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Evaluation of Gentamicin Ototoxicity in Newborn Infants: A Retrospective Observational Study

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Abstract

Background

The main purpose of this study was to demonstrate the effect of gentamicin on hearing tests in newborns treated with gentamicin in our NICU, and to contribute to the selection of antibiotics more consciously.

Materials and Methods: Infants who were hospitalized and followed up in the NICU of Karabük University Medical Faculty Hospital, Karabük, Turkey, between December 2019 and November 2020 were included in our study. During the study period, 331 infants hospitalized in the NICU and meeting the inclusion criteria were included.The infants were divided into two groups, with and without gentamicin treatment, and their demographic characteristics, respiratory support treatment and hearing test results were retrospectively analyzed and the results were compared. Automated auditory brainstem response (ABR) was used for newborn hearing screening at discharge.

Results: Demographically, maternal age and birth weight were found to be significantly lower in gentamicin patients. Delivery method and gestational age were similar between the two groups. While the rates of passing the first test in the ABR screening were higher in the gentamicin group (p=0.051), only 1 infant in the same group failed the ABR second screening. This infant was 34 weeks old, a fraternal twin born at 2200 g, and no hearing loss was found in the infant's twin. When the anamnesis was observed in detail, the infants' uncle manifested a history of hospitalization for the treatment of urinary tract infection in his youth. In the meantime, his history of amikacin treatment and consequent experience of sensorineural hearing loss was revealed.

Conclusion

We concluded that gentamicin does not affect the hearing test when it is not used in the short-term (5-7 days), extended dosing intervals (24-48 hours), and ototoxic drugs such as loop diuretics.

Key Words: Infants, Gentamicin, Ototoxicity, hearing, NICU.

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1- INTRODUCTION

Aminoglycosides are used in newborn infants in combination with other antibiotics with which they show synergistic effects, especially with penicillin, in many infectious conditions such as sepsis, pneumonia, necrotizing enterocolitis (1). The ototoxic side effects of aminoglycoside antibiotics have been demonstrated in larger scale studies in the pediatric and adult populations (2-4). However, neonatal studies are rare, and most have emphasized that aminoglycosides are safe and that there is no clear ototoxic association as is the case in adults. Aminoglycoside ototoxicity is affected by many factors such as the type of aminoglycoside, dose, dose interval, duration of treatment, and genetic predisposition (5). Gentamicin is the most preferred aminoglycoside antibiotic in newborn infants (1, 6).

It has been found that prolonging the gentamicin dose interval (24 hours) is more effective in reaching therapeutic plasma concentrations without increasing the toxic side effects (7). In a study by Pourarian et al., it was suggested that the use of aminoglycoside in the neonatal period is an important risk factor for hearing loss (16). Potential ototoxic effects of aminoglycosides lead to the use of 3rd generation cephalosporins as alternative antibiotics in neonatal intensive care units (NICU). This situation opens the door to increased frequency of antibiotic-resistant infections in the units and the development of invasive fungal infections (8-11). The main purpose of this study was to demonstrate the effect of gentamicin on hearing tests in newborns hospitalized in our NICU and treated with gentamicin, and to contribute to the selection of antibiotics more consciously.

2- MATERIALS AND METHODS

2-1. Study design and population

This retrospective observational study was conducted at the NICU of Karabük University Medical Faculty Hospital, Turkey, between 01 December 2019 and 30 November 2020. During the study period, 331 infants hospitalized in the NICU and meeting the inclusion criteria were included.

2-2. Methods

The infants were divided into two groups, with and without gentamicin treatment, and their demographic characteristics, respiratory support treatment and hearing test results were retrospectively analyzed and the results were compared. The fluid content was regulated so that the glucose infusion rate was approximately 4-6 mg/kg/min. According to the recommendations of the Turkish Neonatal Society, ampicillin and gentamicin combination is preferred in situations of suspected sepsis, the presence of chorioamnionitis in the mother where the cause of preterm birth cannot be explained, and the presence of infiltration on chest radiography. Ampicillin is administered as an empirical antibiotic in 2 split doses per day (50-100 mg/kg/dose) whereas the starting dose for gentamicin is 4 mg/kg/day in infants over 35 weeks, 4.5 mg/kg/36 hours for 30-35 week-old infants, and 5 mg/kg/48 hours in infants under 30 weeks. Gentamicin sulfate is diluted with saline to 10 mg/ml and given at a slow infusion rate of 30 minutes. The gestational week was determined primarily according to the mother's last menstrual period. It was calculated according to ultrasound follow-up or Ballard scoring in cases where the last menstrual date was unknown or uncertain. Antibiotic treatment is terminated when there is no growth in the blood culture, the acute phase reactants are negative and there are no clinical signs of sepsis (over an average of 5 days). In our hospital, automated auditory brainstem response (ABR) is used

for newborn hearing screening on the day of discharge (Madsen Accuscreen, Denmark).

