.37 mg/dL). However, this difference was not statistically significant ($p=0.399$) (Table 1).
Study by Gamaleldin[29] et al., stated that the admission TSB values ranged from 25 to 76.4 mg/dL. The study concluded that neonates without risk factors for neurotoxicity had a higher tolerance for hyperbilirubinemia than recognized in management guidelines. Olusanya[14] et al. reported that high total serum bilirubin levels (OR, 1.46; 95% CI:1.10-1.92) were a risk factor for severe hyperbilirubinemia or BIND.
In a study in Egypt, El Houchi et al.[31] reported that all infants with severe acute bilirubin encephalopathy (BIND scores 7-9) either died or suffered residual neurologic and auditory impairment. BIND scores trended higher with severe hyperbilirubinemia ($r^2 = 0.54$, $P < .005$), but 5/39 (13%) infants with TSB ≥36.5 mg/dL (624 μmol/L) had BIND scores ≤3, and normal outcomes at 3-5 months. The study concluded that BIND score could be used to evaluate the severity of acute bilirubin encephalopathy and predict residual neurologic and hearing dysfunction.[31]

CONCLUSION

Neonatal hyperbilirubinemia is very common neonatal problem in day to day practice. Most neonates associated with high risk factors present with significantly elevated bilirubin levels posing a risk of Bilirubin Induced Neurological Dysfunction. The Incidence of bilirubin induced neurological dysfunction (subtle) was 48% in our study. Early detection of BIND by incorporating BIND scoring system will identify sick neonates with bilirubin toxicity prompting early intervention in the form of Intensive Phototherapy along with fluid therapy thereby preventing further complication of bilirubin toxicity. Corroboration of this scoring system could offer a much-needed practice to determine the actual extent of neonatal bilirubin encephalopathy related morbidity and mortality and thereby reduce or eliminate this preventable morbidity which has long-term, tragic consequences for the neonates, their families and their communities.

RECOMMENDATION

The amalgamation of the BIND scoring criteria in the neonatal checklist at the time of admission would help in categorizing the severity of BIND and early interventions for those presenting with manifestations of BIND by eliminating this preventable morbidity which has long-term, tragic consequences for the neonates, their families and their communities.

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