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Original Research Article

A study of effect of aminoglycoside therapy on auditory brainstem evoked responses in preterm and term neonates

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ABSTRACT

Background: Aminoglycosides are widely used drugs in neonates with associated ototoxic side effects, that can be diagnosed with auditory brainstem evoked responses, which is the recommended screening technique in neonatal intensive care unit infants. This study was conducted to evaluate the effect of aminoglycoside therapy on auditory brainstem evoked responses in term and preterm neonates.
Methods: A cross-sectional case control study. Two groups of 26 term and 22 preterm neonates who received aminoglycosides, with no other known risk factors for ototoxicity, were compared with suitable matched control group of 10 neonates in each. ABER was done after at least 5 days of aminoglycoside therapy and results were compared to suitable matched controls.
Results: Mean latency of wave I in term neonates at 90 dB and 60 dB and mean interwave latencies of I-V waves in preterm neonates at 30 dB was higher in study group and statistically significant. No statistically significant difference in any of ABER parameters was observed in any group, at all other intensities.
Conclusions: Wave I latency was prolonged in study group of term neonates at two intensities which indicates effect of aminoglycoside therapy on distal portion of acoustic nerve. But as there were no such findings at other intensities in term study group and in preterm study group and moreover no other ABER abnormalities were observed, it was concluded that the aminoglycoside therapy has low potential for ototoxicity. Authors support the ABER screening for early detection of hearing abnormalities, and recommend study on larger group of neonates and meta-analysis for final conclusion for evidence-based recommendations to use aminoglycosides in neonates, in view of audiometric and neurological abnormalities.

Keywords: Aminoglycosides, Auditory brainstem evoked responses, Hearing screening, Neonates, Ototoxicity

INTRODUCTION

Sensorineural hearing impairment is a serious neurodevelopmental sequela among high-risk neonates with incidence rate varying from 1.6%-46.67%, that can result in poor speech and language acquisition and poor social-emotional development.[1-3] Its incidence rate is much higher than other conditions screened at birth and can be intervened.[4] Aminoglycosides are widely used drugs in neonatal intensive care units and considered safe in therapeutic dosage. Ototoxic effects are usually observed when used in high doses or for longer duration, in underlying disease states, and when used with other ototoxic drugs. But as neonates being highly vulnerable, side effects are noted even in usual dosage within therapeutic concentration level. Ototoxicity is mediated by disruption of mitochondrial protein synthesis and free oxygen radicals mediated irreversible destruction of outer hair cells in the organ of Corti, predominantly at the basal turn of cochlea. Hearing loss usually begins in the high frequencies and progresses to lower frequencies.[5-7] Aminoglycosides exposure is one of the risk indicators

listed by The Joint Committee on Infant Hearing (JCIH) or hearing screening.[8]

JCIH recommended either otoacoustic emissions (OAE) testing or auditory brainstem evoked responses (ABER) techniques, ideal for newborn hearing screening, as both are noninvasive methods of recording physiologic activity that does not require a behavioral response. OAEs reflect the status of the peripheral auditory system only extending to the cochlear outer hair cells. ABER records neural activity generated in the cochlea, auditory nerve, and brainstem in form of seven positive waves, following an acoustic stimulus. ABER determines hearing threshold, degree and type of hearing loss, and results are not affected by the anesthetics or sedatives, which may be used during the test. JCIH recommends only ABER as appropriate screening technique in NICU infants.[8-11]

Many researchers worked in past on aminoglycosides associated ototoxicity and its effect on the ABER and reported contradictory results. The present study was therefore planned to resolve the queries and controversies associated with the effect of aminoglycosides on ABER in term and preterm neonates.

METHODS

This cross-sectional, case control study was conducted in a tertiary care centre from August 2010 to January 2011.

Inclusion criteria

- The study group consist of neonates, who have received aminoglycosides in recommended therapeutic dosage, at least twice a day for 5 days as either of gentamicin (5-7.5 mg/kg/day), amikacin (15 mg/kg/day) or tobramycin (5-7.5 mg/kg/day), for neonatal sepsis but otherwise having normal Apgar rating, normal renal function tests, and normal postnatal course with no clinical or laboratory evidence of severe infection with multiorgan involvement. Jaundice, when present was physiological with maximum values not in range of phototherapy or exchange transfusion. Two study groups were formed, first group of term neonates and the other one of preterm neonates. Control group was taken for each study group. Control group consist of healthy term and preterm newborn drawn at random with normal Apgar rating, normal antenatal, natal and postnatal course, with no evidence of infection, normal renal function and jaundice when present, is physiological and not requiring any interruption and not received any ototoxic medication. 48 neonates fulfilled the predefined inclusion criteria, of which two study groups were formed. First study group consist of 26 term neonates (Group A) with a control group of 10 term neonates (Group B). And other study group of 22 preterm neonates (Group C) with a respective control group of 10 preterm neonates (Group D).

