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A Longitudinal Study on Brainstem Evoked Response Audio metry (BERA) in Term Appropriate for Gestational Age (AGA) Neonates with Hyper bilirubinemia

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Abstract

Background: Neonatal hyperbilirubinemia is a common condition that may lead to bilirubin-induced neurological dysfunction, with the auditory pathway being particularly vulnerable to bilirubin toxicity. Brainstem Evoked Response Audio metry (BERA) is an objective tool for early detection of auditory pathway abnormalities in neonates. This study was conducted to evaluate BERA changes in term appropriate – for - gestational-age (AGA) neonates with hyperbilirubinemia and to assess the progression of abnormalities during follow-up.

Objectives: To evaluate BERA findings in term AGA neonates with hyperbilirubinemia and to determine changes in auditory responses at one and three months of follow-up.

Materials and Methods: A longitudinal observational study was conducted in the Neonatal Intensive Care Unit of the Department of Paediatrics, Mandya Institute of Medical Sciences, Mandya, from July 2021 to July 2022. A total of 150 term AGA neonates with hyperbilirubinemia requiring treatment according to American Academy of Paediatrics guidelines were included by purposive sampling. Detailed clinical evaluation, serum bilirubin estimation, and relevant investigations were performed.

BERA was done within 3–12 hours of initiation of therapy and repeated at one and three months. BERA abnormalities were assessed based on prolongation of wave latencies, increased inter peak intervals, and loss of waves. Data were analysed using descriptive statistics, Chi-square test, and Student's t-test, with $p < 0.05$ considered statistically significant.

Results: Among 150 neonates, 83 (55.3%) were females and 67 (44.7%) were males. The mean age at

presentation was 3.85 ± 1.42 days, and the mean serum bilirubin level was 20.01 ± 3.02 mg/dl.

ABO incompatibility was the most common cause of jaundice (34.7%), followed by inadequate milk output (21.3%) and exaggerated physiological jaundice (20.7%). Phototherapy alone was required in 94% of neonates, while 6% required exchange transfusion along with phototherapy.

Abnormal BERA findings were observed in 12 (8%) neonates at admission. Wave V prolongation was the most common abnormality, followed by prolongation of I–V inter peak latency. At one month, abnormal BERA was present in 6 (4%) neonates, which further reduced to 2 (1.3%) neonates at three months. No statistically significant association was found between serum bilirubin levels and abnormal BERA findings at admission, one month, or three months ($p>0.05$).

Conclusion: BERA abnormalities can occur in term AGA neonates with significant hyperbilirubinemia, even in the absence of clinical neurological manifestations. Most abnormalities showed improvement during follow-up, indicating possible reversibility after treatment. Serum bilirubin levels alone may not predict auditory dysfunction; therefore, BERA screening and follow-up are useful for early identification of bilirubin-induced auditory impairment.

Keywords: Neonatal Hyperbilirubinemia, Brainstem Evoked Response Audio Metry, BERA, Hearing Loss, Bilirubin Neurotoxicity, Term Neonates.

Introduction

Neonatal hyperbilirubinemia is one of the most common clinical conditions encountered during the neonatal period, affecting a significant proportion of term and preterm newborns. Although physiological jaundice is usually benign, excessive accumulation of unconjugated bilirubin can cross the blood–brain barrier and result in bilirubin-induced neurological dysfunction (BIND), with kernicterus being the most severe manifestation. The auditory pathway, particularly the brainstem nuclei, is highly susceptible to bilirubin toxicity, and auditory dysfunction may occur even in the absence of overt neurological signs.[1]

The incidence of neonatal jaundice requiring treatment varies worldwide depending on gestational age, ethnicity, feeding practices, and healthcare facilities. Severe unconjugated hyperbilirubinemia may lead to sensor ineural hearing loss due to selective damage to the cochlear nuclei, inferior colliculus, and other components of the auditory pathway. Unlike permanent hearing loss caused by other etiologies, bilirubin-induced auditory dysfunction may be reversible if detected early and treated appropriately.[2]

Brainstem Evoked Response Audio metry (BERA), also known as Auditory Brainstem Response (ABR), is an objective electrophysiological test used for assessment of auditory pathway function. It evaluates the electrical activity generated by the auditory nerve and brainstem structures in response to sound stimuli.

