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NEONATAL BILIRUBIN LEVELS LINKED TO LATER NEURODEVELOPMENT

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ABSTRACT

Background: Most babies have neonatal jaundice, a common illness that doesn't harm the brain. Serum bilirubin levels that are higher than the bilirubin binding capacity cause ABE (acute bilirubin encephalopathy). Even after effective treatment, brain damage reversibility from ABE is a worry.

Aim: The purpose of this study was to evaluate the relationship between the first week of life's peak blood bilirubin and the neurodevelopmental outcomes of healthy, full-term infants. Future neurodevelopmental outcomes in newborns with exceptionally high blood bilirubin during the first week of life were also evaluated in this study.

Methods: 104 near-term and term infants with bilirubin levels greater than 20 mg/dl and characteristics of acute bilirubin encephalopathy (ABE) were evaluated. The neurodevelopment of these subjects was evaluated at the third and sixth months. BERA (brainstem evoked response audiometry) and DDST-II (Denver Development Screening Test) were used to evaluate neurological outcomes

Results: The study participants' mean peak total serum bilirubin (TSB) was 25.1±2.33 mg/dl. Abnormal development was observed in 23.5% (n=24) of the neonatal patients, and abnormalities were more pronounced in infants with total blood bilirubin levels greater than 28 mg/dl. In 13.7% of newborns, BERA was abnormal.

Conclusion: The current study concludes that the cut-off value for the reversibility of bilirubin-induced acute brain injury is less than 25 mg/dl for total serum bilirubin. In order to avoid missing the opportunity for intervention, the assessing clinicians should take the proper factors into account. Additionally, newborns with advanced stages of ABE, such as stages II and III, and total serum bilirubin values greater than 28 mg/dl are linked to poor outcomes.

Keywords: peak serum bilirubin, bilirubin, hyperbilirubinemia, neurodevelopmental, acute bilirubin encephalopathy

INTRODUCTION

During the first week of life, neonatal jaundice is a prevalent ailment. Approximately 60% of term newborns and 80% of preterm neonates are typically affected. These jaundices are mostly physiological and do not cause brain harm. They may, however, occasionally surpass the essential threshold, causing bilirubin-induced neurological dysfunction, or BIND, in afflicted individuals.[1]

The development of ABE, or acute bilirubin encephalopathy, demonstrates that unconjugated serum bilirubin can pass through the blood-brain barrier due to its lipophilic nature when levels surpass albumin's ability to bind bilirubin. Serum albumin levels and bilirubin conjugating ability are comparatively stable.[2]

As a result, the TSB, or total serum bilirubin level, is directly correlated with the amount of unbound bilirubin with albumin. Therefore, the care guidelines for neonates with hyperbilirubinemia have employed the total serum bilirubin level, or TSB, to illustrate important values to intervene, such as exchange blood transfusion (ET) and phototherapy.[3] Even with effective treatment like exchange blood transfusions, the reversibility of the brain damage caused by acute bilirubin encephalopathy remains a worry. According to AAP (American Academy of Pediatrics) standards, newborns with bilirubin levels higher than 20 mg/dl are more likely to develop kernicterus.[4]

Therefore, the current study was conducted to evaluate the relationship between future neurodevelopmental outcomes in healthy babies born at term and peak blood bilirubin in the first week of life. Future neurodevelopmental outcomes in newborns with exceptionally high blood bilirubin during the first week of life were also evaluated in this study.

MATERIALS AND METHODS

The present clinical observational study was done to assess the correlation between peak serum bilirubin in 1st week of life and future neurodevelopmental outcomes in healthy babies at term. Future neurodevelopmental outcomes in newborns with exceptionally high blood bilirubin during the first week of life were also evaluated in this study. The Institute's Department of Pediatrics provided the study participants. Prior to their involvement in the study, all participants provided written and verbal informed consent.

The study assessed near-term and term neonates who presented to the institute with severe hyperbilirubinemia along with the signs of bilirubin-induced acute brain damage. Neonates with comorbid conditions such meningitis, significant congenital abnormalities, sepsis, intrauterine growth restriction (IUGR), and prenatal hypoxia were excluded from the study since they may have contributed to the neurodevelopmental consequences.

Anthropometry, gestational age, gender, and weight of each subject were recorded as baseline parameters following the final inclusion of the research neonates. G6PD, TSH (thyroid stimulating hormone), serum albumin level, Coomb's test, blood group, blood counts, peripheral smear, hemoglobin levels, and total and indirect bilirubin concentration were all examined in the study participants. In such instance, the highest measured serum bilirubin measurement was considered peak serum bilirubin. In cases where sepsis was suspected, a blood culture and sepsis screening were performed.