2-3. Laboratory measurements

In routine, complete blood count, blood glucose, blood gas and blood culture are taken from all infants admitted to our Unit, and the C-reactive protein test was required at the 6th hour. By establishing vascular access, intravenous fluid was administered at starting doses of 60 ml/kg and 70-80 ml/kg in term and preterm infants, respectively. 1 ml venous blood was collected from all infants. According to the ABR protocol of the Turkish Ministry of Health General Directorate of Public Health, hearing screening with the ABR method is performed just before the newborn is discharged from the hospital during weekdays. If the newborn is discharged in the weekend, the hearing screening is performed on the following first working day y referring to the polyclinical control. Infants who fail the initial ABR screening test are subjected to the 2nd ABR screening test. Those who fail the second test are subjected to a 3rd ABR screening, and those who fail the third test are transferred to the reference center. Besides, infants found to have any risk factors are referred to the reference center upon determination of the risk, even if they pass the ABR screening test.

2-4. Inclusion and exclusion criteria

Infants who were hospitalized and followed up in the NICU of Karabük University Medical Faculty Hospital, Karabük city, Turkey, between 01 December 2019 and 30 November 2020 were included in our study. Patients who died without hearing tests, who were diagnosed with a genetic syndrome, were transferred to another hospital and those whose information could not be obtained were not included.

2-5. Ethical consideration

Our study was approved by the Ethics Committee of Karabuk University Faculty of Medicine with the decision number of 2021/435, dated 14/1/2021. The study conformed to the Helsinki Declaration and good clinical practice guidelines. All parents provided written informed consent.

2-6. Data Analyses

Data were recorded and analyzed with the SPSS software version 20.0. Categorical data were represented by frequency and percentage, while continuous data were represented by mean standard deviation and median (lowest-highest). Compatibility of continuous data to normal distribution was tested with the Kolmogorov-Smirnov test. The T-test or the Mann-Whitney U test were used in the comparison of the means according to their suitability for normal distribution. A Chi-square test was used in comparing the categorical data. The $p<0.05$ value was accepted as the level of significance.

3- RESULTS

During this period, 337 patients were admitted to our NICU. Two infants died, one of them due to immaturity at 23 weeks and the other due to the sudden infant death syndrome at 2 months. Two infants who were admitted to the hospital due to congenital heart disease and another 2 who were admitted to another hospital due to premature retinopathy were not included in the study. The remaining 331 patients were divided into 2 groups as those who received gentamicin treatment and those who did not. Demographically, maternal age and birth weight were found to be significantly lower in those receiving gentamicin. Delivery Method and gestational age were similar between the two groups **(Table.1)**.

Table-1: Demographic features of study population.

	Gentamicin treatment				
	Patient under treatment		Patient not under treatment		
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	P- value
Maternal Age, month	28.4±6	27 (18-45)	30.18±5.53	30 (18-43)	0.002£
Pregnancy, Week	36.9±2.8	38 (26-40)	37.54±1.91	38 (27-41)	0.121£
Weight at Birth, gr	2668.8±821	2710(680-5145)	2985.1±739.1	3095(1245-4950)	0.001*
		Frequency (%)	Frequency (%)		P-value
Delivery Method	NSVD	29 (19.5)	26 (14.3)		0.208
	CS	120 (80.5)	156 (85.7)		

* T-test £ Mann Whitney U, SD: Standard Deviation, NSVD: Normal spontaneous vaginal delivery, CS: Cesarean section.

The monitoring rate in mechanical ventilation was significantly higher in infants who received gentamicin (**Table.2**); while the rates of passing the first test in the ABR screening were higher in the gentamicin group (p=0.051), it was observed that only 1 infant in the group who received gentamicin from the ABR second screening failed (**Tables 3 and 4**). Unilateral mild sensorineural hearing loss was detected in the left ear in the infant who could not pass the second screening test. This infant was 34 weeks old, a fraternal twin born at 2200 g, and no hearing loss was found in the infant's twin. When the anamnesis was observed in detail, the infants' uncle manifested a history of hospitalization for the treatment of urinary tract infection in his youth. In the meantime, his history of amikacin treatment and consequent experience of sensorineural hearing loss was revealed. Genetic screening was recommended to the family for aminoglycoside sensitivity.