Exclusion criteria

- Neonates with birth weight <1500 g (3.3 lb); birth asphyxia (Apgar scores of 0-4 at 1 min or 0-6 at 5 min); unstable general condition and critically ill requiring intensive care and/or inotropic support or mechanical ventilation; hyperbilirubinemia requiring exchange transfusion or phototherapy; ototoxic medications other than aminoglycosides used in study, used in multiple courses or in combination with loop diuretics; bacterial meningitis; in utero infection (such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis); family history of hereditary childhood sensorineural hearing loss; craniofacial anomalies, including those with morphologic abnormalities of the pinna and ear canal; stigmata or other finding associated with a syndrome known to include a sensorineural and/or conductive hearing loss, were excluded from the study.

ABER study was carried out in a quiet and sound treated room, free from electromagnetic disturbances after written informed consent obtained from the parents and a detailed history and thorough ENT examination was done. Neonates were either in natural sleep or sedated with triclofos in a single dose of 20 mg/kg orally.

The machine used was Nicolet compass meridian biomedical USA, with the electrodes mounted on TDH-39P headphone. After skin preparation, conductive gel was applied on the concave side of silver chloride coated cup shaped silver electrodes, and placed on both mastoid process and ground electrode at high forehead in midline. Facility of automatic artefact rejection was used and the recording was manually stopped if there is eye blink, swallowing or movement. Smoothening of the trace was done prior to measurements.

The sweep velocity was kept at 10 m/s. Click acoustic stimuli with a click rate of 11/second alternating in polarity was presented by a headphone to each ear alternately at an intensity of 90 dB hearing level. Non stimulated ear was masked with sound of 40 dB. A two-channel recording was done after stimulation of each ear. The electrical activity was filtered and averaged to 2000 responses.

Thereafter both ears were tested separately with rarefaction clicks of 0.1 m/sec duration administrated at the rate of 50 per second. 2000 responses were averaged and minimum of two tests were performed for reproducibility. Initially 90 dB nHL was administrated, and subsequently recording made on 75, 60, 45 and 30 dB. 30 dB intensity was taken to determine the normal threshold of wave V.

The records were analysed in terms of auditory threshold, peak latency of wave I, III and V (measured from the time of click stimulus to the peak of particular wave), I-III, III-V and I-V interpeak latency/inter-wave interval (time interval between the peaks of respective waves). I-V interpeak latency denoted the conduction time from peripheral nerve (wave I) to successive central relay station, most commonly inferior follicular region (wave V)). I-III interpeak latency represents conduction in lower brainstem. III-V interpeak latency denotes conduction in the upper brainstem. The values of the parameters under study were said to be abnormal when they exceeded 3SD above mean value in the control group. An infant was considered to have passed the test if wave V was present at 30 dB nHL in both ear or in one ear at 30 dB and the others 45 dB. Many waves were not identifiable at lower intensities, across all groups, and thus, absent waves were not included into final statistical analysis.

Statistical analysis

The statistical analysis was performed by using student's "t" tests and chi square test to find out the significance of difference in mean between two variables. In this study, p value <0.05 was considered as significant with either negative or positive correlation on account of biological variability. Correlation coefficient was evaluated using the r^2 value to determine a linear relationship between the parameters concerned.

RESULTS

In the present study, male-female ratio in study group of term neonates and their control group was 2.25:1 and 2.33:1, while in preterm study group and their control group was 2.14:1 and 2.33:1, respectively. Mean birth weight of study group of term neonates was 2.93±0.21 kg (range of 2.6-3 kg) and preterm neonates was 1.98±0.30 kg (range of 1.6-2.6 kg) compared to 3.12±0.29 kg (range of 2.7-3.6 kg) and 1.95±0.27 kg (range of 1.6-2.5 kg) in respective control groups.

