Research Article

INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com

ISSN 2230-8407 [LINKING]

CORRELATION OF PEAK SERUM BILIRUBIN IN 1ST WEEK OF LIFE AND FUTURE NEURODEVELOPMENTAL OUTCOMES IN HEALTHY BABIES AT TERM

Dr. Sushil Kumar,[1] Dr. Archana Singh,[2] Dr. Sunil Kaval,[3] Dr. Satyaprakash[4*]

[1]Associate Professor, Department of Physiology, Saraswathi Institute of Medical Sciences, Pikhuwa, Hapur, Uttar Pradesh

[2]Assistant Professor, Department of Physiology, Muzaffarnagar Medical college, Muzaffarnagar, Uttar Pradesh

[3]Associate Professor, Department of Surgery, Saraswathi Institute of Medical Sciences, Pikhuwa, Hapur, Uttar Pradesh

[4*]Associate Professor, Department of Psychiatry, Venkateshwara Institute of Medical Sciences, Gajraula, Uttar Pradesh

Corresponding author

Dr. Satyaprakash

Email id: dr.sushilsharma1989@gmail.com

How to cite: Kumar S, Singh A, Kaval S, Satyaprakash. Studying the variability in the heart rate of overweight and underweight young subjects. Kumar S et al. International Research Journal of Pharmacy, 2024,15:10:17-21.

Doi: 10.7897/2230-8407.110352

==========

ABSTRACT

Background: Neonatal jaundice is a common condition affecting the majority of infants without causing any damage to the brain. ABE (acute bilirubin encephalopathy) is seen with serum bilirubin levels exceed bilirubin binding capacity. Brain damage reversibility from ABE is a concern matter even after successful therapy.

Aim: The present study aimed to assess the correlation between peak serum bilirubin in 1st week of life and future neurodevelopmental outcomes in healthy babies at term. The study also assessed future neurodevelopmental outcomes in infants with extremely high serum bilirubin at 1st week of life.

Methods: The study assessed 104 near-term and term babies having features of ABE (acute bilirubin encephalopathy) having bilirubin levels>20mg/dl. These subjects were assessed at the 3rd and 6th month to assess their neurodevelopment. Neurological outcomes were assessed using BERA (brainstem evoked response audiometry) DDST-II (Denver Development Screening Test).

Results: The study results showed that the mean peak TSB (total serum bilirubin) was 25.1±2.33 mg/dl in the study subjects. In 23.5% (n=24) neonate subjects, abnormal development was seen and abnormalities were higher in babies where total serum bilirubin was more than 28mg/dl. BERA was abnormal in 13.7% of neonates.

Conclusions: 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.

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

INTRODUCTION

Neonatal jaundice is a common condition in the first week of life. It commonly affects nearly 60% of the term and 80% of preterm babies. Mostly, these jaundices are physiological and do not lead to brain damage. However, some of the time, they can cross the critical level leading to bilirubin-induced neurological dysfunction or BIND in affected subjects.[1]

The development of ABE or acute bilirubin encephalopathy shows that when unconjugated serum bilirubin levels exceed the bilirubin binding capacity of the albumin, it can cross the blood-brain barrier owing to its lipophilic nature. The level of serum albumin and bilirubin conjugating capacity are relatively constant. Hence, the level of unbound bilirubin with albumin is directly proportional and related to the TSB or total serum bilirubin level.[2]

Hence, the total serum bilirubin level or TSB has been used for the management guidelines in neonates with hyperbilirubinemia to depict critical values to intervene including ET (exchange blood transfusion) and phototherapy. However, the reversibility of the brain damage owing to acute bilirubin encephalopathy is a matter of concern even after successful therapy such as exchange blood transfusion. Following the guidelines of AAP (American Academy of Pediatrics), the preponderance of cases of kernicterus is seen in infants with bilirubin levels greater than 20 mg/dl.[3]

Hence, the present 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. The study also assessed future neurodevelopmental outcomes in infants with extremely high serum bilirubin at 1st week of life.

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. The study also assessed future neurodevelopmental outcomes in infants with extremely high serum bilirubin at 1st week of life. The study subjects were from the Department of Physiology of the Institute. Verbal and written informed consent were taken from all the subjects before study participation.

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. The exclusion criteria for the study were neonates with comorbidities such as meningitis, major congenital anomalies, sepsis, IUGR (intrauterine growth restriction), and perinatal asphyxia as these comorbidities might pose contributory effects on the neurodevelopmental sequelae.

After the final inclusion of the study neonates, baseline characteristics recorded were anthropometry, gestational age, gender, and weight of all the subjects. Investigations done in study subjects were 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 in all the study neonates. The highest value for serum bilirubin assessed was taken as peak serum bilirubin in that case. Blood culture and screening for sepsis were done in cases with suspicion of sepsis.

