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EVALUATION OF OTOTOXICITY IN GENTAMICIN TREATED MODERATELY AND LATE PREMATURE INFANTS

Berfin UYSAL,MD, 0000-0001-6267-0454

Saime CEYLAN,MD, 0009-0007-3899-7052

Hakan ERDOĞAN, Professor of Pediatrics, 0000-0002-5212-9282

Correspondence: *Berfin Uysal, berfing@yahoo.com*

ABSTRACT

Objective: The objective of our research is to investigate the prevalence of ototoxicity throughout the early stages of infancy in middle and late preterm infants who were hospitalized and treated with gentamicin in the Neonatal Intensive Care Unit (NICU).

Materials & Method: Our study focused on premature babies admitted to the Neonatal Intensive Care Unit of our hospital between 1 May 2015 and 30 April 2016, in their middle and late stages. Patients were divided into two groups as receiving and not receiving gentamicin treatment. One patient from each group were unable to succeed the initial auditory brainstem response (ABR) assessment. There was no discernible distinction between the two groups.

Results It was determined that 8 patients failed the TEOAE test. Four of these patients were assigned to the group receiving gentamicin, whereas four were assigned to the control group. These 8 patients were directed to the Ear Nose and Throat Clinic for examination. Otitis media was diagnosed in six cases and treatment was initiated, whereas the evaluation of two patients yielded unremarkable results. Following the therapies, the second auditory brainstem response (ABR) test was conducted once more on these eight individuals. Each patient exceeded this test. Upon evaluation, no auditory impairment is detected. There was no documented occurrence of gentamicin-induced damage to the auditory system (ototoxicity).

Conclusion: We think that neonatal intensive care patients who are exposed to ototoxic agents such as gentamicin and other hearing loss risk factors and long-term follow-up of especially premature ones are important in this respect. Considering factors such as duration of use and dose, we observed that gentamicin-induced ototoxicity did not develop in our study group.

Key Words: Gentacimin, ototoxicity, treatment

GENTAMİSİNLE TEDAVİ EDİLEN ORTA VE GEÇ PREMATÜRE BEBEKLERDE OTOTOKSİSİTENİN DEĞERLENDİRİLMESİ

Özet

Amaç: Araştırmamızın amacı, Yenidoğan Yoğun Bakım Ünitesinde yatırılarak gentamisin ile tedavi edilen orta ve geç prematüre bebeklerde bebeklik döneminin erken dönemleri boyunca ototoksisite prevalansını belirlemekti.

Materyal & Metod: Çalışmamız hastanemiz Yenidoğan Yoğun Bakım Ünitesine 1 Mayıs 2015 ile 30 Nisan 2016 tarihleri arasında kabul edilen orta ve ileri evre prematüre bebekler ile yürütüldü. Hastalar gentamisin tedavisi alan ve almayan olarak iki gruba ayrıldı.

Bulgular: Her gruptan bir hasta, ilk işitsel beyin sapı tepkisi (ABR) değerlendirmesini geçemedi. İki grup arasında belirgin bir ayrım yoktu. 8 hastanın TEOAE testini geçemediği belirlendi. Bu hastaların dördü gentamisin alan gruba, dördü ise kontrol grubuna atandı. Bu 8 hasta muayene için Kulak Burun Boğaz Kliniğine yönlendirildi. Altı olguda otitis media tanısı konularak tedavi başlandı, iki olguda ise değerlendirmede özellik saptanmadı. Terapilerin ardından bu sekiz kişiye bir kez daha ikinci işitsel beyin sapı tepkisi (ABR) testi uygulandı. Her hasta bu testi aştı. Yapılan değerlendirmede herhangi bir işitme bozukluğu tespit edilmiyor. İşitme sisteminde gentamisinin neden olduğu hasara (ototoksisite) ilişkin belgelenmiş bir olay yoktu.

Sonuç: Çalışmada elde ettiğimiz sonuçlara göre gentamisin gibi ototoksik ajanlara ve diğer işitme kaybı risk faktörlerine maruz kalan yenidoğan yoğun bakım hastalarının ve özellikle prematüre olanların uzun süreli takiplerinin bu açıdan önemli olduğunu düşünmekteyiz. Kullanım süresi ve doz gibi faktörler göz önüne alındığında çalışma grubumuzda gentamisine bağlı ototoksisite gelişmediğini gözlemledik.

