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*Original article*

# Effect of Gentamicin Therapy on Auditory Brainstem Evoked Response in Full Term Infant

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**ABSTRACT**

*Gentamicin, an aminoglycoside antibiotic widely used in neonatal nurseries and intensive care units for treating neonatal sepsis, is known to have nephrotoxicity and ototoxicity. The evaluation of the ototoxicity can be achieved through auditory brainstem response, which is recommended in neonatal screening programs. This study aimed to evaluate the effect of gentamicin on auditory brainstem response in term neonates. A cross-sectional prospective study was conducted on 42 term neonates who received gentamicin for the treatment of neonatal sepsis, along with 30 normal neonates as controls. Auditory brainstem response tests were performed on all neonates after one month. There was a statistically significant prolongation of latency in wave I at intensities of 90dB and 70dB. Prolongation was also observed in waves III and V, although it was not statistically significant. There was no statistically significant difference between the two groups in terms of interpeak latency I-III, III-V, and I-V. The delay in wave I latency suggests distal auditory nerve affection in term neonates who received gentamicin at regular therapeutic doses. The authors recommend the use of auditory brainstem response for monitoring gentamicin usage in neonatal units.*

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## INTRODUCTION

Gentamicin is one of the widely used aminoglycosides in the neonatal intensive care unit to treat sepsis. Despite the development of third- and fourth-generation cephalosporins and other new antibiotics, gentamicin continues to be an important tool for treating serious infections in neonates due to its relatively low rate of bacterial resistance, low cost, and its ability, when used concurrently with beta-lactam antibiotics, to yield synergistic activity against both gram-negative and gram-positive bacteria [1-3].

It is considered safe at therapeutic doses; however, ototoxicity and nephrotoxicity are usually observed when used for longer durations or at high doses, or when used with other ototoxic drugs. In neonates, ototoxic effects may occur even at therapeutic doses (5-7.5 mg/kg/day) [3,4]. 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 the cochlea. Hearing loss usually begins in the high frequencies and progresses to lower frequencies [5-7].

Aminoglycoside exposure is one of the high-risk factors listed by The Joint Committee on Infant Hearing (JCIH) for hearing screening and assessment. JCIH recommends either otoacoustic emissions (OAE) testing or auditory brainstem evoked responses (ABR) techniques, which are ideal for newborn hearing screening, as both are noninvasive methods of recording physiologic activity that do not require a behavioral response from the patient. OAEs reflect only the status of outer hair cells in the inner ear, while ABR records neural activity generated in the cochlea, auditory nerve, and brainstem in the form of seven positive waves following an acoustic stimulus. ABR determines hearing threshold, degree, and type of hearing loss, and results are not affected by anesthetics or sedatives and are less sensitive to noise resulting from NICU incubators, which may be used during the test. JCIH recommends only ABR as an appropriate screening technique in NICU infants [8-10].
Due to controversies regarding the effect of gentamicin on auditory brainstem response at therapeutic doses, this study is planned to resolve these controversies and determine the effect of gentamicin on ABR in full-term neonates.

## METHODS

### *Study design*

A comparative prospective case study was conducted in nursery unit at Albyda Medical Center, from October 2021 to September 2022. The protocol of this study was approved by the Pediatric Department of Albyda Medical Center.
A total of 72 term infants participated, with 42 infants receiving gentamicin in recommended therapeutic dosages (at least twice a day for 5 days at 5-7.5 mg/kg/day) for neonatal sepsis, forming the patient group, and 30 term normal infants forming the control group.