Following the AAP guideline, neonates who fulfilled the necessary criteria were subjected to double volume exchange transfusion to prevent future damage to the brain. These subjects were assessed at the age of 3 months and 6 months respectively. Subjects at high risk to the Institute to assess neurological outcomes using BERA at 3 months and DDST-II (Denver Developmental Screening test) utilizing four main domains including language, personal social, fine motor/adaptive, and gross motor.

The data gathered were analyzed statistically using SPSS (Statistical Package for the Social Sciences) software version 24.0 (IBM Corp., Armonk. NY, USA) for assessment of descriptive measures, one-way ANOVA (analysis of variance), and chi-square test. The results were expressed as mean and standard deviation and frequency and percentages. The p-value of <0.05 was considered statistically significant.

RESULTS

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. The study also assessed future neurodevelopmental outcomes in infants with extremely high serum bilirubin at 1st week of life. The study assessed 104 near-term and term babies having features of ABE (acute bilirubin encephalopathy) having bilirubin levels>20mg/dl. These subjects were assessed at the 3rd and 6th month to assess their neurodevelopment. Neurological outcomes were assessed using BERA (brainstem evoked response audiometry) DDST-II (Denver Development Screening Test). The mean gestational age was 37.3±0.82 weeks in study neonates. The mean admission weight was 2.4±0.35 kg in study neonates. There were 66.6% (n=68) male and 33.3%

(n=34) female neonates in the study. Mean albumin levels were 3.6±0.37 mg/dl and exchange transfusion age was 4.6±0.93 days in study neonates (Table 1).

On assessing peak serum bilirubin levels in study subjects, it was seen that the mean peak ISB (indirect serum bilirubin) was 23.15±2.89 mg/dl. The mean DSB (direct serum bilirubin) level was 1.90±0.50 mg/dl in study subjects, and the mean TSB (total serum bilirubin) level in study subjects was 25.2±2.59 mg/dl (Table 2). Concerning the distribution of study neonates based on the ABE (acute bilirubin encephalopathy), it was seen that ABE stages 1, 2, and 3 were seen in 88.23% (n=50), 7.84% (n=8), and 3.92% (n=3) study subjects respectively (Table 3).

It was seen that for the assessment of the correlation of peak TSB levels to fine motor and gross motor developmental anomalies, mean TSB (total serum bilirubin) levels were 28.3±2.68mg/dl in subjects with abnormal fine motor and gross motor developmental anomalies and were 25.1±2.33mg/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 with $p<0.01$. There were 24 and 78 subjects respectively in subjects from abnormal and normal fine motor and gross motor developmental anomalies (Table 4).

The study results showed that concerning the correlation of peak TSB levels to language milestones in study subjects, 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 compared to mean total serum bilirubin level of 25.3±2.33mg/dl in subjects with normal correlation of peak TSB levels to language milestones with $p<0.01$. There were 20 and 82 subjects respectively in subjects from abnormal and normal language milestones (Table 5).

It was also seen that for correlation of peak TSB levels to personal social developmental milestones, mean peak TSB levels were 28.3±2.45 in subjects with abnormal correlation of peak TSB levels to personal social developmental milestones which were significantly higher compared to 25.3±2.29 in subjects with normal correlation of peak TSB levels to personal social developmental milestones with $p<0.01$. There were 16 and 86 subjects respectively from abnormal and normal personal social developmental milestones respectively (Table 6). Abnormal BERA was seen in 14 subjects among 102 assessed study subjects.

DISCUSSION

The present study assessed 104 near-term and term babies having features of ABE (acute bilirubin encephalopathy) having bilirubin levels>20mg/dl. These subjects were assessed at the 3rd and 6th month to assess their neurodevelopment. Neurological outcomes were assessed using BERA (brainstem evoked response audiometry) DDST-II (Denver Development Screening Test). The mean gestational age was 37.3±0.82 weeks in study neonates. The mean admission weight was 2.4±0.35 kg in study neonates. There were 66.6% (n=68) male and 33.3% (n=34) female neonates in the study. Mean albumin levels were 3.6±0.37 mg/dl and exchange transfusion age was 4.6±0.93 days in study neonates. These data were similar to the previous studies of Babu TA et al[4] in 2012 and Yilmaz Y et al[5] in 2001 where authors assessed subjects with demographic data comparable to the present study.

It was seen that on assessing peak serum bilirubin levels in study subjects, it was seen that the mean peak ISB (indirect serum bilirubin) was 23.15±2.89 mg/dl. The mean DSB (direct serum bilirubin) level was 1.90±0.50 mg/dl in study subjects, and the mean TSB (total serum bilirubin) level in study subjects was 25.2±2.59 mg/dl. Concerning the distribution of study neonates based on the ABE (acute bilirubin encephalopathy), it was seen that ABE stages 1, 2, and 3 were seen in 88.23% (n=50), 7.84% (n=8), and 3.92% (n=3) study subjects respectively. These results were consistent with the findings of Ahlfors CE et al[6] in 2009 and Weng YH et al[7] in 2009 where authors reported similar peak serum bilirubin levels and studied neonates based on the ABE as in the present study in their respective studies.

