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AN OBSERVATIONAL STUDY TO ASSESS THE EFFECT OF NEONATAL HYPERBILIRUBENEMIA AS A RISK FACTOR ON THE HEARING OF THE TERM INFANTS ADMITTED IN THE HOSPITAL.

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ABSTRACT

Background: Neonatal hyperbilirubinemia is a matter of concern as it is increased due to bilirubin induced neurological dysfunction with damage to the auditory system occurring in healthy term infants.

Objective: To identify and assess the significance of neonatal hyperbilirubinemia as a risk factor causing hearing loss in term babies.

Methods: This observational prospective cohort study was carried out in tertiary care centre, Jaipur, Rajasthan. 62 Full term newborns delivered in our hospital having TSB level >15 mg/dl requiring phototherapy / exchange transfusion were included. These newborns underwent OAE screening before discharge, repeat OAE was done at 3-4 weeks from discharge date and BERA test was done around at 3 months of age.

Result: 62 term babies (TSB level >15 mg/dl) were assessed to analyze the effect of neonatal hyperbilirubinemia as a risk factor on the hearing of term babies. significant P value (< 0.05) was found in LSCS delivery, male neonates, term babies weighing< 2500gm and SGA Neonates & S.bilirubin was not a significant risk (p value >0.05) factor for 1stOAE Test (at discharge). The correlation of Repeat OAE test vs. BERA showed that Repeat OAE test had a sensitivity of 90%, specificity 100% and accuracy 90.3%.

Conclusion: This study was an attempt to show the importance of developing a hearing screen with OAE that when repeated appropriately and when required combined with BERA for cases that fail serves as an effective screening test.

Keywords: Neonatal Hyperbilirubinemia (NNH), BERA, OAE, BIND, Hearing

INDRODUCTION

Neonatal hyperbilirubinemia (NNH) is a cause of apprehension for the parents as well as for the pediatricians.[1] Concerns regarding Jaundice have increased after reports of bilirubin induced brain damage occurring in healthy term infants even without hemolysis.[2] Early discharge of healthy term newborns after delivery has become a common practice because of medical and social reasons as well as economic constraints.[3] Thus, the recognition, follow-up, and early treatment of jaundice has become more difficult as a result of earlier discharge from the hospital. Phototherapy is now a viable alternative to the planned use of exchange transfusion in the treatment of even moderate to severe HDN.[4] Hyperbilirubinemia affects up to 84% of term and late preterm infants in the first week of life.[5] The elevation of total serum/plasma bilirubin (TB) levels is generally mild, transitory, and, for most children, inconsequential. However, a subset of infants experiences lifelong neurological sequelae & kernicterus remains a significant problem in the global arena.[6] Bilirubin-induced neurologic dysfunction (BIND) is a spectrum includes kernicterus, acute bilirubin encephalopathy, and isolated neural pathway dysfunction.[7] However, there is a significant association between hyperbilirubinemia and damage to the auditory system.[8] In fact, auditory system damage may occur at TB levels previously thought to be harmless, and may occur in the absence of other signs of classic kernicterus.[9] These auditory effects can range from subtle abnormalities in hearing and speech processing to complete deafness.[10] Permanent hearing loss is one of the most common congenital disorders, with an estimated incidence of 1-3 per thousand live births.[11] The secondary prevention strategy is based on evidence that early diagnosis and intervention allow for improved outcomes in hearing-impaired children. Universal Neonatal Hearing Screening (UNHS) programs aim for screening by one month of age, confirmation of the diagnosis by three months, with intervention by six months. Hearing loss is categorized based on etiology (sensorineural, conductive or mixed), and may be fixed or progressive. Most neonatal hearing loss is sensorineural; a known genetic cause is found in50% of children. The remaining causes of neonatal sensorineural hearing loss include congenital infections, hyperbilirubinemia and ototoxic medications.[12] Admission to a neonatal intensive care unit is an established risk factor for hearing loss in infants, particularly for

auditory neuropathy[13]. Without early intervention, children with hearing loss demonstrate predictable irreversible deficits in communication and psychosocial skills, cognition and literacy[14]. Currently, hearing screening in newborns is performed via Oto-Acoustic Emission (OAE) and Brainstem Evoked Response Audiometry (BERA) testing. These physiological, noninvasive, automated screening tests can be performed at the bedside in term and pre-term infants. Depending on the screening protocol, they may be performed singly (OEA or BERA) or sequentially.