### *Inclusion and exclusion criteria*

All neonates in this study, both patient and control groups, had normal Apgar scores, normal renal function tests, and normal antenatal, natal, and postnatal courses with no clinical or laboratory evidence of severe infection with multiorgan involvement. Any jaundice present was physiological, with maximum values not in the range requiring phototherapy or exchange transfusion.
While we exclude any neonates with low birth weight (<1500g), preterm babies, low Apgar scores, hyperbilirubinemia requiring blood exchange or phototherapy, critically ill infants requiring intensive care unit or mechanical ventilation, congenital anomalies in the outer or middle ear leading to conductive or sensorineural hearing loss that would interfere with the test, family history of hereditary sensorineural hearing loss, or undergoing any other medication with a synergistic effect to gentamicin causing ototoxicity, were excluded from this study. All children in this study were on regular antenatal follow up and underwent full neonatal screening, otoscopic examination, and Tympanometer 1000Hz probe.

### *ABR analytical test*

ABR studies were performed on naturally sleeping neonates in a sound-treated room to avoid electromagnetic interference, after one month of neonatal discharge. Verbal informed consent was obtained from parents. The ABR test commenced after skin preparation, with the negative electrode attached at both mastoids and the ground electrode at the forehead. The default parameters were as the following; stimulus intensity: 70.50.30dBSPL through binaural insert phone; stimulus type: 100µs rarefaction filtered clicks from 100-3000Hz; number of stimuli: 1024; and analysis window: 15ms.

### *Statistical analysis*

Statistical analysis was performed using Student's t-tests and chi-square tests to determine the significance of differences in means between variables. In this study, a p-value <0.05 was considered significant, indicating either negative or positive correlation due to biological variability. The correlation coefficient was evaluated using the r^2 value to determine a linear relationship between the parameters concerned.
ABR Default Analytical Parameters:

## RESULTS

The current study included 72 full-term neonates, with 37 (51.4%) females and 35 (48.6%) males. These neonates were divided into two groups: group A (patient group), comprising 42 newborns who received gentamicin, and group B (control group), consisting of 30 healthy normal neonates. The mean gestational age in Group A was 39.4 weeks (range from 38 to 42 weeks), while in Group B, it was 39.6 weeks (range from 38 to 42 weeks). The mean postnatal

age at the time of the ABR test was 30 days (range from 29 to 31 days). No statistically significant differences were found between the patient and control groups in terms of sex, gestational age at the time of the ABR test, or differences between the right and left ears.

As seen in table 1, the mean latency in wave I was higher in group A (patient group) than in group B (control group) at all intensities, but the difference was statistically significant only at 90dB and 70dB (p-value < 0.05). Additionally, the latency of wave III and wave V was also higher in the patient group than in the control group at all intensities, but these differences were not statistically significant.

***Table 1. ABR latency difference in wave I, III, V in both patient and control group.***

| Intensity | Group A (patient group)peak latency wave I | | Group B (control group)peak latency wave I | | Group A (patient group)peak latency wave III | | Group B (control group)peak latency wave III | | Group A (patient group)peak latency wave V | | Group B (control group)peak latency wave V | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Latency (ms) | n | Latency (ms) | n | Latency (ms) | n | Latency (ms) | n | Latency (ms) | n | Latency (ms) |
| **90dB** | 42 | 1.89±0.29* | 30 | 1.6±0.30* | 42 | 4.34±0.55 | 30 | 4.30±0.6 | 42 | 6.5±0.8 | 30 | 6.44±0.3 |
| **70dB** | 42 | 2.85±0.45* | 30 | 2.7±0.64* | 42 | 5.2±0.50 | 30 | 5.3±0.65 | 42 | 7.5±0.58 | 30 | 7.4±0.78 |
| **50dB** | 42 | 3.4±0.24 | 30 | 3.39±0.33 | 42 | 5.9±0.44 | 30 | 5.9±0.74 | 42 | 8.15±0.9 | 30 | 8.14±0.59 |
| **30dB** | 42 | 4±0.58 | 30 | 3.94±0.54 | 42 | 6.6±0.67 | 30 | 6.4±0.78 | 42 | 8.7±0.33 | 30 | 8.59±0.43 |

** p value<0.05, n=number*

There was no statistically significant difference between the mean interpeak latencies in waves I-III, III-V, and I-V between the patient and control groups at all intensities, except for the interpeak latency between I-III at the 90dB intensity level, where there was a statistically significant difference (p-value < 0.05) as seen in table 2.There was no correlation between the duration of gentamicin treatment and the latencies of wave I, III, V, or the interpeak latencies I-III, III-V, and I-V in the patient group compared to the control group.