Neonates who met the requirements were given double volume exchange transfusions in accordance with the AAP guideline to stop further brain injury. At three and six months of age, respectively, these patients were evaluated. The Denver Developmental Screening Test (DDST-II), which uses four primary domains—language, personal social, fine motor/adaptive, and gross motor—and BERA at three months are used to evaluate neurological outcomes in high-risk subjects.

The collected data was statistically examined using the chi-square test, one-way ANOVA (analysis of variance), and SPSS (Statistical Package for the Social Sciences) software version 24.0 (IBM Corp., Armonk, NY, USA). The mean, standard deviation, frequency, and percentages were used to express the results. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

The current clinical observational study was conducted to evaluate the relationship between future neurodevelopmental outcomes in healthy babies born at term and peak blood bilirubin during the first week of life. Future neurodevelopmental outcomes in newborns with exceptionally high blood bilirubin during the first week of life were also evaluated in this study. 104 near-term and term infants with bilirubin levels greater than 20 mg/dl and characteristics of acute bilirubin encephalopathy (ABE) were evaluated in this study.

The neurodevelopment of these subjects was evaluated at the third and sixth months. BERA (brainstem evoked response audiometry) and DDST-II (Denver Development Screening Test) were used to evaluate neurological outcomes. The research neonates' mean gestational age was 37.3±0.82 weeks. The study neonates' average weight at entry was 2.4±0.35 kg. The study included 33.3% (n=34) female infants and 66.6% (n=68) male neonates. The research infants' exchange transfusion age was 4.6±0.93 days, and their mean albumin levels were 3.6±0.37 mg/dl (Table 1).

When research participants' peak serum bilirubin levels were measured, the mean peak ISB (indirect serum bilirubin) was found to be 23.15±2.89 mg/dl.

The research participants' mean levels of direct serum bilirubin (DSB) and total serum bilirubin (TSB) were 1.90±0.50 mg/dl and 25.2±2.59 mg/dl, respectively (Table 2). ABE stages 1, 2, and 3 were observed in 88.23% (n=50), 7.84% (n=8), and

3.92% (n=3) study subjects, respectively, according to the distribution of study neonates based on the ABE (acute bilirubin encephalopathy) (Table 3).

The mean TSB (total serum bilirubin) levels were 28.3±2.68 mg/dl in subjects with abnormal fine motor and gross motor developmental anomalies and 25.1±2.33 mg/dl in subjects with normal fine motor and gross motor developmental anomalies, which was significantly higher in subjects with abnormal fine motor and gross motor developmental anomalies ($p<0.01$). The number of participants with aberrant and normal fine motor and gross motor developmental abnormalities was 24 and 78, respectively (Table 4).

According to the study's findings, subjects with abnormal correlations of peak TSB levels to language milestones had mean TSB (total serum bilirubin) levels of 28.1±2.56 mg/dl, which was significantly higher than the mean total serum bilirubin level of 25.3±2.33 mg/dl in subjects with normal correlations of peak TSB levels to language milestones ($p<0.01$). The number of patients from aberrant and normal language milestones was 20 and 82, respectively (Table 5).

Additionally, it was observed that when peak TSB levels were correlated with personal social developmental milestones, the mean peak TSB levels were 28.3±2.45 in subjects with an abnormal correlation, which was significantly higher than the mean peak TSB levels of 25.3±2.29 in subjects with a normal correlation ($p<0.01$). Table 6 shows that there were 16 patients with aberrant personal social developmental milestones and 86 subjects with normal milestones. Of the 102 study participants who were evaluated, 14 had abnormal BERA.

DISCUSSION

In this study, 104 near-term and term infants with bilirubin levels greater than 20 mg/dl and characteristics of ABE (acute bilirubin encephalopathy) were evaluated. The neurodevelopment of these subjects was evaluated at the third and sixth months. BERA (brainstem evoked response audiometry) and DDST-II (Denver Development Screening Test) were used to evaluate neurological outcomes. The research neonates' mean gestational age was 37.3±0.82 weeks. The study neonates' average weight at entry was 2.4±0.35 kg. The study included 33.3% (n=34) female infants and 66.6% (n=68) male neonates. The research neonates had mean albumin levels of 3.6±0.37 mg/dl and exchange transfusion ages of 4.6±0.93 days.

These results were comparable to those of earlier research by Babu TA et al. (2012) and Yilmaz Y et al. (2001), in which the authors evaluated participants with identical demographic information.

