ORIGINAL RESEARCH

BRAINSTEM EVOKED RESPONSE AUDIOMETRY AND RISK FACTORS IN PREMATURE INFANTS

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ABSTRACT

Objective: In this study; we evaluated the effects of possible risk factors according to the Joint Committee on Infant Hearing in preterm infants and physiologic anemia of prematurity on brainstem auditory evoked response (BAER) measurement variables.

Methods: For this aim, twenty-nine term newborn infants underwent the BAER recording session between 48 hours to 7 days of age. In 29 preterm infants, BAER was performed at a mean postconceptional (gestational age + age after birth) age of 39.4 ± 0.8 weeks (38-42 weeks). Type of delivery, birth weight <1500 g, hyperbilirubinemia exceeding phototherapy limits, aminoglycoside therapy, respiratory distress syndrome, low Apgar scores, and physiologic anemia of prematurity were evaluated. I,III,V peak latencies and I-III, III-V, I-V interpeak latencies were measured and analyzed.

Results: There were no significant differences for latencies and interpeak latencies between term and preterm groups at the same postconceptional age. We found that type of delivery (caesarean section), birth weight <1500 g, hyperbilirubinemia exceeding phototherapy limits, and low Apgar scores affected some of the BAER parameters ($p<0.05$). However, we did not find any effect of aminoglycoside (amicasin and/or netilmicin) therapy, respiratory distress syndrome on BAER measurement variables. Although the mean latencies and interpeak latencies in anemic preterm group were higher than non-anemic preterm group, statistically significant difference was not found ($p>0.05$).

Conclusion: We suggest that the effect of anemia of prematurity on BAER parameters should be studied in a larger group of infants.

Key words: Brainstem auditory evoked response (BAER), Preterm infant, Anemia of prematurity, Risk factor

PRETERM BEBEKLERDE RİSK FAKTÖRLERİ VE İŞİTSEL BEYİN SAPI CEVABI

ÖZET

Amaç: Bu çalışmada preterm bebeklerde "Joint Committee on Infant Hearing"e göre olası risk faktörlerinin ve preterm anemisinin işitsel beyin sapı cevabı (BAER) üzerine etkisi incelenmiştir.

Yöntem: Bu amaçla, 29 term bebekten doğumdan sonraki 48.saat ve 7.günler arası BAER kaydı alındı. Yirmidokuz preterm bebeğe ise BAER, postkonsepsiyonel yaşları (gebelik haftası+doğum sonrası yaşı) 39.4±0.8 hafta (38-42) olunca uygulandı. Doğum şekli, 1500 g'ın altında doğum ağırlığı, fototerapi sınırlarını aşan hiperbilirubinemi, aminoglikozid tedavisi, respiratuar distres sendromu, düşük Apgar skoru ve prematüre anemisi risk faktörü olarak değerlendirmeye alındı. I,III,V latens ve I-III, III-V, I-V interpik latensleri analiz edildi.

Bulgular: Term ve preterm bebeklerde aynı postkonsepsiyonel yaşta BAER parametreleri karşılaştırıldığında (latens ve interpik latensları) istatistiksel bir fark saptanmadı. Doğum şekli, <1500 g'ın altında doğum ağırlığı, fototerapi gerektiren hiperbilirubinemi ve düşük Apgar skorunun bazı BAER parametrelerini etkilediği görüldü ($p<0.05$). Aminoglikozid tedavisi (amikasin ve/veya netilmisin) ve respiratuar distres sendromunun BAER paremetrelerini etkilemediği saptandı. Latens ve interpik latens ortalamaları preterm anemisi olan grupta anemik olmayan preterm gruba göre daha yüksek olsa da istatistiksel anlamlılık taşımıyordu ($p>0.05$).

Sonuç: Prematüre anemisi olan bebeklerde BAER parametrelerinin daha büyük bir grupta çalışılmasının uygun olacağını düşünüyoruz.