***Table 2. ABR inter peak latency difference in wave I-III, II-V, I-V in both patient and control group.***

| Intensity | Group A (patient group) Inter peak latency I-III | | Group B (control group) peak latency wave I Inter peak latency I-III | | Group A (patient group) Inter peak latency III-V | | Group B (control group) Inter peak latency III-V | | Group A (patient group) Inter peak latency I-V | | Group B (control group) Inter peak latency I-V | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | IPL (ms) | n | IPL (ms) | n | IPL (ms) | n | IPL (ms) | n | IPL (ms) | n | IPL (ms) |
| **90dB** | 42 | 2.4±0.5* | 30 | 2.68±0.01* | 42 | 2.2±0.2 | 30 | 2.14±0.3 | 42 | 4.69±0.4 | 30 | 4.82±0.3 |
| **70dB** | 42 | 2±0.37 | 30 | 2.39±0.2 | 42 | 2.1±0.12 | 30 | 2.1±0.3 | 42 | 4.12±0.3 | 30 | 4.49±0.4 |
| **50dB** | 42 | 2.49±0.2 | 30 | 2.59±0.1 | 42 | 2.2±0.5 | 30 | 2.2±0.34 | 42 | 4.69±0.4 | 30 | 4.71±0.6 |
| **30dB** | 42 | 2.6±0.1 | 30 | 2.5±0.0 | 42 | 2.3±0.4 | 30 | 2.15±0.42 | 42 | 4.75±0.5 | 30 | 4.7±0.7 |

## DISCUSSION

In this study, there was an increase in latency of waves I, III, and V in the patient group compared to the control group at all intensities, but the difference was statistically significant only in wave I at 90dB and 70dB (p-value < 0.05). There was statistically significant difference in interpeak latency between wave I-III, and no statistically significant difference in interpeak latency between waves III-V, and I-V.

Kumar et al. also investigated the impact of aminoglycosides on the auditory brainstem in both term and preterm neonates. They administered gentamicin, amikacin, and tobramycin at regular therapeutic doses to 26 term and 20 preterm neonates, compared with 10 neonates in each group. Similar to our findings, they observed a significant prolongation in the latency of wave I at 90dB and 60dB in the term infant group, with no significant difference in interpeak latency. However, these effects were not observed in the preterm study group, and no other ABR abnormalities were noted. Thus, they concluded that the short course of aminoglycoside therapy did not result in significant ABR abnormalities. [12]

In contrast, Puia-Dumitrescu et al. Investigated the impact of gentamicin on the failure of auditory screening at discharge of neonates. Their study, spanning twelve years and involving 84,808 neonates, revealed that gentamicin administration within the observed doses and durations of exposure did not correlate with hearing screen failure at the time of discharge from the initial neonatal intensive care unit (NICU) stay. The authors acknowledged a limitation of their study, stating that their conclusions were restricted to the effects of gentamicin on in-hospital failed hearing screening. They emphasized an inability to exclude the possibility of a risk for long-term sensorineural hearing loss associated with gentamicin exposure beyond the initial hospitalization period. This suggests that while their findings indicated no immediate impact on hearing screening failure at discharge, the potential for long-term hearing impairment due to gentamicin exposure was not fully addressed in their study. [13]

Elbarbary et al. found that extended interval dosing of gentamicin in neonates does not increase the incidence of hearing loss. They concluded that hearing loss in neonates admitted to the neonatal intensive care unit may be due to factors other than gentamicin treatment [14].