The study results showed that for the assessment of the correlation of peak TSB levels to fine motor and gross motor developmental anomalies, mean TSB (total serum bilirubin) levels were 28.3±2.68mg/dl in subjects with abnormal fine motor and gross motor developmental anomalies and was 25.1±2.33mg/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 with $p<0.01$. There were 24 and 78 subjects respectively in subjects from abnormal and normal fine motor and gross motor developmental anomalies. These findings were in agreement with the results of Vohr BR et al[8] in 2000 and Oh W et al[9] in 2003 where the correlation of peak TSB levels to fine motor and gross motor developmental anomalies reported by authors in their studies were comparable to the results of the present study.

It was also seen that concerning the correlation of peak TSB levels to language milestones in study subjects, 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 compared to mean total serum bilirubin level of 25.3±2.33mg/dl in subjects with normal correlation of peak TSB levels to language milestones with $p<0.01$. There were 20 and 82 subjects respectively in subjects from abnormal and normal language milestones. These results were in line with the recordings of Ip S et al[10] in 2004 and Khan NZ et al[11] in 2006 where authors also reported significantly higher serum bilirubin levels in subjects with abnormal language milestones compared to subjects with normal language milestones.

Concerning the assessment of the correlation of peak TSB levels to personal social developmental milestones, mean peak TSB levels were 28.3±2.45 in subjects with abnormal correlation of peak TSB levels to personal social developmental milestones which were significantly higher compared to 25.3±2.29 in subjects with normal correlation of peak TSB levels to personal social developmental milestones with $p<0.01$. There were 16 and 86 subjects respectively from abnormal and normal personal social developmental milestones respectively (Table 6). Abnormal BERA was seen in 14 subjects among 102 assessed study subjects. These findings correlated to the results of Newman TB et al[12] in 2003 and Martin CR et al[13] in 2004 where a similar correlation of peak TSB levels to personal social developmental milestones to the present study was also confirmed by the authors.

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.

REFERENCES

1. Usman, F., Diala, U.M., Shapiro, S.M., Le Pichon, J.B. and Slusher, T.M., 2018. Acute bilirubin encephalopathy and its progression to kernicterus: current perspectives.
2. Stark AR, Bhutani VK: Neonatal Hyperbilirubinemia. In: Cloherty and Stark's Manual of Neonatal Care (Eichenwald EC, Hansen AR. eds) 8th ed:2016; p 349-50.
3. Kumar M, Tripathi S, Singh SN, Anand V. Outcome of neonates with severe hyperbilirubinemia in a tertiary level neonatal unit of North India. Clinical Epidemiology and Global Health. 2016;4:51-6.
4. Babu TA, Bhat V, Joseph NM. Association between peak serum bilirubin and neurodevelopmental outcomes in term babies with hyperbilirubinemia. The Indian Journal of Pediatrics. 2012;79:202-6.
5. Yilmaz Y, Karadeniz L, Yildiz F, Degirmenci SY, Say A. Neurological prognosis in term newborns with neonatal indirect hyperbilirubinemia. Indian Pediatr. 2001;38:165–8.
6. Ahlfors CE, Wennberg RP, Ostrow JD, Tiribelli C. Unbound (free) bilirubin: improving the paradigm for evaluating neonatal jaundice. Clin Chem. 2009;55:1288–99.
7. Weng YH, Chiu YW. Spectrum and outcome analysis of marked neonatal hyperbilirubinemia with blood group incompatibility. Chang Gung Med J. 2009;32:400–8.
8. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994. Pediatrics. 2000;105:1216–26.
9. Oh W, Tyson JE, Fanaroff AA, et al. Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. Pediatrics. 2003;112:773–9.
10. Ip S, Chung M, Kulig J, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics. 2004;114:e130–53.
11. Khan NZ, Muslima H, Parveen M, et al. Neurodevelopmental outcomes of preterm infants in Bangladesh. Pediatrics. 2006;118:280–9.
12. Newman TB, Liljestrand P, Escobar GJ. Infants with bilirubin levels of 30 mg/dL or more in a large managed care organization. Pediatrics. 2003;111:1303–11.

13. Martin CR, Cloherty JP. Neonatal hyperbilirubinemia. In: Cloherty JP, Eichenwald EC, Stark AR, editors. Manual of neonatal care. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2004. pp. 181–212.

TABLES

Characteristics	n (%)/ Mean ± S. D
Mean gestational age (weeks)	37.3±0.82
Mean admission weight (kg)	2.4±0.35
Gender	
Males	68 (66.6)
Females	34 (33.3)
Albumin level (mg/dl)	3.6±0.37
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