Anahtar Kelimeler: Gentamisin, ototoksisite, tedavi

1. INTRODUCTION

Neonates with auditory impairments may experience developmental challenges so timely diagnosis and treatment within a 3-6 month timeframe are crucial for minimizing the impact. If those with congenital hearing loss can be diagnosed and treated early, their social, language and intelligence development is close to that of individuals with normal hearing. Gentamicin is one of the most common antibiotics used in newborns. And otoxicity is a significant side effect which may occur with the use of aminoglycosides in the neonatal period.

The primary objective of this study is to ascertain the prevalence of ototoxicity during the early post-discharge period in neonates who were admitted to NICU and underwent gentamicin treatment.

2. MATERIALS & METHODS

This study was conducted in premature babies born on the 32nd (0-7) to 33rd (6-7) weeks of gestation and babies born on 34th (0-7) to 36th (6-7) weeks of gestation in NICU of Bursa University of Health Sciences, Yuksek Ihtisas Education and Research Hospital (YIERH). It is an observational cohort study conducted between May 2015 and April 30, 2016. Patients who possessed at least one risk factor for hearing loss according to the 2007 publication of Joint Committee on Infant Hearing (JCIH) were excluded from the study (Table 1)(1). Patients were divided into two groups; group 1, receiving intravenous (IV) gentamicin therapy for any indication for at least 5 days and group 2, those who did not receive any gentamicin treatment during their hospitalization.

A hearing test was performed in a soundproofed and secluded room, while ensuring the newborn is in a relaxed state by an audiometry technician. Within the initial month following discharge from NICU, routine Auditory Brainstem Response (ABR) testing was conducted on patients. Patients were contacted and requested to undergo another hearing test at intervals between 3 to 9 months. During this time span, Transient Evoked Otoacoustic Emission Test (TEOAE test), which is crucial for identifying gentamicin-induced hearing loss, was administered to the subjects. As the test was believed believed to be potentially influenced by external ear diseases, patients who are unable to pass the test were referred to the Otorhinolaryngology Polyclinic for assessment. After the inspection and treatment, patients underwent a second ABR test and the results were recorded. The TEOAE and ABR tests are conducted using a 35 dB click stimulus with Madsen Accuscreen, hearing screening apparatus (Otometrics, Taastrup, Denmark). The TEOAE test was performed with the appropriate probe when the baby was asleep or quiet to both ears. Responses were elicited following a 35 dB auditory stimulation in the form of a click. Upon successful emission, the result is indicated as "pass"; if there is insufficient emission, the result is indicated as "fail". Babies' forehead, cheek and neck area are cleaned with conductive gel and disposable electrodes are applied to these areas for the ABR test and measurements were taken with headphones placed on the auricle.

The birth weight, gestational age, mode of delivery, maternal age, consanguinity between parents, dosage of gentamicin if administered, presence of early or late neonatal sepsis, whether there was a culture growth during follow-up, presence of any additional anomalies at birth, and reason for admission to the neonatal intensive care unit (NICU) were obtained from the medical records.

Statistical Analysis

The statistical analysis of the data was conducted using SPSS 23.0 (IBM Corporation, New York, USA), a statistical software package. Numerical data that follows a normal distribution is expressed as mean ± standard deviation (SD), while numerical data that does not follow a normal distribution is expressed as median (minimum-maximum). The normal distribution of the data was examined using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare two groups of non-normally distributed numeric data. The analysis of categorical data utilized the Pearson chi-square test, Fisher's exact test, and the Fisher-Freeman-Halton test. The level of significance has been determined as $p<0.05$.

3. RESULTS

Transient Evoked Otoacoustic Emission Test was applied to 143 premature babies, 65 of whom received IV gentamycin (group 1) and 78 of whom did not (group 2). Considering the possibility of TEOAE test being affected by external ear pathologies, 8 patients whose test results were determined as "failed" were referred to the Ear, Nose, and Throat Clinic for examination. Treatment was initiated once otitis was detected in six patients, two patients had normal examination. After completing the treatments, a second ABR test was conducted on these 8 patients, and all of their test results were determined to be "pass." We did not have any patients with hearing loss based on the results of first ABR, TEOAE and second ABR tests.