Table-2: Comparison of respiratory support parameters between the two groups.

Variables		Gentamicin treatment				
		Patient under treatment		Patient not under treatment		
		Frequency	Percentage (%)	Frequency	Percentage (%)	P-value
Mechanical Ventilation	Not received	105	70.5	166	91.2	0.001
	Received	44	29.5	16	8.8	
Non-invasive ventilation	Not received	94	63.1	121	66.5	0.519
	Received	55	36.9	61	33.5	

Table-3: Comparison of ABR screening results between the two groups.

Variables		Patient under gentamicin therapy				
		Patient under treatment		Patient not under treatment		
		Frequency	Percentage	Frequency	Percentage	P- value
ABR screening	0	130	87.2	144	79.1	0.051
	1,2,3	19	12.8	38	20.9	

ABR: auditory brainstem response.
0: successfully passed the initial ABR screening test.
1: one-sided failure at the initial ABR screening test, successfully passed the 2nd ABR screening test.
2: double-sided failure at the initial ABR screening test, successfully passed the 2nd ABR screening test.
3: double-sided or one-sided failure at the initial ABR screening test, failed the 2nd ABR screening test.

Table-4: Comparison of ABR screening results between the two groups (detailed).

Variables		Patient under gentamicin therapy				
		Patient under treatment		Patient not under treatment		
		Frequency	Percentage	Frequency	Percentage	P- value
ABR screening	0	130	87.2	144	79.1	0.106
	1	9	6.0	15	8.2	
	2	9	6.0	23	12.6	
	3	1	0.7	0	0.0	

ABR: auditory brainstem response.
0: successfully passed the initial ABR screening test.
1: one-sided failure at the initial ABR screening test, successfully passed the 2nd ABR screening test.
2: double-sided failure at the initial ABR screening test, successfully passed the 2nd ABR screening test.
3: double-sided or one-sided failure at the initial ABR screening test, failed the 2nd ABR screening test.

4- DISCUSSION

The aim of this study is to reveal the reality of concerns related to the ototoxic effect of gentamicin use in newborns and to contribute to better awareness of antibiotic selection. In our study, hearing loss was found in only 2 of our infants hospitalized in the NICU. One of our patients was not included in the study because the patient was diagnosed with the 7-14 chromosome translocation. Our other patient who did not pass the tests manifested hearing loss after aminoglycoside in his family history (the ratio among all patients: 0.7%). Severe hearing loss is reported with a frequency of 1-3% in infants hospitalized in NICU. This rate is approximately 10 times higher than those who are not admitted to NICU (12-13). The reason why ototoxicity is so low in infants hospitalized in the NICU is avoidance of the use of ototoxic drugs together, termination of gentamicin treatment as soon as the sepsis is eliminated in infants with suspected sepsis, not continuing gentamicin therapy for more than 7 days unless gram-negative bacteria grow in the blood culture, the strategy of early termination of mechanical ventilator treatment and transition to non-invasive ventilation in a short time; the low number of infants with very low birth weight in our Unit can be remarkable. During the working period, 18 infants below 1500 g were monitored in our Unit. Gentamicin is still one of the most commonly used antibiotics in neonatal infections (14). Concerns about ototoxicity of gentamicin sometimes direct physicians to other alternative antibiotics, especially 3rd generation cephalosporins. In recent years, increased interest in these antibiotics has reemerged, with the, after it was demonstrated that the administration of gentamicin treatment once a day or at 36-48-hour intervals reaches therapeutic levels without causing toxic effects (15). Although there are studies suggesting

monitoring serum gentamicin levels and individualization of appropriate therapeutic doses (16), this approach does not seem to be a practical since it has potential risks such as anemia, secondary infection and adverse effects of painful process-related neurodevelopment and it will result in frequent blood draws in newborn infants. In 2016, Fuchs et al. found sensorineural hearing loss of 1.58% in a very low birth weight and/or premature infant population under 32 weeks. No difference was found in the cumulative dose of gentamicin between the groups with or without hearing loss, however, the pneumothorax incidence was determined significantly high and it has been suggested that it causes hypoxemia and predisposes to ototoxicity. It was concluded that gentamicin ototoxicity in infants with very low birth weight can be reduced by keeping the dose low, monitoring serum blood levels and adjusting the dose accordingly (17).