BERA is particularly useful in neonates because it does not require behavioural responses and can detect subtle abnormalities in auditory conduction, including prolonged wave latencies, increased inter peak intervals, and raised auditory thresholds.[3] Hyperbilirubinemia - associated auditory dysfunction may present as isolated abnormalities in BERA despite normal clinical examination. Therefore, routine auditory screening of neonates with significant hyperbilirubinemia requiring intervention is recommended in many centres.

Early identification allows timely audio logical monitoring and rehabilitation, thereby reducing the

impact of hearing impairment on speech and language development.[4]

Previous studies have demonstrated that increased serum bilirubin levels are associated with abnormalities in BERA parameters, particularly prolongation of wave V latency and I–V inter peak interval. However, the relationship between bilirubin levels and auditory abnormalities remains variable, with some studies reporting abnormalities even at moderate bilirubin concentrations. [5]

The reversibility of BERA abnormalities following reduction of serum bilirubin levels highlights the importance of serial monitoring. A longitudinal assessment at different time intervals helps differentiate transient bilirubin-induced auditory dysfunction from persistent hearing impairment. [6]

Hence, the present study was undertaken to evaluate BERA changes in term appropriate-for-gestational-age neonates with hyperbilirubinemia and to assess the progression of auditory abnormalities over a three-month follow-up period.

Materials and Methods

Study Design and Setting

A longitudinal observational study was conducted in the Neonatal Intensive Care Unit (NICU) of the Department of Paediatrics, Mandya Institute of Medical Sciences (MIMS), Mandya. The study was carried out over a period of one year, from July 2021 to July 2022.

Study Population

The study included term appropriate-for-gestational-age (AGA) neonates admitted to the NICU with hyperbilirubinemia requiring intervention as per the American Academy of Paediatrics (AAP) guidelines.

Sample Size

The sample size was calculated based on the prevalence of hearing impairment in hyperbilirubinemic neonates from a previous study, which was reported as 42.5%. The required sample size was calculated using the formula:

- $n = 4PQ/L^2$
- Where,

n=samplesize

P=prevalence(42.5%)

Q=100–P(57.5%)

L = allowable error at 20% relative error (8.5%)

- $n = (4 \times 42.5 \times 57.5) / (8.5 \times 8.5)$

The minimum required sample size was calculated to be 135 neonates. A total of 135 neonates were included in the study using purposive sampling.

Inclusion Criteria

Neonates fulfilling the following criteria were included

1. Term appropriate-for-gestational-age neonates delivered at Mandya Institute of Medical Sciences with total serum bilirubin levels requiring intervention according to American Academy of Pediatrics guidelines.
2. Neonates whose parents provided informed consent for participation.

Exclusion Criteria

Neonates with the following conditions were excluded:

1. Hyperbilirubinemia associated with complications such as sepsis, respiratory distress syndrome, and birth asphyxia.
2. Babies born to mothers who received ototoxic drugs.
3. Babies delivered outside the institute.

Methodology

After obtaining informed consent from the parents, detailed history and thorough physical examination were

performed for all enrolled neonates admitted with hyperbilirubinemia.

Serum bilirubin levels were estimated at the time of admission along with other relevant investigations, including complete blood count (CBC), renal function tests (RFT), and serum electrolytes.

Initial Brainstem Evoked Response Audio metry (BERA) was performed within 3–12 hours of initiation of therapy. Neonates who were awake during the procedure were administered oral triclofos at a dose of 20 mg/kg.