Anahtar kelimeler: İşitsel beyin sapı cevabı, BAER, Preterm , Prematüre anemisi, Risk faktörleri

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Marmara Medical Journal 2007;20(1);21-28

INTRODUCTION

Sensorineural hearing loss represents a serious neurodevelopmental sequela among high-risk neonates. In the literature, its incidence varies widely from 1.5 to 17 % [1]. Between 1987 and 1991, 8 children among 547 infants of 34 weeks gestation or less developed progressive bilateral hearing loss requiring auditory aids. This corresponded to an incidence of 1.46 % [1]. Early hearing-loss detection in at-risk neonates is vital. Brainstem auditory evoked response (BAER) is commonly used as an objective, non-invasive tool in the detection of neonatal deafness and the evaluation of the auditory pathway's maturation [2,3].

The risk factors according to the Joint Committee on Infant Hearing are family history, in utero infections, craniofacial anomalies, birth weight <1500 g, hyperbilirubinemia at serum levels requiring exchange transfusion, ototoxic medications, bacterial meningitis, postnasal asphyxia, mechanical ventilation lasting 5 days or longer, stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductional hearing loss [4-6]. However, the significance of various aetiological factors in the pathogenesis of sensorineural hearing loss is not fully understood and controversy remains regarding their respective roles. In addition; the influences of "physiologic anemia of prematurity" on sensory brain function have not been studied before.

The purpose of the study was to identify the effects of possible risk factors according to the Joint Committee on Infant Hearing in preterm infants and physiologic anemia of prematurity on BAER recordings.

PATIENTS AND METHODS

BAER recording has been carried out in a group of 29 preterm and 29 term newborn infants at Pamukkale University Hospital. Informed consent was obtained from parents of the patients in the study, and the study was approved by the local ethics committee.

Group I: The control group which consisted of 29 normal term neonates who did not suffer from any of the risk factors listed below in the perinatal period.

*Group II:*The study group which consisted of 29 preterm neonates admitted to the neonatal intensive care unit and having one or more of the perinatal complications or risk factors according to the Joint Committee on Infant Hearing listed below.

Criteria for Selection of Newborns for Control Group

1. Term babies with birth weight >2500 g. All of the babies were appropriate for gestational age according to the Dubowitz score [7].
2. Normal perinatal period.
3. Absence of family history of deafness.
4. Serum bilirubin levels less than phototheraphy limits.
5. Absence of history of birth trauma and anoxia, and no findings of any infection or metabolic disorders.

Criteria for Selection of Newborns for Study Group

1. Gestational age < 37 weeks. All of the babies were appropriate for gestational age according to the Dubowitz score [7].
2. Birth weight <1500 g (n:11).
3. Apgar scores ≤5 at 1 and/or ≤6 at 5 min (n:8). Postnatal asphyxia was diagnosed if the Apgar score ≤5 at 1 and/or ≤6 at 5 min [8].
4. Hypoxic-ischemic encephalopathy (n:1).
5. Grade I (n:1), or grade II (n:1) intracranial hemorrhage.
6. Hyperbilirubinemia at a serum level requiring phototherapy (n:12). No infant required exchange transfusion for hyperbilirubinemia. Newborns with hyperbilirubinemia were started on phototherapy according to the guidelines of the American Academy of Pediatrics [9].
7. Respiratory distress syndrome (n:6), surfactant therapy (n:5).
8. Requiring artificial ventilation lasting 5 d or longer (5-14 days) (n:7).

9. Aminoglycoside (amicasin and/or netilmicin) (n:10) or furosemide (n:4) administration.
10. Bacterial meningitis (n:2) or sepsis (n:2).

Fifteen infants whose hemoglobin concentrations were below 10.0 g/dl were accepted as anemic preterm infants (group I) [10]. The preterm infants' hemoglobin concentrations in group II were above 10.0 g/dl.