In a retrospective cohort study conducted by Puia et al. in 2018, hearing test results of infants who received gentamicin in the 330 NICU centers between 2002 and 2014 were evaluated during discharge. The rate of the hearing screening failure results were higher in 84,808 infants who met the inclusion criteria with low birth weight and being small-for-gestational-age. However when the hospitalization rates and morbidities of these infants were taken into consideration and analyzed, it was concluded that the gentamicin dose and the duration of treatment did not increase the rate of failure in the hearing test (18). The effect of a single dose and multiple doses on ototoxicity was researched in a Cochrane meta-analysis conducted in 2016. Only 5 of 11 studies were evaluated and ototoxicity was evaluated in 4 of them. No difference was observed between the two groups, and vestibular toxicity was not evaluated in any of these studies. In a review where the aminoglycoside-related ototoxicity was evaluated, it was suggested that mutations in the mitochondrial 12S rRNA are responsible for approximately 10-20% of the sensorineural hearing losses. Therefore they stated that the investigation of these mutations prior to aminoglycoside treatment would be beneficial, yet such an approach does not seem practical (19-20). Some studies stated that there is also a genetic predisposition for aminoglycoside toxicity (20). However, since there is no study investigating genetic mutations that generate predisposition to aminoglycosides in our country, it is difficult to predict its role in hearing loss developing after aminoglycoside. According to our study, we can declare that the risk of gentamicin for sensorineural hearing loss is very low when its use with other ototoxic drugs is avoided in a short-term (less than 7 days) dose range of 24-48 hours. In a systematic evaluation evaluating gentamicin ototoxicity in 2014 (21), it was found that 22 of 577 patients in 8 studies could not pass the hearing test (3.8%).

When these studies were evaluated, it was determined that the incidence of gentamicin ototoxicity was high in some studies, and long-term use of gentamicin was found in infants with hearing loss (on average: 30 days). These studies were generally conducted before the year 2000, and no relationship was shown with the trough level of gentamicin (21). In an article published by Hemmingsen et al. in 2020, 219 children who received high-dose gentamicin treatment in the neonatal period between 2004 and 2012 were analyzed audiologically during the school period. After adjustment for birth weight, no difference was found in hearing thresholds that could complete audiometry between those exposed to gentamicin and those who were not (22). El Barbary et al. in their study in 2015, reported no significant difference in hearing loss between those who were hospitalized in

the NICU and received a single daily dose of gentamicin and those who did not (23). The data of our study are in line with studies showing that the ototoxicity can be reduced to very low rates by extending the dose range of gentamicin (18, 23). In our study, failure to pass the second ABR test after gentamicin exposure was observed in only one patient (0.7%). Although these findings are encouraging, we think that it would be appropriate to discontinue gentamicin as soon as possible in newborn infants.

4-1. Study Limitations

The limitations of our study include the low number of cases due drawing data from a single center, the retrospective-observational design, and since there is no study investigating genetic mutations that generate predisposition to aminoglycosides in our country, it is difficult to predict its role in hearing loss development after aminoglycoside.

5- CONCLUSION

Based on the results, gentamicin appears to have low ototoxicity rates in neonates when not given with loop diuretics or other ototoxic drugs and when used in the short term and with extended dosing intervals.

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7- AUTHOR'S CONTRIBUTIONS

Sadrettin Ekmen: Conceptualization;; Formal analysis; Investigation; Methodology; Project administration; Software; Supervision; Visualization; Writing - original draft; Writing - review & editing. Erkan Doğan: Data curation; Validation; Software; Writing - review & editing.

8- CONFLICT OF INTEREST: None.

9- REFERENCES

1. B. Chattopadhyay, Newborns and gentamicin-how much and how often? J. Antimicrob. Chemother. 49 (2002) 13–16.

2. Buszman E,Wrzesniok D, Trzcionka J. Interaction of neomycin, tobramycin and amikacin with melanin in vitro in relation to aminoglycosides induced ototoxicity. Pharmazie 2007;62: 210-5.

3. Durante-Mangoni E,Grammatikos A,Utili R, Falagas ME. Do we still need the aminoglycosides? Int J Antimicrob Agents 2009;33: 201-5.