Mean gestational age in the study group of term neonates was 39.30±1.25 (range of 38-42 weeks) and preterm neonates was 34.4±1.29 weeks (range of 32-36 weeks), compared to 40±1.55 weeks (range of 38-42 weeks) and 34.6±1.36 weeks (range of 32-36 weeks) in control group of term and preterm neonates, respectively. Mean postnatal age at the time of ABER in the study group of term neonates was 8.5 days (ranging 6-21 days) and preterm neonates was 11.7 days (ranging 5-30 days) compared to 12.2 days (ranging 5-25 days) and 9.1 days (ranging 5-17 days) in respective control groups. There was no significant difference in the sex distribution, mean birth weight, gestational age and postnatal age in both the study groups when compared to their respective control groups.

Table 1: Wave I, III and V latencies in study and control groups of term neonates.

Intensity	Group A (term study group) peak latencies wave I		Group B (term control group) peak latencies wave I		Group A (term study group) peak latencies wave III		Group B (term control group) peak latencies wave III		Group A (term study group) peak latencies wave V		Group B (term control group) peak latencies wave V	
	n	Latencies (ms)	n	Latencies (ms)	n	Latencies (ms)	n	Latencies (ms)	n	Latencies (ms)	n	Latencies (ms)
90 dB	52	1.88±0.29*	20	1.71±0.17*	52	4.34±0.52	20	4.27±0.60	52	6.50±0.61	20	6.40±0.69
75 dB	52	2.27±0.29	20	2.13±0.28	52	4.82±0.58	20	4.66±0.77	52	7.00±0.67	20	6.98±0.73
60 dB	52	2.86±0.45#	20	2.64±0.30#	52	5.43±0.50	20	5.28±0.67	52	7.52±0.58	20	7.47±0.69
45 dB	51	3.40±0.39	20	3.34±0.37	51	5.93±0.47	20	5.93±0.65	51	8.14±0.58	20	8.13±0.75
30 dB	32	4.01±0.48	10	3.64±0.54	32	6.68±0.45	10	6.38±0.40	32	8.79±0.35	10	8.32±0.52

*p value <0.01, #p value <0.05.

Table 2: I-III, III-V and I-V interpeak latencies in study and control groups of term neonates.

Intensity	Group C (preterm study group) peak latencies wave I		Group D (preterm control group) peak latencies wave I		Group C (preterm study group) peak latencies wave III		Group D (preterm control group) peak latencies wave III		Group C (preterm study group) peak latencies wave V		Group D (preterm control group) peak latencies wave V	
	n	Latencies (ms)	n	Latencies (ms)	n	Latencies (ms)	n	Latencies (ms)	n	Latencies (ms)	n	Latencies (ms)
90 dB	52	2.46±0.51	20	2.86±0.61	52	2.16±0.41	20	2.14±0.45	52	4.61±0.62	20	4.70±0.71
75 dB	52	2.50±0.60	20	2.53±0.69	52	2.18±0.50	20	2.32±0.54	52	4.73±0.68	20	4.85±0.62
60 dB	52	2.57±0.54	20	2.64±0.58	52	2.09±0.49	20	2.18±0.50	52	4.66±0.67	20	4.82±0.62
45 dB	51	2.51±0.57	20	2.59±0.60	51	2.22±0.43	20	2.20±0.52	51	4.73±0.71	20	4.79±0.79
30 dB	32	2.67±0.56	10	2.73±0.40	32	2.10±0.41	10	1.90±0.50	32	4.78±0.40	10	4.67±0.60

Table 3: Wave I, III and V latencies in study and control groups of preterm neonates.

Intensity	Group C (preterm study group) peak latencies wave I		Group D (preterm control group) peak latencies wave I		Group C (preterm study group) peak latencies wave III		Group D (preterm control group) peak latencies wave III		Group C (preterm study group) peak latencies wave V		Group D (preterm control group) peak latencies wave V	
	n	Latencies (ms)	n	Latencies (ms)	n	Latencies (ms)	n	Latencies (ms)	n	Latencies (ms)	n	Latencies (ms)
90 dB	44	2.05±0.40	20	1.98±0.37	44	4.29±0.65	20	4.34±0.58	44	6.53±0.72	20	6.58±0.58
75 dB	44	2.53±0.54	20	2.41±0.40	44	4.71±0.74	20	4.79±0.52	44	6.88±0.62	20	7.10±0.81
60 dB	42	2.87±0.53	20	2.89±0.42	42	5.27±0.61	20	5.34±0.58	42	7.40±0.62	20	7.50±0.70
45 dB	39	3.46±0.44	20	3.56±0.62	39	5.78±0.56	20	5.96±0.66	39	7.95±0.54	20	8.08±0.62
30 dB	26	4.27±0.57	11	3.77±0.75	26	6.54±0.59	11	6.57±0.49	26	8.43±0.59	11	8.61±0.45

Table 4: I-III, III-V and I-V interpeak latencies in study and control groups of preterm neonates.