Ibrahem et al. Conducted a study on 314 term neonates admitted to the neonatal unit over one year to investigate risk factors for hearing loss. Their findings indicated that the combined use of aminoglycosides and prematurity emerged as significant risk factors for hearing loss, as evidenced by changes in auditory brainstem response (ABR) waves and otoacoustic emission results. They concluded that ototoxic medications and oxygen therapy play pivotal roles in contributing to hearing impairment, emphasizing the need for vigilant monitoring of their administration, dosage adjustments, and duration of intake to mitigate potential adverse effects on auditory function. [15]

Studies, including those conducted by Finitzo-Hieber et al, McCracken, Adelmen et al, Kilic et al, Nanavati et al, Chayasirisobhon et al, Hess et al, Maqbool et al, and Zamani et al, collectively indicate that administering aminoglycoside therapy to infants may not result in significant abnormalities in auditory brainstem response (ABR) or hearing impairment, particularly when used within therapeutic ranges and in infants without underlying health [16-24]. However, Chayasirisobhon et al, Hess et al, Maqbool et al, and Zamani et al [21-24] that there could be a link between aminoglycoside use and hearing impairment when other risk factors, such as meningitis, low birth weight, mechanical ventilation, prenatal infections, and genetic predispositions, are present. This emphasizes the importance of considering individual patient characteristics and potential additional health factors when evaluating the impact of aminoglycoside therapy on infants' auditory function

## CONCLUSION

In this study, the prolongation of wave I latency in the auditory brainstem response indicated involvement of the peripheral auditory nerve, mainly affecting the outer hair cells in the inner ear. It was concluded that low doses of gentamicin administered regularly have a low potential effect on auditory function. Based on these findings, we recommend evidence-based adjustments to the protocol of gentamicin usage in term neonates for various indications, particularly in cases of audiometric abnormalities. However, further research, including larger meta-analyses, is needed to strengthen these recommendations. In the meantime, the authors advocate for the use of auditory brainstem response in assessing term neonates who have received gentamicin in their treatment protocol.

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# تأثير دواء الجنتاميسين علي منعكس جذع المخ السمعي لدى الأطفال حديثي الولادة


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**المستخلص**

الجنتاميسين هو مضاد حيوي من مجموعة الامينوجليكوسيدات تستخدم بشكل شائع لعلاج حالات التسمم لدى الأطفال حديثي الولادة. كما له سميه كلوية وسميه سمعية للأطفال حديثي الولادة يمكن تقييم السميه السمعية من خلال استجابة الجذع السمعي للدماغ والذي يوصى بيه في برامج المسح السمعي لحديثي الولادة. تهدف هذه الدراسة إلى تقييم مدى تأثير دواء الجنتاميسين على منعكس جذع المخ السمعي لدى الأطفال حديثي الولادة. تضمنت هذه الدراسة عدد 72 طفلا من حديثي الولادة 42منهم ممن عولجوا بدواء الجنتاميسين كدواء علاجي لتسمم الدم و30 آخرون كمجموعة ضابطة حيث اجري لهم جميعا قياس منعكس جذع المخ السمعي بعد فترة شهر من تاريخ الولادة.أظهرت هذه الدراسة وجود فرقات إحصائية واضحة بين المجموعتين في مدى تأخر الموجة الأولى عند درجتي 70و90 ديسبلو كما وجد تأخر موجي عند الموجة الثالثة والخامسة ولكن ليس ذا أهميه إحصائية كما وجد عد عدم اختلاف إحصائي في المسافة بين الموجات الأولى والثالثة ,الثالثة و الخامسة, الأولى والخامسة. تأخر الموجة الأولى يبين مدى تأثر الجهة البعيدة العصب السمعي جراء تأثير دواء الجنتاميسين لدى الأطفال الرضع ,كما يجب التوصية باستخدام فحص المنعكس لجذع المخ السمعي للأطفال الذين يخضعون لعلاج الجنتاميسين.

الكلمات الدالة. الجنتاميسين، السمية الأذنية، الرضيع الناضج، استجابة جذع الدماغ السمعي.