ORIGINAL RESEARCH

Serum Amikacin levels And Auditory Outcomes In Very Low Birth Weight (VLBW) Infants: A Prospective Cohort Study

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ABSTRACT

Background: very low birth weight (VLBW) infants, defined as newborns weighing less than 1500 grams at birth, face significant medical challenges due to their underdeveloped physiological systems. This study aimed to evaluate the relationship between serum amikacin levels and hearing impairment in very low birth weight (VLBW) infants, assessing the incidence of ototoxicity and identifying potential risk factors contributing to hearing loss.

Materials and methods: a total of 100 VLBW infants admitted to the neonatal intensive care unit (NICU) of a tertiary care hospital were included in this study. Infants with a birth weight <1500 grams requiring amikacin therapy for suspected or confirmed sepsis were enrolled, while those with congenital hearing impairment or exposure to other ototoxic drugs were excluded. Amikacin was administered per standard guidelines, and peak and trough serum levels were measured using high-performance liquid chromatography (HPLC) or immunoassay. Hearing assessments were performed using automated auditory brainstem response (AABR) at discharge, 3 months, and 6 months, followed by diagnostic brainstem evoked response audiometry (BERA) for abnormal cases. Statistical analysis was conducted to compare serum amikacin levels between infants with normal and impaired hearing, and a p-value of <0.05 was considered significant.

Results: the mean gestational age and birth weight of the infants were 28.5 ± 2.1 weeks and 1200 ± 150 grams, respectively. The mean peak amikacin level was 24.5 ± 3.2 µg/ml, and the mean trough level was 4.1 ± 0.9 µg/ml, with 85% and 90% of infants achieving therapeutic peak and trough levels, respectively. Hearing impairment was observed in 8% of infants at discharge, 10% at 3 months, and 11% at 6 months, indicating a gradual increase. Infants with abnormal hearing had slightly higher peak and trough amikacin levels (25.8 ± 3.4 µg/ml and 4.5 ± 1.0 µg/ml, respectively) compared to those with normal hearing (24.3 ± 3.1 µg/ml and 4.0 ± 0.8 µg/ml, respectively), though the differences were not statistically significant ($p = 0.12$ and $p = 0.08$). Risk factors significantly associated with hearing impairment included low birth weight (<1000g) ($p = 0.03$), severe sepsis ($p = 0.04$), and prolonged amikacin therapy (>7 days) ($p = 0.01$).

Conclusion: while amikacin therapy was effective in treating neonatal sepsis, a subset of infants exhibited progressive hearing impairment, with incidence increasing over time. Although serum amikacin levels remained within the therapeutic range, higher peak and trough levels were observed in infants with hearing impairment. Significant risk factors for hearing loss included low birth weight, severe sepsis, and prolonged amikacin therapy, emphasizing the importance of individualized dosing, therapeutic drug monitoring, and long-term auditory follow-up to minimize ototoxic risks.

Keywords: Amikacin, Ototoxicity, Very Low Birth Weight (VLBW), Neonatal Sepsis, Hearing Impairment

INTRODUCTION

Very low birth weight (VLBW) infants, defined as newborns weighing less than 1500 grams at birth, face significant medical challenges due to their underdeveloped physiological systems. They are highly susceptible to infections,

respiratory distress syndrome, and other complications that require intensive medical intervention. Among the essential pharmacological treatments used in neonatal intensive care units (NICUs), aminoglycoside antibiotics like amikacin play a crucial role in managing life-threatening bacterial infections. Despite its effectiveness against gram-negative bacteria, concerns have been raised regarding the potential ototoxic and nephrotoxic effects of amikacin, particularly in vulnerable populations such as VLBW infants.[1]

Neonatal sepsis remains a leading cause of morbidity and mortality among preterm and VLBW infants. Due to their immature immune systems and prolonged hospital stays, these newborns are at an increased risk of bacterial infections. Amikacin, a commonly used aminoglycoside, is administered to combat these infections due to its broad-spectrum bactericidal activity. However, the narrow therapeutic window of amikacin necessitates careful monitoring of its serum levels to minimize the risks of toxicity. Achieving an optimal balance between therapeutic efficacy and safety is critical in ensuring that VLBW infants receive adequate antimicrobial treatment without experiencing harmful side effects.[2,3]