All of the babies were stable enough for the baby to be taken to the BAER room and be subjected to the test. Term newborn infants underwent the BAER recording session between 48 hours to 7 days of age. In the preterm newborns group, BAER was performed at a mean postconceptional (gestational age + age after birth) age of 39.4 ± 0.8 weeks (38-42 weeks). The person performing the BAER test had no knowledge of the condition of the infant. BAERs were measured with Medelec Premiere Plus (U.K) equipment. Taking into consideration the factor of acoustic interference, the room was made sound proof. Care was also taken to eliminate any source of electrical interference. The click stimulations used in the BAER test were 70 and 90 dB, and the stimulations were repeated 1024 times. Filter setting was between 500-2000 Hz. Generation of five electrical waves within the first 10 ms of click stimulation was obtained. The stimuli were delivered first to the right ear and then to the left ear. I,III,V peak latencies and I-III, III-V, I-V interpeak latencies were measured. The I,III,V peak latencies and I-III, III-V, I-V interpeak latencies obtained for the left and right ears were averaged to represent each case by one value in statistical analysis. In addition to the risk factors listed above, the effects of physiologic anemia of prematurity, type of delivery, head circumference, and body weight on I,III,V peak latencies and I-III, III-V, I-V interpeak latencies were evaluated.

Sedation was achieved by chloral hydrate syrup used in the dosage of 50 mg/kg body weight to sedate the neonates [8]. The effect was evident between 20-30 minutes of administration of the drug.

Hemoglobin, hematocrit, MCV, and RDW were detected using Cell-Dyn 3500 R (Abbott, San Francisco, USA). Serum iron measurement was performed with calorimetric assay by using Roche Modular PE autoanalyser (Roche Diagnostics, IN, USA), and serum ferritin level was determined by Chemyl-immunoassay Immulite One (Bio DPC, CA, USA).

Statistics

The mean and SD of each BAER variable at each stimulus condition were compared between groups using T test or Mann-Whitney U Test with Statistical Package for Social Sciences (SPSS 9.0 for windows). The correlation between BAER variables and head circumference, and hematologic parameters (iron, ferritin, hemoglobin) was also analyzed. Statistical significance was considered at $p<0.05$.

RESULTS

Clinical data of term and preterm babies are presented in Table I. There were no differences in terms of gender, type of delivery, postconceptional age at the time of BAER records between the two groups ($p>0.05$). The head circumference and weight at the time of BAER testing were also not different between two groups ($p>0.05$). Apgar scores were lower in the preterm group ($p<0.05$).

There were no significant differences for latencies and interpeak latencies between term and preterm babies at the same postconceptional age ($p>0.05$) (Table II). Besides, no correlation was found between BAER parameters and head circumference and body weight at the time of BAER testing in preterm infants (r values for head circumference at I,III,V peak latencies and I-III, III-V, I-V interpeak latencies –0.18, -0.22, -0.12, -0.21, 0.14, -0.04 respectively and for body weight –0.25, -0,24, -0.31, -0.13, 0.06, 0.16 respectively.)

On the basis of preterm babies' hemoglobin content, preterm infants were divided into anemic group (group I, n=15, Hb<10 g/dl) and control group (group II, n=14, Hb>10 g/dl) [10]. The hematologic data ,s shown in Table III.

The peak latencies and interpeak latencies in anemic preterm group were higher than non-anemic preterm group. However; when the preterm infants with anemia of prematurity compared with nonanemic preterm infants in terms of BAER parameters, no significant difference was found (p>0.05) (Table IV). There was no correlation between BAER parameters and hematologic parameters (iron, ferritin, hemoglobin). (r values for iron at I,III,V peak latencies and I-III, III-V, I-V interpeak latencies –0.13, -0.06, 0,11, -0.01, -0.17, 0.16 respectively, for ferritin –0.12, 0,06, 0.24, 0.01, 0.22, 0.2 respectively, for hemoglobin –0.12, -0,17, 0.32, 0.3, 0.09, 0.37 respectively).