4. Jiang M, Karasawa T, Steyger PS. Aminoglycoside-Induced Cochleotoxicity: A Review. Front Cell Neurosci. 2017 Oct 9;11:308. doi: 10.3389/fncel.2017.00308. PMID: 29062271; PMCID: PMC5640705.

5. R. Probst, J. Smuizynski, N. Schmuziger, Otoacoustic emissions and extended high frequency hearing sensitivity in young adults, Int. J. Audiol. 44 (1) (2005) 24–30.

6. Hsieh EM, Hornik CP, Clark RH, Laughon MM, Benjamin DK Jr, Smith PB, et al.Medication use in the neonatal intensive care unit. AmJ Perinatol 2014;31: 811-21.

7. Rao SC, Srinivasjois R, Moon K. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database Syst Rev. 2016 Dec 6;12(12):CD005091.

8. Tzialla, C., Borghesi, A., Serra, G. et al. Antimicrobial therapy in neonatal intensive care unit. Ital J Pediatr 2015;41: 27.

9. Kelly MS, Benjamin DK Jr, Smith PB. The epidemiology and diagnosis of invasive candidiasis among prematüre infants. Clin Perinatol 2015; 42: 105-17.

10. Carr D, Barnes EH, Gordon A, et al. Effect of antibiotic use on antimicrobial antibiotic resistance and late-onset neonatal infections over 25 years in an Australian tertiary neonatal unit. Archives of Disease in Childhood - Fetal and Neonatal Edition 2017;102: F244-F250.

11. Satar M, Arısoy AE, Çelik İH. Turkish Neonatal Society guideline on neonatal

infections-diagnosis and treatment. Turk Pediatri Ars. 2018 Dec 25;53(Suppl 1):S88-S100. doi: 10.5152/TurkPediatriArs.2018.01809. PMID: 31236022; PMCID: PMC6568293.

12. American Academy of Pediatrics, Joint Committee on Infant Hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. Pediatrics 2007;120:898-921.

13. Vohr B. Infants and children with hearing loss—part 2: overview. Ment Retard Dev Disabil Res Rev 2003;9:218-9.

14. Cantey JB, Wozniak PS, Sanchez PJ. Prospective surveillance of antibiotic use in the neonatal intensive care unit: results from the SCOUT study. Pediatr Infect Dis J 2015; 34:267–72.

15. ao SC, Ahmed M, Hagan R. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005091. doi: 10.1002/14651858.CD005091.pub2.

16. S. Pourarian, B. Khademi, N. Pishva, A. Jamali, Prevalence of hearing loss in newborns admitted to neonatal intensive care unit, Iran. J. Otorhinolaryngol. 2012; 24 (68):129–34.

17. uchs A, Zimmermann L, Bickle Graz M, Cherpillod J, Tolsa JF, Buclin T, Giannoni E. Gentamicin Exposure and Sensorineural Hearing Loss in Preterm Infants. PLoS One. 2016 Jul 8;11(7):e0158806. doi: 10.1371/journal.pone.0158806.

18. Puia-Dumitrescu M, Bretzius OM, Brown N, Fitz-Henley JA, Ssengonzi R, Wechsler CS, Gray KD, Benjamin DK Sr, Smith PB, Clark RH, Gonzalez D, Hornik CP. Evaluation of Gentamicin Exposure in the Neonatal Intensive Care Unit and Hearing Function at Discharge. J Pediatr. 2018 Dec;203:131-136. doi: 10.1016/j.jpeds.2018.07.101.

20. Nguyen T, Jeyakumar A. Genetic susceptibility to aminoglycoside ototoxicity. Int J Pediatr Otorhinolaryngol. 2019 May;120:15-19. doi: 10.1016/j.ijporl.2019.02.002.

21. A. Kent, M.A. Turner, M. Sharland, P.T. Heath, Aminoglycoside toxicity in neo- nates: something to worry about? Expert Rev. Anti Infect. Ther. 2014;12(3): 319–31.

22. Dagny Hemmingsen, Camilla Mikalsen, Alexander Rydland Hansen, Jon Widding Fjalstad, Niels Christian Stenklev, Claus Klingenberg. Hearing in Schoolchildren After Neonatal Exposure to a High-Dose Gentamicin Regimen. Pediatrics February 2020; 145 (2):e20192373.

23. Mohamed N. El-barbary, Rania I.H. Ismail, Adel A.A. Ibrahim, Gentamicin extended interval regimen and ototoxicity in neonates, International Journal of Pediatric Otorhinolaryngology. 2015;79 (8):1294-98. ISSN 0165-5876.