Effects of Phototherapy on Outer Hair Cell Function in Infants with Hyperbilirubinemia

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Abstract

Introduction: Hyperbilirubinemia in newborns has been hypothesized to cause damage to inner ear, thus leading to sensorineural hearing loss. Phototherapy is treatment protocol in most of the hospitals for newborns with high bilirubin levels. The present study aimed to determine the effects of phototherapy on outer hair cell (OHC) function of cochlea. **Methods:** Twenty-two neonates with hyperbilirubinemia undergoing phototherapy and 22 neonates without any high-risk registers were included in the study. Distortion product otoacoustic emission (DPOAE) was administered before and after phototherapy. Auditory brainstem response (ABR) evaluation was done during the postphototherapy recording. **Results:** Results showed that DP amplitude and signal-to-noise ratio improved significantly after phototherapy. ABR evaluation revealed; 19 neonates had significantly prolonged wave V latency compared to normal, whereas no peaks were identified among three neonates. Most of the infantile hyperbilirubinemia are found to be harmless until and unless treatment is not initiated at the earliest, but still it is found that short-term increase in bilirubin level can induce temporary changes in OAEs and ABR measures. ABR needs to be repeated over a period of time for these three neonates to rule out auditory dyssynchrony (AD). **Conclusion:** The results indicate that phototherapy has temporary effects on OHC function and can improve as the bilirubin levels reduce. Follow-up testing over a period of time helps in discriminating the sensory pathology and AD.

Keywords: Hyperbilirubinemia, otoacoustic emissions, phototherapy

Introduction

Hyperbilirubinemia is a condition where the level of bilirubin is high in the blood and is one of the most common problems during the infantile period. Bilirubin is a natural byproduct of the breakdown of red blood cells, wherein this condition is caused by the buildup of bilirubin in the bloodstream. Higher bilirubin level is considered physiological when nonconjugated bilirubin levels appear within first 2 weeks after birth. Hyperbilirubinemia has been hypothesized to cause damage to cochlear hair cells, thus leading to sensorineural hearing loss.[1] Depending on the amount of bilirubin in the serum, severity of the hearing loss may vary and it may be reversible and sometimes not. Research on bilirubin levels and hearing loss has found variable levels of bilirubin in blood that could lead to sensorineural hearing loss. Among these, few studies have found that bilirubin level of 14 mg/dl[1] or >20 mg/dl[2] could cause sensorineural hearing loss. High level of bilirubin is toxic to the brain, endocochlear hair cells, basal nuclei, and central auditory pathways and can cause hearing problem by interfering with the ways in the transmission of information.

Hyperbilirubinemia can be treated efficiently with phototherapy. Phototherapy has been used since 1958 for the treatment of neonatal hyperbilirubinemia.[3] Phototherapy is a process where light is used to eliminate excessive bilirubin in the blood. In this procedure, the light waves are emitted by lamps between the wavelength of 400 and 500 nm which is based on the bilirubin level and the rate of rise in serum bilirubin which are absorbed by skin and blood. Thus, bilirubin is changed into products which can pass through the system. Phototherapy aims to decrease the level of unconjugated bilirubin in the blood.

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All infants with hyperbilirubinemia should undergo otoacoustic emissions (OAEs) and auditory brainstem response (ABR) to rule out the possibility of sensory and neural deficits. OAEs are believed to be the acoustic byproducts of outer hair cell (OHC) motility which assess the cochlear function and the status of auditory periphery and in the absence of middle ear disorders, the likelihood of sensory hearing loss. Few researchers have identified the absence of OAEs in both ears which indicates cochlear pathology,[2] whereas other researchers have suggested high bilirubin levels as a cause for retrocochlear pathology.[4-6]