The gestational age and birth weight were lower in anemic preterm group (p<0.05), but the weight and the head circumference at the time of BAER recording, type of delivery, Apgar scores, and the number of hyperbilirubinemia cases exceeding phototherapy limits were not statistically different between two groups (Table III).

We did not find any effect of aminoglycoside (amicasin and/or netilmicin) therapy, respiratory distress syndrome, and gender type (male or female) on BAER parameters in preterm infants. But, we found that type of delivery (caesarean section), birth weight <1500g, hyperbilirubinemia exceeding phototherapy limits, and low Apgar scores affected some of the BAER parameters (Table IV). By comparison, the preterm babies with spontaneous delivery had a significant decrease in wave V peak latencies at 70 dB, and in wave III and V peak latencies at 90 dB. In addition, the preterm babies with birth weight <1500g had a significant increase in wave V peak latencies at 70 dB, and wave III peak latencies at 90 dB. Prolonged III-V and I-V interwave interval at 70 dB and prolonged I-V interwave interval at 90 dB was found in hyperbilirubinemia subgroup in preterm babies. Low Apgar score caused an increase in I-V interpeak latencies at 90 dB in preterm babies.

Table I. The clinical data of term and preterm babies (mean± SD).

	Group I (term) (n:29)	**Group II (preterm) (n:29)**
Sex (male/female)	19/10	18/11
Gestational age (week)	38.8 ± 0.7*	32.6 ±3.3*
Caesarean/spontaneous birth	20/9	18/11
Birth weight (g)	3387 ± 374*	1942 ± 661*
Weight (g) at the time of BERA recording	3372 ± 398	3132 ± 807
Head circumference (cm)) at the time of BERA recording	34.8± 0.7	34.8± 1.7
Apgar score at 1 min (min-max)	8.9± 0.7* (5-9)	6.6 ±3.1* (1-9)
Apgar score at 5 min (min-max)	9.9± 0.4* (8-10)	8.4 ±1.8* (4-10)

Table II. BAER parameters of preterm and term babies (mean± SD).

Parameter	Term (n:29)		Preterm(n:29)	
Peak latencies (ms)	**70 dB**	**90dB**	**70dB**	**90 dB**
I	1.96±0.63		1.94±0.53	
III	1.92±0.54		1.93±0.32	
V	4.52±0.54		4.45±0.63	
	4.40±0.67		4.46±0.76	
	7.22±0.76		7.12±0.35	
	7.10±0.77		7.05±0.40	
Interpeak latencies	**70 dB**	**90dB**	**70 dB**	**90 dB**
(ms)	2.45±0.53		2.52±0.58	
I-III	2.41±0.60		2.44±0.50	
III-V	2.52±0.43		2.72±0.41	
I-V	2.49±0.44		2.70±0.42	
	4.92±0.67		5.24±0.64	
	4.87±0.76		5.17±0.65	

Table III. The clinical and hematologic data of anemic preterm and non-anemic preterm babies (mean± SD).

	Group 1 (n:15) (anemic preterm)	**Group 2 (n:14) (non-anemic preterm)**
Sex (male/female)	11/4	7/7
Gestational age (week)	30.4 ±2.5*	35 ± 2.1*
Caesarean/spontaneous birth	8/7	10/4
Birth weight (g)	1594 ± 466*	2315 ± 645*
Weight (g) at the time of BERA recording	3287 ± 898	2966 ± 690
Head circumference (cm)) at the time of BERA recording	35.1± 1.6	34± 1.9
Low Apgar score (n)	4	4
Phototherapy (n)	7	5
Iron (µg/dl)	74 ±21	89 ±22
Iron binding capacity (µg/dl)	239± 59	234± 55
Ferritin (ng/ml)	137± 121	189± 119
Hb (g/dl)	8.9 ±0.6*	13.5± 1.8*
Htc (%)	26± 2.2*	38.3± 4.7*
MCV (fL)	91± 4*	98± 5*
RDW	16± 2	16± 2