Intensity	Group C (preterm study group) mean inter peak latencies I-III		Group D (preterm control group) mean inter peak latencies I-III		Group C (preterm study group) mean inter peak latencies III-V		Group D (preterm control group) mean inter peak latencies III-V		Group C (preterm study group) mean inter peak latencies I-V		Group D (preterm control group) mean inter peak latencies I-V	
	n	IPL (ms)	n	IPL (ms)	n	IPL (ms)	n	IPL (ms)	n	IPL (ms)	n	IPL (ms)
90 dB	44	2.23±0.62	20	2.35±0.63	44	2.24±0.51	20	2.23±0.44	44	4.47±0.79	20	4.59±0.59
75 dB	44	2.20±0.62	20	2.39±0.47	44	2.13±0.40	20	2.30±0.52	44	4.37±0.64	20	4.69±0.72
60 dB	42	2.39±0.57	20	2.45±0.60	42	2.13±0.50	20	2.16±0.46	42	4.53±0.62	20	4.61±0.69
45 dB	39	2.31±0.51	20	2.38±0.61	39	2.16±0.50	20	2.12±0.41	39	4.48±0.47	20	4.51±0.72
30 dB	26	2.30±0.49	11	2.80±0.83	26	1.88±0.50	11	2.04±0.22	26	4.15±0.55*	11	4.84±0.86*

*p value <0.02.

In study group of term neonates, out of total 26 cases, 16 (61.5%) received amikacin (15 cases for >5 days but ≤7 days and 2 cases for >7 days), 8(30.7 %) received gentamicin (all for > 5 days but ≤7 days), and 1(3.8%) received tobramycin for 5 days. The mean duration of therapy was 6.11 days in the Group A of term neonates study group. In preterm neonate's study group, out of the total 22 cases, 15 (68.2%) received amikacin (10 cases for >5 days but ≤7 days and 5 cases for >7 days), 6 (27.3%) received gentamicin (all for >5 days but ≤7 days) and 1 (4.5%) received tobramycin for 5 days. The mean duration of therapy was 7.3 days.

Mean latency of wave I was higher in Group A (Term neonates study group) at all intensities than Group B (term neonates control group) but the difference was statistically significant only at 90 dB (p value <0.01) and 60 dB (p value <0.05). Similarly, the mean latency of wave III and V were also higher in Group A compared to control Group B at all intensities but the difference was not statistically significant (Table 1). There was no statistically significant difference between the mean interpeak latencies of I-III, III-V, and I-V waves in Group A and B at all observed intensities (Table 2).

Table 3 and Table 4 showed no statistically significant difference between the mean latency of wave I, III, V, and mean interpeak latencies of I-III, III-V, and I-V waves in Group C (preterm neonates study group) and D (preterm neonates control group) at all observed intensities, except mean interpeak latencies of I-V waves at 30 dB (p value <0.02). Many waves were unidentifiable or absent at lower intensities in all four groups.

No correlation was found between the latencies of wave I and V and I-V interpeak latencies with the duration of aminoglycosides in both the study groups (term and preterm neonates) in comparison to their respective control groups.

DISCUSSION

In this study, mean latency of wave I, III and V was higher in study group of Term neonates at all intensities compared to respective controls, but the difference was statistically significant only found in mean latency of wave I at 90 dB (p value <0.01) and 60 dB (p value <0.05). No similar observations were noted in preterm study group and difference between the mean latency of wave I, III, V were statistically insignificant. There was no statistically significant difference between the mean interpeak latencies of I-III, III-V, and I-V waves in both the study groups (term and preterm neonates) with respective controls except mean interpeak latencies of I-V waves in preterm study group at 30 dB (p value <0.02).