AIMS AND OBJECTIVE

1. To identify and assess the significance of neonatal hyperbilirubinemia as a risk factor which cause hearing loss in term babies admitted in the hospital.
2. To detect early hearing loss in term babies discharged from hospital.
3. To determine if early repeat hearing screening at 3-4 weeks after discharge should be the standard of care for all term babies with neonatal hyperbilirubinemia.

MATERIALS AND METHOD

This hospital based observational prospective cohart study was conducted in the Department of Pediatrics Mahatma Gandhi medical college, Jaipur, Rajasthan from 15th May 2022 to 15th April 2023 after receiving approval from Institute of Ethical Committee. All term neonates were included in this study with TSB level > 15 mg/dl requiring phototherapy/ exchange transfusion. Sample size of 62 was calculated as per the statistical formula applied.

Inclusion criteria:

1. Healthy term babies (gestation 37 to 42 weeks) born in MGH.
2. Birth weight (2200 to 3900 gram)
3. Requirement of phototherapy or exchange transfusion.
4. Total serum bilirubin level greater than15 mg/dl.

Exclusion criteria:

1. Parents not willing to take part in the study
2. Preterm babies shifted in NICU.
3. Babies with congenital anomalies.
4. Chromosomal defects.
5. Family history of sensorineural hearing loss.
6. In-utero infection/bacterial meningitis/hypoxia ischemic injury at birth/persistent pulmonary hypertension.
7. Infants on ototoxic drugs.

METHOD

All healthy term neonates were enrolled in this study. Informed and written consent was taken from the parents/guardian and consultant in-charge was also informed.OAE screening was performed before discharge from the hospital with the help of IHS-OAE Autometrix machine. Results were entered in the study proforma. No intervention was undertaken at this stage. Parents were counseled to bring the child for follow up between 3-4 weeks. Follow up date was fixed at 3-4 weeks after the 1stOAE test (done before discharge). All study babies were studied at 1st follow up period after discharge (3-4 weeks from discharge date) with the repeat OAE screening. Subjecting the baby to BERA at this stage was done only upon failure of 1st follow up OAE screen 3-4 weeks from discharge & BERA done before 3 months. Babies who failed BERA, referred to rehabilitation/interventional centre for further care. This was the end point of study. The data collected soon before discharge and that at 1stfollow up period were studied for statistical significance of the risk factors. Final conclusion was based upon collation of the data collection. The data analysis was done using IBM SPSS software 20. Categorical data were expressed as percentage and frequency, where as numerical data were expressed as mean and standard deviation. Association among the study groups were assessed with the help of Odds Ratio (OR) & Confidence Interval (CI). 'p' value less than 0.05 is taken as a significant.

RESULTS

The present study was done at our tertiary care centre to observe and follow up the babies with neonatal hyperbilirubinemia (TSB level >15mg/dl), up to the age of 3 months, to study neonatal hyperbilirubinemia as a risk factor and mandatory repeat hearing screening for all newborns born at our centre who had a history of hyperbilirubinemia.

Table1: Association of Risk Factors with 1stOAE Test (at discharge)

Parameters	**OR**	**95%CI**	**p Value**
Duration of gestation			
≥37-38weeks	0.958	0.324-2.975	p>0.05

≥38-39weeks	1.0	Reference	
≥39-40weeks	1.278	0.965-1.533	p>0.05
≥40-41weeks	1.392	0.854–2.313	p>0.05
Mode of Delivery			
LSCS	2.214	1.024-1.708	**p<0.05**
Normal	1.0	Reference	
Mother's Blood Group	0.816	0.264-2.749	p>0.05
Gender			
Male	9.615	1.192-4.587	**p<0.05**
Female	1.429	0.547-4.582	p>0.05
Birth weight (gms)			
≤2500	1.705	1.154–2.503	**p<0.05**
2501– 3000	2.094	0.869-1.573	p>0.05
3001-3500	1.0	Reference	
3501-4000	0.862	0.742-1.529	p>0.05
SGA Status	1.554	1.178–2.059	**p<0.05**
Term Babies's Blood Group	0.759	0.681-1.328	p>0.05
APGAR Score at 1min	1.239	1.285-2.681	p>0.05
APGAR Score at 5mins	1.610	0.995-1.922	p>0.05
Phototherapy (hours)	1.423	0.548-4.618	p>0.05

p<0.05–StatisticallySignificant

Table 1showed that caesarean delivery (OR-2.214; 95%CI 1.024 - 1.708), male gender (OR-9.615; 95%CI 1.192-4.587), birth weight ≤2500gms (OR-1.705; 95%CI 1.154–2.503) and SGA status (OR-1.554; 95%CI 1.178–2.059) were significantly associated with1stOAE test (at discharge). There was significant P value (< 0.05) in LSCS delivery, male neonates, term babies weight < 2500gm and SGA Neonates.