Silver–silver chloride electrodes were used for recording. The electrodes were placed according to the international 10–20 system of electrode placement. Click acoustic stimuli with a click rate of 10/second and alternating polarity were delivered through an earphone to each ear separately at an intensity of 90 dB hearing level. A masking sound of 40 dB was provided during stimulation of each ear. The electrical activity was filtered and averaged over 4000 responses. Auditory threshold was recorded separately for the right and left ears. All neonates were followed up at the first and third months, and BERA was repeated during follow-up visits.

BERA abnormalities associated with hyperbilirubinemia were assessed based on loss of one or more waves (I–V), raised auditory threshold, increased latency of waves I, III, or V, and increased inter peak intervals.

Statistical Analysis

The data obtained were compiled in Microsoft Excel and analysed using appropriate statistical methods. Descriptive statistics such as mean, standard deviation, and proportions were used for data presentation.

Inferential statistical tests, including the Chi - square test, were used to assess the association between hyperbilirubinemia and hearing loss detected by BERA. The Student's t-test was used to compare mean values between groups. A significance level of 5% was considered, and a p-value of <0.05 was considered statistically significant.

Results and Observations

A total of 150 term neonates with hyperbilirubinemia fulfilling the inclusion and exclusion criteria were included in the study. All neonates were evaluated clinically and underwent BERA assessment at admission, followed by follow-up BERA evaluation at 1 month and 3 months.

Table 1: Baseline Characteristics of Study Population (N=150)

Characteristics	Frequency (n)	Percentage (%)
Gender		
Male	67	44.7
Female	83	55.3
Age at presentation (days)		
1 day	4	2.7
2 days	19	12.7
3 days	43	28.7
4 days	42	28.0
>5 days	42	28.0
Mean age (days)	3.85 ± 1.427	

Among 150 neonates, females constituted the majority (55.3%). The commonest age at presentation was 3 days (28.7%), followed by 4 days and >5 days (28% each).

Table 2: Maternal and Birth Characteristics of Study Population (N=150)

Variables	Frequency (n)	Percentage (%)
Parity of mother		
Primigravida	92	61.3
Multigravida	58	38.7
Mode of delivery		
FTND	60	40.0
Assisted delivery	13	8.7
LSCS	77	51.3
Birth weight (kg)		
2.3–2.49	18	12.0
2.5–2.99	62	41.3
3–3.49	50	33.3
3.5–4	20	13.3
Mean birth weight	2.94 ± 0.38 kg	

Majority of mothers were Primigravida (61.3%). LSCS was the most common mode of delivery (51.3%). Most neonates had birth weight between 2.5–2.99 kg (41.3%).

Table 3: Distribution According to Maternal and Neonatal Blood Groups (N=150)

Blood group	Mother n (%)	Neonate n (%)
A+	33 (22.0)	44 (29.3)
A-	3 (2.0)	3 (2.0)
B+	26 (17.3)	38 (25.3)
B-	5 (3.3)	2 (1.3)
O+	60 (40.0)	54 (36.0)
O-	13 (8.7)	3 (2.0)
AB+	10 (6.7)	6 (4.0)

O positive was the most common blood group among both mothers (40%) and neonates (36%).

Table 4: Causes of Hyperbilirubinemia Among Study Subjects (N=150)

Cause of jaundice	Frequency (n)	Percentage (%)
ABO incompatibility	52	34.7
Inadequate milk output	32	21.3
Exaggerated physiological jaundice	31	20.7

Polycythemia	12	8.0
Rh incompatibility	10	6.7
Instrumental delivery	8	5.3
IDM	5	3.3

Among the causes of jaundice, ABO incompatibility was the most common cause (34.7%). Among ABO incompatibility cases, O-A incompatibility was seen in 17 (54%) and O-B incompatibility in 14 (45%) neonates.

Table 5: Serum Bilirubin Levels and Treatment Intervention (N=150)

Variables	Frequency (n)	Percentage (%)
Serum bilirubin at admission (mg/dl)		
10–14.9	5	3.3
15–19.9	77	51.4
20–24.9	62	41.3
>25	6	4.0
Mean serum bilirubin	20.01 ± 3.02 mg/dl	
Intervention		
Only phototherapy	141	94.0
Exchange transfusion + phototherapy	9	6.0

The majority of neonates had serum bilirubin levels between 15–19.9 mg/dl (51.4%). Phototherapy alone was the most common intervention (94%).