Logistic regression analysis was used to examine the effect of confounding factors on the results, due to the observed heterogeneity in terms of gestational week and birth weight between the groups receiving and not receiving Gentamicin. Both groups underwent multivariate tests to see whether gestational week and birth weight had an impact on the ABR test result and there was no significant difference observed between the groups receiving gentamicin and those not receiving it ($p=0.9$). Similarly, the impact of gestational age and birth weight on the OAE test results conducted between 3-9 months was examined by multivariate tests. It was observed that there was no difference in passing or failing the test between the group receiving gentamicin and the group not receiving it. It was determined that the administration of gentamicin did not have an effect on the test results ($p=0.8$).

4. DISCUSSION

The speech and language development of infants is particularly rapid throughout the first years of life, especially in the first few months (2,3). The possession of a healthy auditory ability from infancy is crucial not only for speech and language development, but also for social, emotional, and cognitive development. Therefore, the later congenital hearing loss is detected, the more the child's overall development and communication skills would be hindered. These negative effects will lead to learning difficulties in the child and reduce their academic performance (4-7).

Children with congenital or acquired hearing loss have a socio-economic cost of almost 1 million dollars over their lifetime, due to expenses such as hearing rehabilitation, special education resources, and decreased work productivity (8). With the development of technologies that enable the objective diagnosis of hearing loss during infancy, the opportunity to detect congenital hearing loss early has emerged. It is shown that infants who receive early diagnosis and treatment and undergo special education show performance levels similar to their peers in terms of development and academic achievements (9-11).

Children in whom hearing loss was detected and early intervention was provided during the first 6 months have shown significantly better outcomes in terms of vocabulary development compared to children in whom hearing loss was later detected (12).

In our country, newborn hearing screenings were initiated at the national level in 2004.

The 2007 report published by JCIH states that in order to not miss neural hearing loss in newborns staying in the neonatal intensive care unit for more than 5 days, ABR should be applied as part of the screening tests in NICU screening protocols (1). In accordance with this report, we conducted Auditory Brainstem Response (ABR) tests on the patients and no difference was detected between the two groups in terms of the results of the first ABR test.

The prevalence of congenital hearing loss is considered to be 1 in every 1000 live births worldwide (13). In our country, 1 or 2 out of every 1000 babies are born with severe hearing loss (14). In high-risk newborns, this rate can increase up to tenfold (13).

The rates of hearing loss among infants admitted to neonatal intensive care units are 2-15%, while in full-term births it is 0.3% (15). In a study conducted in NICU, Von Straten et al. found that the percentage of those who did not pass the ABR test was 3.1% (16). Another study from

New Zealand revealed a prevalence of 4.7% (17). The risk of hearing loss is greater in very low birth weight (VLBW) preterm infants compared to healthy neonates. The prevalence of hearing loss in 95 infants from Portugal weighing between 640 and 1500 grams was found to be 6.3% (18). A study carried out at Oxford including 70 newborns with a birth weight less than 1500 g found that the prevalence of hearing loss was 2.7% (19). In another study, a total of 337 very low birth weight (VLBW) infants and 1205 healthy newborns underwent otoacoustic emissions (OAE) testing. The results showed that 12.4% of VLBW infants and 7.8% of healthy infants did not pass the hearing test. Weeks after discharge, ABR test was performed and hearing loss was detected in only 3% of VLBW babies (20). A study on preterm infants whose birth weight is less than 1500 g and gestation is less than 34 weeks, revealed a hearing loss prevalence of 6.3% (21). The data on hearing loss acquired from various regions of the world reveal variations in the prevalence rates, ranging from 1.4% to 6.3%. The retention rate for ABR hearing screenings conducted in the initial month of life for moderately and late preterm infants discharged from YIERH is 1.4%. Although this rate is compatible with the literature, it only includes the hearing screening results for moderately and late premature babies.

Bacterial infections are the most important causes of morbidity and mortality in newborns (22). And gentamicin is one of the most common antibiotics used in newborns (23). When used together with beta-lactam antibiotics, it provides synergistic activity against common pathogens in the newborn period (24).

Ototoxicity is the term used to describe the sudden appearance of auditory impairment, vestibular problems, or a combination of both resulting from the administration of a pharmaceutical or chemical substance. When there is a decrease in hearing ability of 20 dB or more at multiple frequencies in a row, after ruling out alternative causes of hearing loss, it should be documented as drug-induced hearing loss (25).