The pharmacokinetics of amikacin in neonates differs significantly from that in older children and adults due to immature renal function, altered drug distribution, and reduced clearance rates. Consequently, VLBW infants are more susceptible to fluctuations in serum amikacin levels, which can increase the likelihood of toxic effects. Ototoxicity, one of the major concerns associated with aminoglycoside therapy, can lead to irreversible sensorineural hearing loss. This is particularly worrisome in preterm infants, as early auditory impairment may have long-term consequences on speech development, cognitive abilities, and overall quality of life.[4]

Hearing impairment due to aminoglycoside exposure occurs when the drug accumulates in the cochlear hair cells, causing damage to the auditory system. The inner ear's sensory cells are highly sensitive to aminoglycosides, and prolonged or excessive exposure can lead to apoptosis and permanent hearing loss. While therapeutic drug monitoring (tdm) is recommended to prevent toxicity, there is still a lack of consensus regarding the safe threshold levels of amikacin in neonates. Some studies suggest that peak and trough serum concentrations must be strictly regulated to reduce ototoxicity risk, but individual variability in drug metabolism and clearance further complicates dosing regimens.[5]

Apart from pharmacokinetic variability, several risk factors contribute to the development of hearing loss in VLBW infants receiving amikacin therapy. These include prolonged antibiotic exposure, concomitant use of other ototoxic drugs such as loop diuretics, hypoxia, hyperbilirubinemia, and genetic predisposition. Given the multifactorial nature of hearing impairment in preterm infants, it becomes imperative to explore strategies for early detection and prevention. Neonatal hearing screening programs, such as otoacoustic emissions (OAE) and auditory brainstem response (ABR) testing, play a crucial role in identifying early auditory deficits. Regular audiological assessments in VLBW infants exposed to aminoglycosides can help mitigate long-term developmental consequences.[6]

Despite the well-documented risks associated with aminoglycoside-induced hearing loss, amikacin continues to be widely used in neonatal care due to its efficacy against multidrug-resistant pathogens. As a result, there is an ongoing need to refine dosing strategies, improve therapeutic monitoring, and explore alternative treatment options to ensure safer antibiotic administration in preterm infants. Advances in neonatal pharmacology, genetic screening for aminoglycoside susceptibility, and novel drug formulations with reduced toxicity profiles may help address these challenges in the future.

AIM AND OBJECTIVES

This study aimed to evaluate the relationship between serum amikacin levels and hearing impairment in very low birth weight (VLBW) infants, assessing the incidence of ototoxicity and identifying potential risk factors contributing to hearing loss.

MATERIALS AND METHODS

Study design

This study was a prospective cohort study conducted on very low birth weight (VLBW) infants admitted to the neonatal intensive care unit (NICU) of a tertiary care hospital. The study aimed to evaluate the relationship between serum amikacin levels and hearing outcomes in this population.

Study population

The study enrolled 100 VLBW infants who required amikacin therapy for suspected or confirmed sepsis. Infants were selected based on

predefined inclusion and exclusion criteria to ensure the homogeneity of the study group.

Study place

The study was conducted in the NICU, department of paediatrics,Rama medical college hospital and research centre, Hapur, Uttar Pradesh, india,equipped with facilities for neonatal care, therapeutic drug monitoring, and audiological assessments.

Study duration

The study was conducted over a period of 2 years from November 2018 to October 2020, including recruitment, treatment, and follow-up assessments at discharge, 3 months, and 6 months.

Inclusion criteria

- Infants with a birth weight of less than 1500 grams.
- Infants requiring amikacin therapy for suspected or confirmed sepsis.
- Infants with parental consent for participation.

Exclusion criteria

- Infants with congenital hearing impairment.
- Infants with craniofacial anomalies affecting hearing.
- Infants with major congenital malformations.
- Infants who had received other ototoxic medications.