Research on ABR measures on thirty neonates with hyperbilirubinemia soon after birth found that the absolute and interpeak latencies were prolonged in neonates with hyperbilirubinemia.[7] They also found that, even after repeated testing during follow-up for ABR, ten neonates with hyperbilirubinemia had prolonged absolute Peak III and Peak V latencies. Few researchers have reported that the V peak was discretely prolonged who had undergone repeated phototherapy.[4,5] Other researchers have discovered great variation in the amount of recovery after some form of treatment for hyperbilirubin levels.[1,6] Few studies have noticed that infants with severe hyperbilirubinemia had normal ABRs and others have found impaired ABRs.[1,6]

The literature surrounding the hyperbilirubin level and phototherapy has found to be the risk factors for hearing loss after birth. Although several studies have shown the effect of high bilirubin levels on auditory system, the threshold level of bilirubin levels causing an effect on auditory system is unclear.[8] Furthermore, there is a dearth of studies reporting on the phototherapy and posteffects of phototherapy on newborn hearing. It is essential to establish the risk factors of hearing loss among infants and to assess whether phototherapy should be considered as a high-risk register (HRR) for hearing loss. Hence, the aim of the study was to determine the effects of phototherapy on OHC function of cochlea.

Methods

Participants

Participants of the study included 22 neonates of age range of 1–18 days (mean age of 4.1 days) with higher bilirubin level of 20 mg/dl or more who were undergoing phototherapy and 22 age-matched neonates (mean age of 5.5 days) without any HRRs whose hearing was found to be normal through auditory brainstem evaluation (ABR) who served as control group. Infants who had a bilirubin level of <20 mg/dl who were admitted to Neonatal Intensive Care Units were selected for the study. Information regarding the pregnancy care, prenatal history, and family history was collected from the parents. The perinatal and postnatal information was taken from the mother's and infant's medical records. Neonates with any other complicated risk factors as per the HRRs by Joint Committee on Infant Hearing[9] were excluded from the study. The purpose and nature of the study were explained to parents of the neonates and written informed consent was obtained before the commencement of the study. Ethical clearance was also obtained from the relevant Ethical Committee of the institute.

Procedure

Ethical treatment of experimental subjects (human)

All procedures performed in this study involving human participants were in accordance with the ethical guidelines of the institute and with the 1975 Helsinki declaration and its later amendments.

Distortion product OAE (DPOAE) was administered using Oto-Read instrument. Responses were recorded at frequency bands of 1000, 2000, 3000, 4000, 5000, 6000, 8000, and 10,000 Hz. The analytical parameters that were used for interpreting results were stimulus intensity 65 and 55 dB (intensity of L1 and L2), response region of 2f1-f2, and DP amplitude equal to or above 6 dB over the noise spectrum. Three recordings were taken during phototherapy. Two recordings of DPOAE were done before the first session of phototherapy, with a gap of half an hour. The average of these recordings was considered for pretherapy data. A follow-up recording was considered as third recording which was done on same infants 30–45 days after phototherapy which included DPOAE and ABR which was considered as posttherapy data. Neonates who had undergone 3–5 sessions of phototherapy were included in the study. Similar recordings were carried out for the control group, wherein first two recordings were taken within 5 days of birth and third recording being taken after 30–40 days after birth to check for the improvement in DP amplitude as a function of age.

ABRs were recorded 30–45 days after phototherapy using Intelligent Hearing Systems software. The protocol for ABR evaluation was electrode montage-inverting electrode on mastoid, noninverting electrode-forehead, ground electrode – opposite ear mastoid, filter setting was 30–3000 Hz with time window of 0–20 ms, averaging of 2000 sweeps, click stimulus of rate 11.1/s, polarity of the stimulus was rarefaction, and initial start intensity being 90 dBnHL. Absolute latencies of Wave I, III, V, and inter-peak latencies of I-III, III-V, and I-V waves were measured at 90 dBnHL. For threshold estimation, bracketing procedure was used where if the response was present at 90 dBnHL, then the stimulus intensity was decreased in 20 dB steps and if peaks were not identified the stimulus intensity was increased by 10 dB.