Ototoxicity is a significant side effect that may occur with the use of aminoglycosides. The frequency of ototoxicity has been reported 2-45% in adults and 0-2% in infants (26).

Otoacoustic emissions (OAE) measures are commonly used in clinical settings due to their non-invasive nature, which eliminates the need for anesthesia. These measurements are not affected by the overall health of the patient and so are advised for infants or children with mental retardation. The application is straightforward, the test is objective and the measurement is sensitive, resulting in precise outcomes. It is often favored for its benefits, including quick testing time and efficiency. A healthy middle ear is required to detect OAEs occurring in the

inner ear. An open external auditory canal and a structure are also necessary (27). Furthermore, a robust inner ear structure is necessary for the assessment of OAEs.

Stimulated otoacoustic emissions are used to detect early effects of ototoxic drugs (28).

Aminoglycosides cause ototoxicity by disrupting the integrity of outer hair cells in the inner ear. Hotz et al. claimed theTEOAE test as a method for early diagnosis in the prevention of aminoglycoside-induced ototoxicity (29,30). A research involving patients who did not possess any other risk factors other than aminoglycoside use observed that it does not pose a risk factor for hearing loss (31). Four-year follow-up of 81 patients who were administered aminoglycosides during infancy without the concurrent use of aminoglycosides and diuretics, found no evidence to suggest that the use or duration of aminoglycosides is associated with hearing loss (32). According to another author comparing two healthy infant groups with no hearing loss, there was no differences in vestibular functions between the group receiving gentamicin and not receiving gentamicin (33). As we conducted a longitudinal study on infants born moderately and late premature, tracking their development from 3 to 9 months of age, we also did not encounter any hearing loss and therefore no gentamicin ototoxicity. Furthermore, as ototoxicity caused by aminoglycosides occurs with a frequency of 2-45% in adults and 0-2% in infants, failing to detect a gentamicin-related ototoxicity in our study is acceptable.

Pourarian et al. considered the administration of aminoglycosides to neonates as a significant risk factor for hearing loss and argued that tight control of serum levels of aminoglycosides may help prevent hearing loss (34). This may also explain our healty premature babies with no hearing loss as they were treated with appropriate dosages and duration of gentamicin.

Contrary to our findings, Raveh et al. (35) and Saunders et al. (36) have documented instances of irreversible ototoxicity following gentamicin treatment. Gentamicin is mentioned to be a risk factor especially in patients who have a genetic susceptibility to hearing loss and in patients treated together with ototoxic drugs such as diuretics and for long periods of time (136-143).

Given the inadequate sample size of patients in our study, we believe that conducting a fresh, extensive clinical investigation is imperative.

Consequently, our study did not find hearing damage during the early post-discharge period in neonates who were admitted to NICU and underwent gentamicin treatment. However, it is crucial to closely monitor premature infants for an early detection of hearing impairment.

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Tables

Table 1- New risk criteria for hearing loss- (JCIH) – 2007

Risk factors associated with progressive, late-type permanent congenital hearing loss in childhood.

1- Caregiver anxiety (in terms of hearing, speech, language, and developmental delay)

2- Family history of permanent childhood hearing loss

3- Staying in the Neonatal Intensive Care Unit for more than 5 days or existence of any of the following:

- Extracorporeal membrane oxygenation (ECMO)

- Auxiliary respiration

- Ototoxic medication (gentamicin, tobramycin) or loop diuretics (furosemide)

-Hyperbilirubinemia requiring exchange transfusion

4- Intrauterine infections (CMV, rubella, syphilis, toxoplasma)

5- Craniofacial anomalies including external auditory canal and temporal bone anomalies

6- Identification of syndromes that result in sensorineural or conductive hearing impairment

7- Syndromes linked to a gradual and delayed onset-Neurofibromatosis, osteopetrosis, Usher syndrome, and less commonly, hearing loss conditions such as Waardenburg, Alpert, Pendred, and Jervell-Lange-Nielsen syndromes.

8- Neurodegenerative disorders (such as Hunter syndrome) or sensorimotor

neuropathies (such as Friedrich's ataxis and Charcot-Marie-Tooth syndrome).

9- Blood culture positive postnatal infections associated with sensory hearing loss such as bacterial and viral (such as HSV, varicella) meningitis.

10- Fractures of the basal skull/temporal bone, especially those requiring hospitalization.

11- Chemotherapy