ASIA PACIFIC JOURNAL of MEDICAL TOXICOLOGY
APJMT 14;4 http://apjmt.mums.ac.ir December 2025

ORIGINAL ARTICLE

# Once vs. Twice Daily Gentamicin Therapy in Neonates: a Comparison of Its Induced Nephro- and Ototoxicity

AHMADSHAH FARHAT[1], ASHRAF MOHAMMADZADEH[1], EZZAT KHODASHENAS[1], ABBAS ALIZADEH[1], NAZLI PARIZADEH[2]

[1]Neonatal Research Center, Pediatric Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Pediatric and Congenital Cardiology Division, Pediatric Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

## Abstract

***Background*:** Gentamicin is a commonly used antibiotic in neonatal intensive care units with known renal and auditory toxic effects. Several studies have aimed to reduce these adverse effects, which are mainly related to dosage and infusion rate. Reducing the frequency of gentamicin injections may save time, money, and human resources. This study aimed to compare the toxic effects of gentamicin administered once daily versus twice daily in neonates.
***Methods*:** All neonates hospitalized in the NICU who met eligibility criteria and were receiving gentamicin therapy were recruited using a non-random, target-based sampling method. Participants were randomly assigned to two groups: group A received gentamicin once daily, and group B twice daily. Therapeutic efficacy, nephrotoxicity, ototoxicity, and mortality rates were compared between the groups based on clinical evaluation, laboratory data, and audiometric tests. Serum urea and creatinine levels were assessed to evaluate nephrotoxicity, while otoacoustic emissions (OAE) and automated auditory brainstem response (AABR) tests were used to assess ototoxicity.
***Results*:** Therapeutic effectiveness and nephrotoxicity were similar between the groups. Audiometric tests were normal in group A, whereas 6 patients in group B showed abnormal OAE and AABR results, which was statistically significant (P=0.012). No neonatal deaths occurred in either group.
***Conclusion*:** Once-daily gentamicin administration results in fewer audiological side effects compared to twice-daily dosing, highlighting its importance in reducing toxicity and conserving resources.

**Keywords:** Gentamicin, Neonate, Toxicity

**How to cite this article:** Farhat A, Mohammadzadeh A, Khodashenas E, Alizadeh A, Parizadeh N. Once vs. twice daily gentamicin therapy in neonates: a comparison of its induced nephro- and ototoxicity. Asia Pac J Med Toxicol 2025; 14(4): 151-4.

## INTRODUCTION

Annually, approximately 4 million neonatal deaths occur worldwide, 99% of which are in developing countries [1, 2]. Bacterial infections are among the most common causes of neonatal morbidity and mortality [3, 4]. In developing countries, 20% of infants are infected during infancy, and infectious diseases and sepsis account for 40% of neonatal deaths [5]. Early detection and treatment of infections can prevent many of these deaths [6-8]. Gentamicin is a widely used antibiotic for treating neonatal infections. Its major side effects include nephrotoxicity, which is generally reversible, and ototoxicity, which is often irreversible [9, 10]. Gentamicin can be administered either as a single daily dose or in multiple doses. Studies suggest that single daily dosing results in lower trough levels and higher therapeutic concentrations compared to two or three daily doses. Additionally, single dosing is more cost-effective and requires less time and human resources for administration [11-15].

While several studies have compared single versus multiple daily gentamicin dosing in infants and children, limited evidence exists specifically in neonates using both OAE and AABR for hearing assessment. Most prior studies focused on nephrotoxicity and did not evaluate auditory effects systematically. Additionally, data from developing countries are scarce, where simplified dosing schedules can reduce nursing workload and healthcare costs.

In this study, we aimed at comparing the antibacterial effects, adverse effects, and mortality rates of gentamicin in the two groups of single versus twice daily dosing administration among neonates in the northeast of Iran hospitalized in the neonatal intensive care unit (NICU).

*Correspondence to: Dr. Nazli Parizadeh, Pediatric and Congenital Cardiology Division, Pediatric Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Tel: +98 51 3854 3031, Email: Parizadehn961@mums.ac.ir

## METHODS

This study was conducted on neonates hospitalized in the NICU with a definite or suspected diagnosis of infection who were receiving gentamicin therapy. Participants were selected using a non-random, target-based sampling method and followed for up to seven days.