Table 6: Duration of Phototherapy and BERA Status During Follow-up

Variable	Frequency (n)	Percentage (%)
Duration of phototherapy		
<24 hours	9	6.0
24–48 hours	20	13.3
48–72 hours	75	50.0
>72 hours	40	26.7
BERA status at admission		
Normal	138	92.0
Abnormal	12	8.0
BERA status at 1 month		
Normal	144	96.0
Abnormal	6	4.0
BERA status at 3 months		
Normal	148	98.7
Abnormal	2	1.3

Table 7: BERA Wave Abnormalities at Admission (N=12 abnormal cases)

Wave abnormality	Right ear n (%)	Left ear n (%)
Wave I prolonged	8 (66.7)	5 (41.7)
Wave III prolonged	10 (83.3)	7 (58.3)
Wave V prolonged	12 (100)	9 (75)
I–III latency prolonged	4 (33.3)	3 (25)
I–V latency prolonged	10 (83.3)	11 (91.7)
III–V latency prolonged	8 (66.7)	6 (50)

Wave V prolongation was the most common abnormality detected at admission.

Table 8: BERA Wave Abnormalities at 1 Month and 3 Months

Wave Abnormality	1 Month Right Ear N (%)	1 Month Left Ear N (%)	3 Months Right Ear N (%)	3 Months Left Ear N (%)
Wave I Prolonged	3 (50)	0	2 (100)	0
Wave III Prolonged	4 (66.7)	0	1 (50)	0
Wave V Prolonged	6 (100)	1 (16.7)	2 (100)	0
I–V Latency Prolonged	4 (66.7)	1 (16.7)	1 (50)	1 (50)
III–V Latency Prolonged	1 (16.7)	1 (16.7)	1 (50)	0

The number of abnormal BERA findings decreased during follow-up.

Table 9: Comparison of Serum Bilirubin Levels According to BERA Status

Follow-up period	BERA status	Mean serum bilirubin (mg/dl) ± SD	P value
Admission	Abnormal	20.95 ± 2.25	0.262
	Normal	19.93 ± 3.07	
1 month	Abnormal	21.58 ± 2.60	0.196
	Normal	19.94 ± 3.03	
3 months	Abnormal	22.20 ± 4.66	0.306
	Normal	19.98 ± 3.01	

There was no statistically significant difference in mean serum bilirubin levels between neonates with normal and abnormal BERA findings.

Table 10: Association Between Serum Bilirubin Level and BERA Abnormality

Serum bilirubin level	BERA abnormal at admission n (%)	BERA abnormal at 1 month n (%)	BERA abnormal at 3 months n (%)
15–20 mg/dl	5 (6.1)	2 (2.4)	1 (1.2)
20–25 mg/dl	7 (11.3)	4 (6.5)	1 (1.6)
>25 mg/dl	0	0	0
P value	0.756	0.523	0.749

No significant association was found between serum bilirubin levels and abnormal BERA findings at admission, 1 month, or 3 months.

Discussion

Neonatal hyperbilirubinemia remains an important cause of morbidity due to its potential neurotoxic effects, particularly on the auditory system. The present longitudinal study evaluated BERA findings among 150 term AGA neonates with hyperbilirubinemia requiring treatment and assessed changes at admission, one month, and three months of follow-up.

In the present study, females constituted 55.3% and males 44.7% of the study population. The majority of neonates presented on the third day of life (28.7%), followed by the fourth day and beyond the fifth day of life. Similar patterns of presentation have been described in previous studies, where neonatal jaundice commonly peaks during the first week of life due to increased bilirubin production and immature hepatic conjugation mechanisms.[7]

The mean birth weight of neonates in the present study was 2.94 ± 0.38 kg, indicating that most infants were within the normal birth weight range. The majority of mothers were Primigravida (61.3%), and LSCS was the commonest mode of delivery (51.3%). These findings suggest that demographic and perinatal factors may contribute to the occurrence and clinical presentation of neonatal jaundice.