Table 2:- Distribution of term babies according to 1stOAE Test (at discharge)

1stOAETest(at discharge)	N	%
Pass	49	79.1%
Refer	13	20.9%
Total	62	100%

Table 2 showed that 79.1% term babies passed the 1st OAE test (at discharge) while 20.9% term babies failed the test.

Table 3:- Association of Bilirubin with1stOAE Test (at discharge)

Parameters	OR	95%CI	p Value
Bilirubin	1.423	0.548-4.618	p>0.05

Table 3 showed that bilirubin was not a significant risk (p value >0.05) factor for 1stOAE Test (at discharge).

Table 4: Correlation of Repeat OAE test and BERA

Test		Results
Repeat OAE Test	True Pass	54
	False Pass	0
	False Fail	6

	True Fail	2
BERA	Pass	60
	Fail	2

Table 4 showed that 60 term babies had cleared the BERA test while 2 term babies had failed it. The repeat OAE test was incorrectly diagnosed in 6 term babies as failed.

Table 5: Correlation of Repeat OAE test as screening tool to BERA

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Repeat OAE vs. BERA	90%	100%	100%	25%	90.3%

Table 5 showed that correlation of Repeat OAE test vs. BERA showed that Repeat OAE test had a sensitivity of 90%, specificity 100%, positive predictive value (PPV) 100%, negative predictive value (NPV) 25% and accuracy 90.3%. Repeat OAE test sensitivity 90%, which signifies that early repeat hearing screening at 3-4 weeks after discharge should be the standard of care for all term babies with neonatal hyperbilirubinemia

DISCUSSION

Present study was a prospective observational cohort study done in tertiary care centre. A 62 term babies (TSB level >15 mg/dl) were assessed to analyze the effect of neonatal hyperbilirubinemia as a risk factor on the hearing of term babies. Screening test for hearing in infants should be simple, cost effective, quick, sensitive, efficient, reliable and effective. In the absence of such objective screening test, hearing loss may not be detected until the child is 2-6 years of age, when intervention outcomes may be suboptimal.

Association of Risk Factors with 1stOAE Test (at discharge)

In present study we found that caesarean delivery (OR-2.214; 95%CI 1.024 - 1.708), male gender (OR-9.615; 95%CI 1.192-4.587), birth weight ≤2500gms (OR-1.705; 95%CI 1.154–2.503) and SGA status (OR-1.554; 95%CI 1.178–2.059) were significantly associated with1stOAE test (at discharge). There was significant P value (< 0.05) in LSCS delivery, male neonates, term babies' weight < 2500gm and SGA Neonates. A similar study conducted by Smolkin T et al (2012)[15] found Variables that were independently

significantly associated with failure on first OAE included male gender (OR 1.42 [1.02–1.98]), birth by CD (emergency CD: OR 3.18 [2.21–4.57], elective CD: OR 3.32 [2.04–5.42]), early age (12–23 hours) of first OAE (OR 3.1 [2.1–4.58]), and SGA status (OR 2.2[1.15–4.28]).

Distribution of term babies according to 1st OAE Test (at discharge)

In Present study, 79.1% term babies passed the 1st OAE test (at discharge) while 20.9% term babies failed the test. A similar study conducted by Shulman S et al (2010)[16] evaluated the 55 state and territorial UNHS programs and reported that most infants (92%) were screened for hearing loss before discharge from the hospital, and, of these, 2% were referred for diagnostic evaluation. Approximately 62% of infants who needed a diagnostic evaluation received one, suggesting that there is still a substantial loss to follow-up for infants who did not pass the initial hearing screen.

Association of Bilirubin with1st OAE Test (at discharge)

In present study, we observed that bilirubin was not a significant risk factor for 1stOAE Test (at discharge). A similar was conducted by Shankar P et al (2014)[17] found abnormal OAE changes in 6 (5.7%) and abnormal BERA was seen in 9 (8.5%) babies out of a total of 105 babies tested with hyperbilirubinemia. Chang KW et al (1993)[18] observed that failure on OAE in neonates can also be caused by external ear canal secretions, and removal of external ear debris increased the OAE pass rate from 76% to 91%.