Ethical Approval: IR.MUMS.MEDICAL.REC88536

Inclusion criteria were: weight > 2000g, age 0-7 days, Apgar score > 5-6, suspicion of sepsis, and hospitalization for at least 7 days. Exclusion criteria included perinatal asphyxia, shock, cardiopulmonary arrest, seizures, neurological disorders, and ear and renal anomalies.

After explaining the study protocol and obtaining written informed consent from parents, neonates were randomly (non-blinded) divided into two groups: group A (case) received gentamicin as a single daily dose of 5mg/kg, whereas in group B (control) it was administered twice daily as 2.5mg/kg/dose (based on similar studies).

Therapeutic effectiveness, nephrotoxicity, ototoxicity, and mortality rates were compared between groups. Therapeutic effectiveness was assessed by a single physician based on complete blood count (CBC), blood culture results, and clinical findings. Treatment duration was also compared.

Serum urea and creatinine levels were measured on day 1, 3, 7, and at treatment completion to assess nephrotoxicity. Otoacoustic emissions (OAE) and automated auditory brainstem response (AABR) tests were performed before treatment initiation and at treatment completion to assess ototoxicity. Neonates with abnormal baseline OAE or AABR were excluded to avoid bias. Confounding variables such as birth weight, gestational age, congenital infections, and age at infection onset were recorded. Neonates were under observation up to infection eradication and sepsis improvement. Data were analyzed using SPSS software, and using independent t-tests, and categorical variables using Chi-square tests. A p-value less than 0.05 was considered statistically significant.

## RESULTS

Of 112 neonates initially enrolled, 48 were excluded due to parental withdrawal, missing auditory tests at treatment completion, or clinical deterioration. A total of 64 neonates completed the study and were included in the analysis.

Demographic characteristics were comparable between groups (table 1). In group A, 52.6% were male, and in group B, 63.3% were male, with no significant difference ($p > 0.05$).

No significant differences were observed between groups in age, birth weight, admission weight, or maternal age ($p > 0.05$). According to Table 1, no significant difference was observed between the two groups in terms of age, birth weight, weight at admission, and maternal age ($P > 0.05$).

In group A, the mean serum urea concentration on days 1 and 3 was 22.16 and 15.80 mg/dL respectively with a t = 2.19 and degree of freedom (DOF) = 31, indicating a significant decrease based on independent samples t-test ($P = 0.01$). The same figures were 26.13 and 19.84 mg/dL in group B, t = 3.99 and DOF = 29, again revealing a significant decrease in the urea concentration by day 3 ($P = 0.001$). Table 2 compares the serum creatinine concentration at the studied time points.

Figure 1 demonstrates the changes in serum BUN concentration on day 1, 3, and 7 in the two studied groups. The mean serum urea level on day 7 was 33.50 and 31.50 mg/dL in group A and B, respectively. Mann-Whitney U test showed no statistically significant difference between the two groups in this respect ($p = 0.31$).

Mean changes in serum creatinine between days 1 and 3 were -0.38mg/dL in groups A and -0.18 mg/dL in group B ($t = -1.21$, DOF = 60; $p = 0.23$), indicating no significant difference.

Figure 2 illustrates serum creatinine levels over time.

**Table 1. The demographic data and independent samples t-test results of the two studied groups**

| Variable | Group | No. | Mean (SD*) | p-value |
|---|---|---|---|---|
| Age | A | 32 | 0.44 (1.095) | 0.41 |
| | B | 30 | 0.13 (0.44) | |
| Birth weight | A | 32 | 2860.78 (528.98) | 0.83 |
| | B | 31 | 2827.58 (707.81) | |
| Admission weight | A | 32 | 2860.78 (528.98) | 0.64 |
| | B | 29 | 2860.78 (706.20) | |
| Maternal age | A | 31 | 37.32 (2.62) | 0.70 |
| | B | 30 | 37.07 (2.61) | |

*SD: Standard deviation

**Table 2. Comparison of serum creatinine level between days 1 and 3 in the two studied groups**

| Group | Mean | No. | Mean Difference | Mean difference SE | p-value |
|---|---|---|---|---|---|
| **Group A** | | | | | |
| Day 1 | 1.07 | 32 | 0.38 | 0.91 | 0.02 |
| Day 3 | 0.69 | 32 | | | |
| **Group B** | | | | | |
| Day 1 | 0.88 | 30 | 0.18 | 0.23 | 0.001 |
| Day 3 | 0.70 | 30 | | | |

The difference in serum creatinine level between day 3 and day 1 is statistically significant in group A and B, respectively (p = 0.02, p = 0.001) (table 2). The mean value was 8.50 and 12.83mg/dL in the two groups, indicating no significant difference based on the Mann-Whitney U test (p = 0.13).