Results and Discussion

The present study aimed to investigate the effects of phototherapy on OHC function. Twenty-two neonates with hyperbilirubinemia were tested for DPOAE function. DP amplitude and signal-to-noise ratio (SNR) were compared for during phototherapy and after phototherapy. The results of the present study showed some interesting findings. Figure 1 represents the comparison of mean SNR across frequencies for infants with hyperbilirubinemia pre and postphototherapy. As can be seen from Figures 1 and 2, the SNR and DP amplitude of post phototherapy was higher than compared to pre phototherapy.

Paired *t*-test was administered to investigate for any changes across two recordings of the experimental group. Results showed that significant main effect was observed across all frequencies ($P < 0.001$) in both ears. Table 1 shows the *t*-test values for the right ear and left ear across frequencies from 1000 to 10,000 Hz.

Furthermore, DP amplitude and SNR were compared between two groups. The SNR of postphototherapy measures was compared with control group SNR. Independent *t*-test was administered to investigate for any changes across two groups. From the Table 2, it can be noted that the results failed to show significant main effect across frequencies in both the ears.

OAE has been widely applied in the assessment of hearing in neonates.[8,10] The results of the present study are similar to the studies in literature,[6,8] where they studied pre and posthyperbilirubinemia testing using OAEs. They speculated that, even though the neonates had severe hyperbilirubinemia, the effects of these were for short duration.[6] Therefore, the results of the OAE have to be analyzed and interpreted not only on the basis of the presence or absence of amplitude but also on the features of the OAE. That is the amplitude and the SNR which can be compared with the control group. Furthermore, the DPOAE increases the reliability of the measures than TEOAE (hence which DP was selected in the present study) making possible to measure a wider frequency range and helps in classifying the analysis for low or high-frequency data comparisons.

ABR evaluation was carried out for threshold estimation for both the groups. The absolute and interpeak latencies were compared between both the groups. Peaks were observed in 19 of 22 neonates with hyperbilirubinemia, whereas no peaks were identified among three neonates. Table 3 represents the absolute latencies of Peaks I, III, and V for both right and left ear. From the Table 3, it can be noted that infants with hyperbilirubinemia had significantly prolonged absolute latencies compared to control group.

Results have shown that the absolute and interpeak latencies of ABR were prolonged compared to controls.[7,11] Investigators in the literature suggested that the reason to be early bilirubin-induced encephalopathy. The results can be interpreted as the alterations could be located at cochlear or at the processing level leading to the prolonging of absolute and interpeak latencies. The results of the present study demonstrate the importance of ABR testing for the detection of hearing loss as the ABR alterations persisted among many of the neonates in the literature.[4,7,11]

Few researchers have found that the OAE was present with strong amplitudes in severe hyperbilirubinemia cases but still altered ABR recordings suggestive of auditory neuropathy (AN).[12] In such conditions where DPOAE is

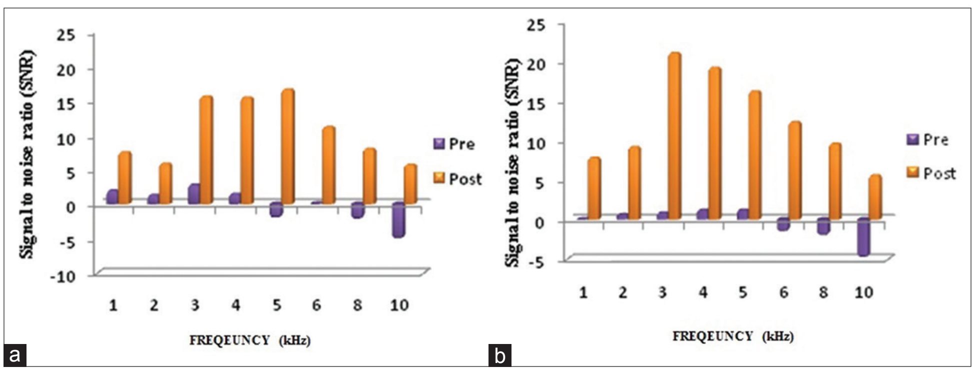

Figure 1: Representing the comparison of signal-to-noise ratio of distortion product otoacoustic emission of pre and postphototherapy of infants with hyperbilirubinemia. (a) Right ear and (b) left ear