Table IV. The effect of risk factors on BAER parameters in preterm babies (mean± SD)

Risk factors (n)	Peak latencies (ms) I	III	V	Interpeak latencies (ms) I-III	III-V	I-V
Anemic Preterm infants (15)						
70 dB	2.29±0.65	4.75±0.55	7.45±0.55	2.99±0.66	2.86±0.57	5.35±0.49
90 dB	1.98±0.61	4.72±0.67	7.39±0.45	2.79±0.51	2.73±0.45	5.43±0.73
Nonanemic preterm infants (14)						
70 dB	2.18±0.51	4.73±0.66	7.39±0.43	2.39±0.45	2.73±0.46	4.92±0.45
90 dB	1.92±0.30	4.26±0.84	6.88±0.73	2.36±0.70	2.63±0.70	4.87±0.80
Caesarean section (18)						
70 dB	2.09±0.51	4.79±0.66	7.39±0.45*	2.89±0.61	2.73±0.62	5.45±0.44
90 dB	2.00±0.31	4.72±0.67*	7.33±0.40*	2.73±0.50	2.61±0.43	5.39±0.49
Spontaneous delivery (11)						
70 dB	1.89±0.54	4.42±0.67	6.75±0.45*	2.19±0.76	2.73±0.63	4.99±0.86
90 dB	1.80±0.33	4.24±0.79*	6.73±0.83*	2.16±0.75	2.80±0.72	4.90±0.95
Birth weight						
<1500 g (11)						
70 dB	2.15±0.52	4.85±0.77	7.41±0.32*	2.87±0.55	2.73±0.67	5.39±0.34
90 dB	2.05±0.34	4.83±0.74*	7.39±0.55	2.74±0.51	2.69±0.52	5.34±0.63
>1500 g (15)						
70 dB	1.98±0.31	4.23±0.75	6.99±0.55*	2.34±0.57	2.73±0.65	5.39±0.49
90 dB	1.94±0.43	4.18±0.86*	6.85±0.76	2.26±0.67	2.68±0.55	5.19±0.79
Phototherapy (12)						
70 dB	1.98±0.33	4.53±0.51	7.39±0.32	2.69±0.31	2.97±0.67*	5.59±0.55*
90 dB	1.94±0.44	4.51±0.77	7.35±0.82	2.54±0.57	2.83±0.44	5.50±0.53*
Control (17)						
70 dB	2.09±0.51	4.53±064	7.09±0.44	2.39±0.36	2.63±0.77*	4.99±0.35*
90 dB	2.01±0.29	4.47±0.81	6.96±0.88	2.34±0.67	2.60±0.48	4.90±0.56*
Low Apgar score (8)						
70 dB	2.15±0.33	4.73±0.67	7.39±0.56	2.79±0.37	2.78±0.60	5.59±0.35
90 dB	1.93±0.37	4.53±0.89	7.31±0.40	2.74±0.44	2.76±0.56	5.54±0.33*
Control (21)						
70 dB	1.99±0.60	4.67±0.72	7.35±0.75	2.69±0.71	2.63±0.57	5.29±0.55
90 dB	1.93±0.36	4.62±0.85	7.30±0.47	2.64±0.60	2.57±0.53	5.16±0.66*

p<0.05

DISCUSSION

The purpose of the study was to determine the presence or absence of the abnormalities of BAER responses in preterm babies with several risk factors.

On the basis of several studies it appears that waves I, III, and V primarily represent volume-conducted electrical activity from the acoustic nerve, superior olivary and inferior olivary nuclei. The interpeak latencies between the waves indirectly reflect neural conduction in the corresponding segments of the central auditory pathway.

We did not find any difference in terms of BAER parameters between preterm and term babies at the same postconceptional age (gestational age + age after birth). It is suggested that all of the risk factors which bring the neonate under intensive care induce a certain amount of hypoxia of the cochlea and brainstem, which leads to various cellular changes such as edema, degeneration and necrosis. Hence, they predispose to hearing impairment, which may be reversible following reversal of the hypoxic changes.