All neonates had normal OAE and AABR tests at baseline. At treatment completion, abnormal tests were observed in 6 neonates in group B (4 bilateral, 2 unilateral), while all neonates in group A had normal results. This difference was statistically significant (p = 0.012).

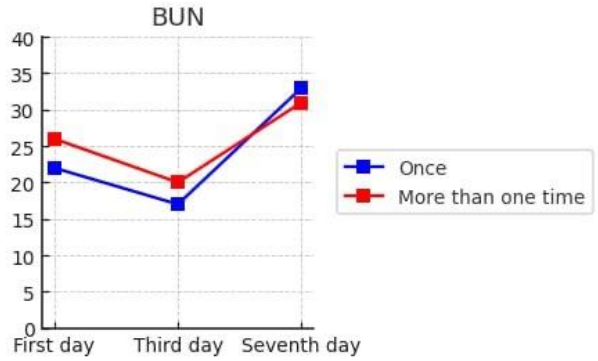


**Figure 1. Changes in serum BUN concentration on day 1, 3, and 7**

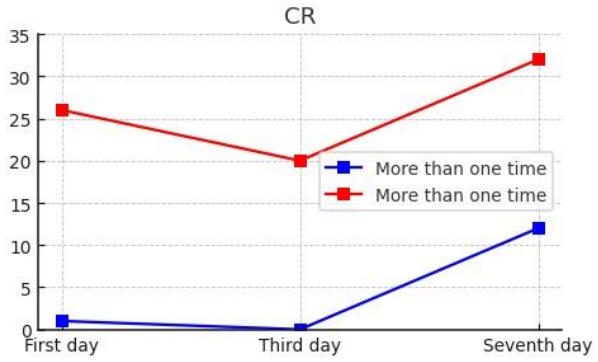


**Figure 2. Changes in serum creatinine level on day 1, 3, and 7**

## DISCUSSION

Gentamicin remains a mainstay in treating early neonatal sepsis, but its renal and auditory toxicities are major concerns. Renal toxicity is generally dose-and time-dependent and reversible, while auditory toxicity, mostly sensorineural, is often irreversible and assessed by AABR testing.

In this study, the two groups were similar in terms of gestational age, weight, and sex (Table 1). As mentioned before, the serum urea and creatinine concentrations reduced significantly from day 1 to day 3, whereas no such difference was observed between day 3 and day 7. Given that the toxic effect of gentamicin on the kidneys is evaluated by a rise in serum urea and creatinine concentration, it can be concluded that toxic renal effects were similar in the two groups and no unusual rise in these factors was observed in either group. The mean difference in urea and creatinine levels between days 1 and 3 was also insignificant between the two groups.

Given that the neonatal urea and creatinine level at birth and during hospitalization has a maternal origin and are similar to those of the neonate's mother, reduction at day 3 due to the improved neonate's renal function and its independent performance is quite predictable. Other studies have reported similar results in this respect (11-15).

The auditory complications of gentamicin are often ignored, whereas they are of great importance in the neonate's developmental period. The OAE test is used to study the conductive pathway up to the cochlea, whereas the AABR test is performed for studying the sensorineural route. No abnormal hearing test was observed in group A at the end of the treatment course. However, 6 neonates in group B had abnormal OAE and AABR tests, indicating a significant difference (P = 0.012). To date, most studies have been focused on gentamicin-related nephrotoxicity, while few studies have taken auditory complications into account or have reported no such complications at the end of their study course (15).

Our findings align with a study by Contopoulos-Ioannidis et al., which reported a lower risk of ototoxicity with extended-interval aminoglycoside dosing. This study similarly concluded that once-daily regimens produce higher peak concentrations (enhancing bactericidal effects) and lower trough levels (reducing cochlear accumulation), thereby lowering auditory risk (16).

However, some earlier studies, such as those by Langhendries et al., reported no detectable hearing impairment with either dosing regimen (17). Differences in study populations, diagnostic methods (absence of AABR in many studies), and follow-up duration may explain discrepancies. The present study provides additional evidence that twice-daily dosing may pose a higher risk of subclinical auditory toxicity, which may otherwise be missed without detailed audiological assessment.