Table 1: Represents the *t*-test values of signal-to-noise ratio of distortion product otoacoustic emission in the right and left ear of the experimental group

t-test values	1 kHz	2 kHz	3 kHz	4 kHz	5 kHz	6 kHz	8 kHz	10 kHz
Right ear	−3.123	−3.951	−9.323	−10.417	−13.509	−11.192	−10.689	−11.166
Left ear	−2.123	−2.265	−7.417	−9.460	−9.011	−6.150	−5.477	−6.717

Table 2: Represents the *t*-test values of signal-to-noise ratio of distortion product otoacoustic emission in the right and left ear of experimental group

t-test values	1 kHz	2 kHz	3 kHz	4 kHz	5 kHz	6 kHz	8 kHz	10 kHz
Right ear	0.758	0.687	0.742	2.307	1.213	3.808	6.343	3.662
Left ear	−0.987	−0.828	−4.085	−0.836	1.913	7.210	4.571	3.470

Table 3: Represents the absolute latencies of peaks I, III, and V in both right and left ear among both the groups

ABR	Right ear			Left ear		
	Wave I	Wave III	Wave V	Wave I	Wave III	Wave V
Infants with hyperbilirubinemia	2.55 (0.23)	4.85 (0.38)	6.95 (0.55)	2.67 (0.2)	4.65 (0.43)	7.07 (0.66)
Control group	1.89 (0.18)	3.99 (0.59)	6.34 (0.35)	1.9 (0.26)	4.01 (0.31)	6.29 (0.44)

ABR: Auditory brainstem response

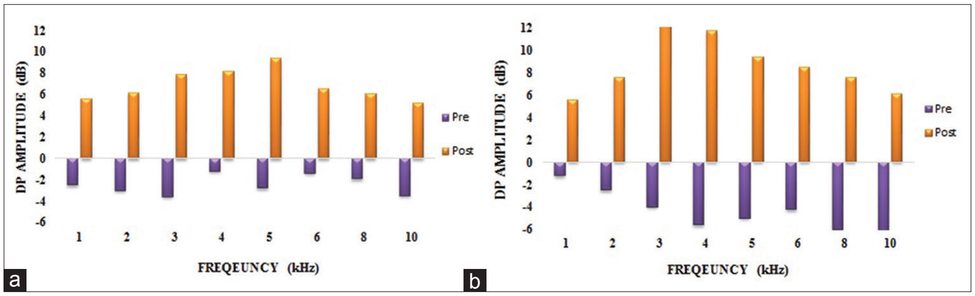

Figure 2: Representing the comparison of distortion product amplitude of pre and postphototherapy of infants with hyperbilirubinemia. (a) Right ear and (b) left ear

found to be normal and ABR measures are altered, provides an evidence that OAE alone is not a sufficient tool to assess the cochlear function.[2] Furthermore, it is difficult to diagnose AN as many of the studies report that neonates with auditory maturation delay also have absent ABR peak latencies. Hence, it becomes crucial to separate the overlapping features in AN/auditory dyssynchrony (AD) and auditory maturation delay at such an early period of life.

Conclusion

The present study highlights on the fact that, in spite of large developments in medicine in recent years, hyperbilirubinemia and its effects on sensory and motor systems are still an important problem. The present study aimed to determine the effects of phototherapy on OHC function of cochlea. Twenty-two neonates undergoing phototherapy and 22 neonates without any HRRs were tested for DPOAE and ABR. Results showed that DP amplitude and SNR were significantly better postphototherapy when compared for prephototherapy measures. ABR evaluation revealed that 19 neonates had significantly prolonged wave V latency compared to normal, whereas no peaks were identified among three neonates. The results of the present study indicate that phototherapy and hyperbilirubinemia have temporary effects on OHC function. Follow-up testing over a period of time with test battery approach rather than a single test can help in discriminating the neonates with sensory pathology or AN / AD as the incidence of AN/AD in hyperbilirubinemia is high.

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Conflicts of interest

There are no conflicts of interest.

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