Correlation of Repeat OAE test and BERA

In the current study, 60 term babies had cleared the BERA test while 2 term babies had failed it. The repeat OAE test was incorrectly diagnosed in 6 term babies as failed. A study was conducted by Jaleh Y et al (2013)[19] showed that 18 cases out of 1000 neonates had failed double–checked OAE tests. From these 18 failed cases, 6 were confirmed by BERA test

Correlation of Repeat OAE test as screening tool to BERA

In present study, the correlation of Repeat OAE test vs. BERA showed that Repeat OAE test had a sensitivity of 90%, specificity 100%, positive predictive value (PPV) 100%, negative predictive value (NPV) 25% and accuracy 90.3%. Repeat OAE test sensitivity 90%, which signifies that early repeat hearing screening at 3-4 weeks after discharge should be the standard of care for all term babies with neonatal hyperbilirubinemia. A

study was conducted by Jaleh Y et al (2013)[19] showed that 9 out of 1000 neonates had impaired BERA tests, from these patients, 6 had failed OAE as well, but 3 had normal OAE (3 false negative result). From these 9 patients 2 had profound hearing loss so cochlear implantation was scheduled for them. They found that OAE has 66.7% sensitivity and 98.8% specificity in diagnosis of neonatal hearing impairment. A similar study done by Shankar P et al (2014)[20] observed in their study OAE findings were significantly associated with BERA findings with P<0.001. Correlation of OAE as Screening tool in relation to BERA results for hearing abnormalities were Sensitivity 66.67, Specificity 100.00, PPV 100.00, NPV 96.97, Accuracy 97.14, Kappa score was 0.785 respectively.

SUMMARY

A prospective observational, cohort study was done in which 62 term babies with TSB level >15 mg/dl were assessed to analyze the effect of neonatal hyperbilirubinemia as a risk factor on the hearing of term babies. The following observations were noted:

1. 79.1% term babies passed the 1st OAE test (at discharge) while 20.9% term babies failed the test.
2. It was observed that bilirubin was not a significant risk factor for 1stOAE Test (at discharge).
3. It was observed that caesarean delivery (OR-2.214; 95%CI 1.024 - 1.708), male gender (OR-9.615; 95%CI 1.192-4.587), birth weight ≤2500gms (OR-1.705; 95%CI1.154–2.503) and SGA status (OR-1.554; 95%CI1.178–2.059) were significantly associated with1stOAE test (at discharge). There was significant P value (< 0.05) in LSCS delivery, male neonates, term babies weight < 2500gm and SGA Neonates.
4. 60 term babies had cleared the BERA test while 2 term babies had failed it. The repeat OAE test was incorrectly diagnosed in 6 term babies as failed.
5. The correlation of Repeat OAE test vs. BERA showed that Repeat OAE test had a sensitivity of 90%, which signifies that early repeat hearing screening at 3-4 weeks after discharge should be the standard of care for all term babies with neonatal hyperbilirubinemia.

CONCLUSIONS

With the development of BERA a new era in hearing screening was introduced. But it is invasive, costly, needs cooperation from patient, costly and a trained audiologist to

conduct. Oto-acoustic Emissions on the other hand is an easy, cost effective and reliable method of testing of large number of infants for hearing loss. OAE as a screening test does hold as a good promise in hearing screening. Also more studies are required to standardize the protocol required and to normalize data. This study concluded that there is an importance of developing a hearing screen with OAE that when repeated appropriately and when required, combined with BERA for cases that fails serves as effective screening test. BERA can be an efficient tool for monitoring the auditory brainstem pathway in neonates who are at risk of neurotoxicity. Diagnosing the earliest stages of auditory damage caused by high levels of bilirubin is a key at a stage where lasting central effects may be preventable.

RECOMMENDATIONS

1. All Terms newborns with serum total bilirubin > 15mg/dl should be screen by OAE before discharge and repeat at 3-4 weeks after first screening.
2. BERA test should be performing at 3 months of age for monitoring.
3. BERA fail babies should be early referred to rehabilitation/interventional centre for further care.

ETHICAL APPROVAL

Ethical Committee of Mahatma Gandhi Medical College, Jaipur, and Rajasthan, India approved this study.

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