## CONCLUSION

Despite no significant difference in gentamicin-induced nephrotoxicity between single and twice daily dosing, the ototoxic effects were notably lower with a single daily dose. This finding is particularly important given the irreversible nature of gentamicin-related hearing loss in neonates.

Additionally, administering gentamicin once daily is more cost-effective, requiring less time, fewer human resources, and less equipment. Future research with larger sample sizes and involving older neonates is recommended to confirm these findings. Monitoring gentamicin serum levels and therapeutic dosing should also be incorporated in subsequent studies.

## ACKNOWLEDGMENTS

We express gratitude to the Research and Technology Vice-Chancellery of Mashhad University of Medical Sciences, the Neonatal Intensive Care Unit (NICU) staff of Imam Reza Hospital, and the supervising and advisory faculty for their support. Special thanks to the Families who participated in this study.

**Informed Consent:** Written informed consent was obtained from the parents.

**Conflict of interest:** The authors declare no conflict of interest.

**Funding and Support:** This research received no funding/support.

## REFERENCES

1. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: When? Where? Why? Lancet 2005; 365:891-900.
2. Saving Newborn Lives. State of the world's newborns. Washington, DC: Save the Children Federation, 2001. 28 p.
3. Baqui AH, Darmstadt GL, Williams EK, Kumar V, Kiran TU, Panwar D et al. Rates, timing, and causes of neonatal deaths in rural India: implications for neonatal health programmes. Bull World Health Organ 2006;84:706-13.
4. Lawn J, Shibuya K, Stein C. No cry at birth: global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths. Bull World Health Organ 2005;83:409-17.
5. Stoll BJ. The global impact of neonatal infection. Clin Perinatol 1997;24:1-21.
6. World Health Organization. Management of the child with serious infection or severe malnutrition: guidelines for care at the first-referral level in developing countries. Geneva: World Health Organization, 2000:74-9. (WHO/FCH/CAH/00.1).
7. Stoll BJ. Neonatal infections: a global perspective (chapter 3). In: Remington JS, Klein JO, editors. Infectious diseases of the fetus and newborn infant. 5th ed. Philadelphia, PA: Saunders, 2001:139-68.
8. World Health Organization. Essential newborn care. Report of a Technical Working Group, Trieste, April 25-29, 1994. Geneva: World Health Organization, 1996. 19, p (WHO/FRH/MSM/96.13).http://www.alianzaipss.org/reproductivehealth/publications/MSM_96_13/MSM_96_13_Chapter1.en.html, accessed on 19 May 2008).
9. Sonntag J, Prankel B, Waltz S. Serum creatinine concentration, urinary creatinine excretion and creatinine clearance during the first 9 weeks in preterm infants with a birth weight below 1500 g. Eur J Pediatr 1996;155:815-9.
10. Vanpee M, Ergander U, Herin P, Aperia A. Renal function in sick, very low-birth-weight infants. Acta Paediatr 1993; 82:714-8.
11. Krishnan L, George SA. Gentamyicin therapy in preterms: a comparison of two dosage regimens. Indian Pediatr 1997; 34:1075-80.
12. Kasalaraksa P, Janthep P, Jirapradittha J, Taksaphan S, Kiatchoosakun P. Once versus twice dose of Gentamicin therapy in Thai neonates. J Med Assoc Thai 2004; 87(4): 372-6.
13. Solomon R, Kuruvilla KA, Job V, Selvakumar R, Jeyaseelan L, Kanagasabapathy AS, et al. Randomized controlled trial of once vs. twice daily gentamicin therapy in newborn. Indian Pediatr 1999; 36:133-7.
14. Chotigeat U, Narongsanti A, Ayudhya DP. Gentamicin in neonatal infection: once versus twice daily dosage. J Med Assoc Thai 2001;84:1109-15.
15. Kiatchoosakun P, Kosalaraksa P, Jirapradittha J, Taksaphan S, Tassniyom S. Once-daily gentamicin dosing of 4 mg/kg/dose in neonates. J Med Assoc Thai 2005;88:934-8.
16. Contopoulos-Ioannidis D, Giotis N, Baliatsa D, Ioannidis J. Extended-interval aminoglycoside administration for children: a meta-analysis. Pediatrics 2004;114(1):e111-8.
17. Langhendries J.P, Battisti O, Bertrand J M , Francois A , Darimont J , Ibrahim S , et al. Once-a-day administration of amikacin in neonates: assessment of nephrotoxicity and ototoxicity. Dev Pharmacol Ther. 1993;20(3-4):220-30.