When research participants' peak serum bilirubin levels were measured, the mean peak ISB (indirect serum bilirubin) was found to be 23.15±2.89 mg/dl. The average TSB (total serum bilirubin) level was 25.2±2.59 mg/dl, while the average DSB (direct serum bilirubin) level was 1.90±0.50 mg/dl. Acute bilirubin encephalopathy (ABE) stages 1, 2, and 3 were observed in 88.23% (n=50), 7.84% (n=8), and 3.92% (n=3) of the study participants, respectively.

These findings were in line with those of Ahlfors CE et al. (2009) and Weng YH et al. (2009), whose authors examined neonates using the ABE and reported comparable peak serum bilirubin levels.

According to the study's findings, the mean TSB (total serum bilirubin) levels were 28.3±2.68 mg/dl in subjects with abnormal fine motor and gross motor developmental anomalies and 25.1±2.33 mg/dl in subjects with normal fine motor and gross motor developmental anomalies. This was significantly higher in subjects with abnormal fine motor and gross motor developmental abnormalities ($p<0.01$).

The number of participants with aberrant and normal fine motor and gross motor developmental abnormalities was 24 and 78, respectively. These results were consistent with those of Vohr BR et al. (2000) and Oh W et al. (2003), who found a similar association between peak TSB levels and developmental abnormalities of fine and gross motor skills.

The mean TSB (total serum bilirubin) levels were 28.1±2.56 mg/dl in subjects with abnormal correlation of peak TSB levels to language milestones, which was significantly higher than the mean total serum bilirubin level of 25.3±2.33 mg/dl in subjects with normal correlation of peak TSB levels to language milestones with $p<0.01$. The number of subjects from aberrant and normal language milestones was 20 and 82, respectively. These findings were consistent with those of Ip S et al. (2004) and Khan NZ et al. (2006), who also found that subjects with abnormal language milestones had significantly higher serum bilirubin levels than patients with normal language milestones.

Regarding the evaluation of the relationship between peak TSB levels and personal social developmental milestones, the mean peak TSB levels were 28.3±2.45 in subjects with an abnormal correlation, which was significantly higher than the mean peak TSB levels of 25.3±2.29 in subjects with a normal correlation ($p<0.01$). Table 6 shows that there were 16 patients with aberrant

personal social developmental milestones and 86 subjects with normal milestones. Of the 102 study participants who were evaluated, 14 had abnormal BERA.

These results were consistent with those of Newman TB et al. (2003) and Martin CR et al. (2004), where the authors similarly verified a similar link between peak TSB levels and personal social developmental stages.

CONCLUSIONS

Considering its limitations, the present study concludes that total serum bilirubin values <25mg/dl can be taken as the cut-off value for the reversibility of bilirubin-induced acute damage to the brain. The assessing clinicians should take appropriate consideration and not miss the chance for intervention. Also, poor outcome is associated in neonates with total serum bilirubin value of >28mg/dl and advanced stages of ABE as stages II and III are seen.

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S. No	Characteristics	n (%)/ Mean ± S. D
1.	**Mean gestational age (weeks)**	37.3±0.82
2.	**Mean admission weight (kg)**	2.4±0.35
3.	**Gender**	
4.	Males	68 (66.6)
5.	Females	34 (33.3)
6.	**Albumin level (mg/dl)**	3.6±0.37
7.	**Exchange transfusion age (days)**	4.6±0.93

Table 1: Demographic data of study neonates at baseline

S. No	Parameters	n (%)/ Mean ± S. D
1.	Mean peak ISB (indirect)	23.15±2.89
2.	Mean peak DSB (direct)	1.90±0.50
3.	Mean peak TSB (total)	25.2±2.59

Table 2: Peak serum bilirubin levels in study subjects

S. No	ABE stages	Number (n)	Percentage (%)
1.	1	50	88.23
2.	2	8	7.84
3.	3	4	3.92

Table 3: Neonates distribution with ABE of varying stages

S. No		Abnormal	Normal
1.	Mean peak TSB (mg/dl)	28.3±2.68	25.1±2.33
2.	Number of neonates	24	78
3.	p-value	<0.01	

Table 4: Correlation of peak TSB levels to fine motor and gross motor developmental anomalies

S. No		Abnormal	Normal
1.	Mean peak TSB (mg/dl)	28.1±2.56	25.3±2.33
2.	Number of neonates	20	82
3.	p-value	<0.01	

Table 5: Correlation of peak TSB levels to language milestones in study subjects

S. No		Abnormal	Normal
1.	Mean peak TSB (mg/dl)	28.3±2.45	25.3±2.29
2.	Number of neonates	16	86
3.	p-value	<0.01	

Table 6: Correlation of peak TSB levels to personal social developmental milestones