Bernard et al, studied the aminoglycoside effect on ABER on 15 neonates who received gentamicin or tobramycin at conventional dosage with control group of 14 neonates (gestational age ranging 29 to 42 weeks). With no significant difference on day 0, (8.51±0.99 ms in study group and 7.89±0.84 ms in controls group, p>0.10), there was a significant prolongation of wave V latency at 90 dB, on fifth (9.13±1.90 ms in study group while 7.75±1.11 ms in the control group, p < 0.01) and tenth day (8.73±1.47 ms in study group and 7.31±1.06 ms in control group, p <0.01) of aminoglycodise treatment.[12]

Kohelet et al, found significantly prolonged latencies of components III and V, interval I-III, and interval I-V with short course gentamicin therapy in term neonates (mean gestational age of 39.3±0.7 weeks and mean birth weight of 3.2±0.3 kg against a control group of mean gestational age of 40.1±1.1 weeks and mean birth weight of 3.5±0.6 kg). The mean III-V interpeak latency was also higher in the Gentamicin treated infant than control group in both ears but statistically significant difference was only in right ear.[13] Tsai CH et al, also observed prolongation of latencies of wave V, intervals I-V and III-V with short course therapy with gentamicin which reversed itself on the tenth day of life. Latency of interval III-V was related with peak and trough level concentration of gentamicin.[14] These findings indicated selective impairment of the central brainstem component of the auditory pathway, without involvement of the peripheral acoustic nerve, as wave I was not affected. This was in contrast to findings in this study.

It observed statistically significant prolongation of I-V IPL in premature infants who received aminoglycosides.[15]

While Finitzo-Hieber et al, McCracken, Adelmen et al, and Kilic et al, found no significant abnormality with aminoglycoside therapy in infants.[16-20] Nanavati et al, also found no impairment in ABER finding in otherwise healthy very low birth weight infants, receiving amikacin with serum concentration in therapeutic range for 7 days and 14 days.[21]

Chayasirisobhon et al, Hess et al, Maqbool et al, and Zamani et al, found no significant ABER abnormality or hearing impairment in neonates with no other risk factor, who received aminoglycosides in therapeutic dose. Hearing impairment was significantly associated when aminoglycoside use was accompanied by other risk factors for hearing impairment (meningitis, icterus, low birth weight, illness requiring NICU admission and mechanical ventilation, prenatal infections, severe perinatal and postnatal complications, craniofacial anomalies, other ototoxic medications, family history of hearing loss and genetic factors).[22-25]

Mitochondria mutations in the 12S rRNA gene are the molecular mechanism of genetic susceptibility to aminoglycoside ototoxicity. Among several mutations, most well studied and strongly associated are 1555A>G and 1494C>T. Predisposed high-risk populations may exist throughout the world. Aminoglycosides levels even within the therapeutic range can result in rapid, profound, and irreversible hearing loss, commonly bilateral and symmetric.[5-7,26]

Cox et al, performed ABER on 50 preterm VLBW infants with a mean gestational age of 29 weeks and had associated multiple risk factors and found that no single risk factor was predictive of ABER abnormality, while combined risk factors were shown to be very predictive.[27]

In this study, there was no correlation found between the wave I and wave V latency with the duration of the aminoglycoside therapy in either of the study group of term and preterm neonates. Similar findings were also observed by Nanavati et al.[21] Bernard et al, in his study mostly included preterm infants and reported a correlation between the initial and final value of wave V and the total dose of antibiotics administrated per kilogram of body weight. He also reported that in the group receiving aminoglycosides, latencies did not decrease normally with time.[12]

Adelman et al, and Nanavati et al, monitored the serum concentration of aminoglycosides in recommended therapeutic range but due to technical limitations, the current study could not monitor the blood aminoglycoside concentration level.[19,21] Authors use multiple daily dose regime in this study. Studies had shown no significant difference between once or multiple daily dose regime in the primary ototoxicity outcomes.[28,29]

CONCLUSION

In the present study, wave I latency was prolonged with aminoglycoside use in term neonates indicating effect on distal portion of acoustic nerve, but as there were no such findings in preterm study group and moreover no other ABER abnormalities were observed, it was concluded that the short course aminoglycoside therapy has low potential for ototoxicity. Final conclusion for evidence-based recommendations to use aminoglycosides in neonates for various indications in view of audiometric and neurological abnormalities need a larger meta-analysis. Till then, authors strictly recommend to continue auditory brainstem evoked response screening in neonates receiving aminoglycoside therapy.

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