ABO incompatibility was the most common cause of hyperbilirubinemia in the present study, accounting for 34.7% of cases, followed by inadequate milk output (21.3%) and exaggerated physiological jaundice (20.7%). ABO incompatibility is a recognised cause of early-onset significant jaundice due to immune-mediated hemolysis and increased bilirubin production. Similar observations have been reported by previous researchers, who identified blood group incompatibility as an important contributor to neonatal hyperbilirubinemia.[8]

The mean serum bilirubin level at admission in the present study was 20.01 ± 3.02 mg/dl. Most neonates (51.4%) had bilirubin levels between 15–19.9 mg/dl, while 41.3% had levels between 20–24.9 mg/dl. Phototherapy alone was required in 94% of neonates, whereas 6% required exchange transfusion along with phototherapy. These findings indicate that early diagnosis and treatment according to standard guidelines can prevent progression to severe bilirubin toxicity.

In the present study, abnormal BERA findings were observed in 12 neonates (8%) at admission. Wave V prolongation was the most frequent abnormality, observed in all abnormal cases in the right ear and in 75% of cases in the left ear. Increased I–V latency was also commonly observed. Similar findings have been reported in previous studies, where prolongation of wave V latency and I–V inter peak interval were considered early indicators of bilirubin-induced auditory dysfunction.[9]

The mechanism of bilirubin-induced auditory injury is attributed to selective neurotoxicity of unconjugated bilirubin on the auditory pathway. The cochlear nuclei, superior olivary complex, and inferior colliculus have high metabolic activity and are particularly vulnerable to bilirubin deposition. This results in delayed neural conduction, reflected as prolonged BERA wave latencies.[10]

On follow-up, the frequency of abnormal BERA findings decreased progressively. At one month, abnormal BERA was detected in 6 neonates (4%), and at three months only 2 neonates (1.3%) continued to show

abnormal findings. This improvement suggests that bilirubin-induced auditory dysfunction may be reversible after appropriate treatment and reduction of bilirubin levels. Similar recovery patterns have been documented by studies demonstrating normalization of BERA parameters following successful management of hyperbilirubinemia.[11]

In the present study, no statistically significant association was found between serum bilirubin levels and abnormal BERA findings at admission, one month, or three months. Although neonates with abnormal BERA showed slightly higher mean bilirubin levels compared with those with normal BERA, the difference was not statistically significant. This suggests that bilirubin concentration alone may not reliably predict auditory dysfunction, and individual susceptibility, duration of exposure, and bilirubin binding capacity may influence neurological outcomes. Similar findings have been reported by other investigators who observed variable correlation between serum bilirubin levels and auditory abnormalities.[12]

The longitudinal nature of this study allowed assessment of the natural course of bilirubin-related auditory changes. Serial BERA evaluation demonstrated improvement in most neonates, emphasising the importance of follow-up rather than relying only on a single assessment. Early identification of abnormalities provides an opportunity for timely intervention and monitoring of hearing and developmental outcomes.

The findings of the present study highlight the usefulness of BERA as a sensitive, objective, and non-invasive tool for monitoring auditory function in neonates with significant hyperbilirubinemia. Routine BERA screening and follow-up may help identify infants at risk of hearing impairment, even when clinical neurological examination is normal.

Conclusion

In the present study, BERA abnormalities were observed in a proportion of term AGA neonates with hyperbilirubinemia, with prolongation of wave V latency and inter peak intervals being the most common findings. The incidence of abnormal BERA decreased during follow-up at one and three months, suggesting that bilirubin-induced auditory dysfunction may be reversible with timely treatment. Serum bilirubin levels alone did not show a significant association with BERA abnormalities, indicating the importance of objective auditory assessment rather than relying only on bilirubin values. Routine BERA screening and follow-up of neonates with significant hyperbilirubinemia can help in early detection and management of auditory dysfunction.

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