It was showed that a reduction in head size implies shortening of intracerebral distances

and thus shortening of transmission distances along the auditory pathways. The reduction in distance led to a reduction in the latencies for wave III and V [11]. In our study; the head circumference at the time of BAER testing was not different between the two groups. No correlation was found between head circumference and BAER parameters.

Hyperbilirubinemia at level exceeding indication for exchange transfusion was a risk factor according to the Joint Committee on Infant Hearing [4-6]. Tan et al [12] demonstrated that the latencies of peak V and interpeaks I-V and III-V in the brainstem auditory evoked response of infants with hyperbilirubinemia before phototherapy were significantly greater than those in a control group of infants. These values of the brainstem auditory-evoked response improved significantly during phototherapy and correlated significantly with declining bilirubin levels. Improvement continued after phototherapy**.** In the present study; prolonged III-V and I-V interwave interval at 70 dB and prolonged I-V interwave interval at 90 dB was found in hyperbilirubinemia subgroup in preterm babies. All the infants' serum bilirubin concentrations were in normal limits at the time of BAER recording.

Although Gupta et al. [13] did not find any correlation between aminoglycoside administration and hearing impairment, in Borradori et al's [1] study; ototoxicity appeared closely related to a prolonged administration and higher total dose of ototoxic drugs, particularly aminoglycosides (gentamicin or tobramycin) and furosemide. We did not find any effect of aminoglycoside (amicasin and/or netilmicin) therapy on BERA parameters in preterm infants. However, we could not measure plasma aminoglycoside levels.

In Gupta et al.'s [13] study; birth weight <1500 g was significantly correlated with the hearing impairment but birth asphyxia had no significant correlation with hearing impairment. In our study; birth weight< 1500 g and hyperbilirubinemia exceeding phototherapy limits caused increased interpeak latencies. However; we found that low Apgar scores also caused increased interpeak latencies. In Samani et al.'s [2] study; the spontaneous delivery subgroup in preterm babies showed higher latencies than the caesarean section subgroup. In contrast; in our study caesarean section caused increased interpeak latencies. Our hospital is a third grade referral center so high risk infants are admitted to our hospital. They usually need more caesarean section.

In this study we did not detect any effect of respiratory distress syndrome and mechanical ventilation on BERA parameters.

Jiang et al.[14] reported that the preterm babies with perinatal complications had a significant increase in wave V latency, I-V and III-V intervals, and III-V/I-III interval ratio. In BAER, I-III and III-V interval, generally reflect functional integrity of the peripheral and central parts of the auditory brainstem, respectively [14]. In our study, the affected variables by several risk factors are wave III and V peak latencies, and I-V interpeak latencies, reflecting central parts of auditory brainstem.

Iron is an important nutrient and essential element involved in myelin formation and neurotransmitter synthesis and thus contributes to normal neurological activity. In iron deficient children; a trend of increased absolute and interpeak latencies suggests a subclinical involvement of the auditory pathway in the brainstem (15,16). Contrary to these studies Sarici et al [17] could not demonstrate hearing loss in infants with moderate-to-severe iron deficiency anemia.

The diminution of erythropoiesis in anemia of prematurity is probably due to decreased erythropoietin production [10]. In our study; the plasma iron and ferritin levels were normal in preterm babies. Although the mean latencies and interpeak latencies in anemic preterm group were higher than non-anemic preterm group, it was not statistically significant. To identify accurately the risk factors, a substantial number of subjects are needed so that each risk factor has a sufficient number of subjects for statistical analysis. We suggest that the effect of anemia of prematurity on

BAER parameters should be studied in a larger group of infants.

Since most of the survivors in the neonatal intensive care units have one or more identified risk factors, their BAER testing is justified for early detection of hearing impairment. We believe that a follow up by means of the study of BAER potentials in newborn infants at risk may offer valuable information on the state of maturation of the acoustic pathways achieved by these children.

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