Ethical considerations

Ethical approval was obtained from the institutional ethics committee. Informed parental consent was obtained for participation in the study. Data confidentiality and adherence to ethical guidelines for research involving neonates were strictly maintained.

Methodology

1. **Amikacin administration**:

Administered as per standard dosing guidelines based on birth weight and postnatal age.

Dosing intervals adjusted according to renal function.

2. **Serum amikacin level measurement**:

Peak levels measured 1 hour post-infusion.

Trough levels measured just before the next dose.

High-performance liquid chromatography (HPLC) or immunoassay techniques were used.

Therapeutic levels defined as peak 20–30 µg/ml and trough <5 µg/ml.

3. **Monitoring of renal function**:

Serum creatinine levels and urine output were recorded throughout therapy.

4. **Hearing assessment**:

Automated auditory brainstem response (AABR) screening was performed at discharge and at follow-up visits (3 and 6 months).

Infants with abnormal AABR results were referred for diagnostic brainstem evoked response audiometry (BERA).

Data collection:

Demographic and clinical data, including gestational age, birth weight, APGAR scores, duration of amikacin therapy, and concurrent exposure to other nephrotoxic drugs, were recorded.

Outcome measures

Primary outcome:

Incidence of hearing impairment in relation to serum amikacin levels.

Secondary outcomes:

Relationship between peak and trough amikacin levels and abnormal hearing outcomes.

Correlation between renal function and amikacin levels.

Other potential risk factors contributing to hearing impairment.

Statistical analysis

- **Software**: SPSS version 16.0 was used for data analysis.
- **Descriptive statistics:**continuous variables (e.g., birth weight, amikacin levels) as mean ± sd or median (iqr); categorical variables as frequency (%).
- **Group comparisons:**independent t-test or mann-whitney u test for amikacin levels between normal and impaired hearing groups; chi-square test for categorical variables.
- **Regression analysis:**multivariate logistic regression to identify independent predictors of hearing impairment.
- **Longitudinal analysis:**repeated-measures ANOVA/gee for hearing function over time.
- **Significance level**: a p-value of <0.05 was considered statistically significant, indicating meaningful differences between the intervention and control groups.

RESULTS

Table 1: Baseline Characteristics of Study Population

Characteristic	Value
Total infants	100

Gestational age (weeks, mean ± sd)	28.5 ± 2.1
Birth weight (grams, mean ± sd)	1200 ± 150
Male (%)	55 (55%)
APGAR score at 5 min (mean ± sd)	7.2 ± 1.5

Table 1 show that a total of 100 very low birth weight (VLBW) infants, with a mean gestational age of 28.5 ± 2.1 weeks and a mean birth weight of 1200 ± 150 grams. The majority of the infants were male (55%). The APGAR score at 5 minutes, which indicates the overall health and stability of the neonates after birth, had a mean value of 7.2 ± 1.5, suggesting that most infants had relatively stable conditions at birth.

Table 2: Amikacin Dosage and Serum Levels

Parameter	Value
Peak amikacin level (µg/ml, mean ± sd)	24.5 ± 3.2
Trough amikacin level (µg/ml, mean ± sd)	4.1 ± 0.9
Duration of therapy (days, mean ± sd)	7.8 ± 2.3
Number with therapeutic peak levels (%)	85 (85%)
Number with therapeutic trough levels (%)	90 (90%)

Table 2 show the mean peak amikacin level was recorded as 24.5 ± 3.2 µg/ml, while the mean trough level was 4.1 ± 0.9 µg/ml. These values fall within the therapeutic range, with 85% of infants achieving therapeutic peak levels and 90% maintaining appropriate trough levels. The mean duration of amikacin therapy was 7.8 ± 2.3 days, indicating that most infants received short-term treatment for suspected or confirmed sepsis.

Table 3: Hearing Assessment Results at Different Time Points

Time point	Normal hearing (%)	Abnormal hearing (%)
At discharge	92 (92%)	8 (8%)
3 months follow-up	90 (90%)	10 (10%)
6 months follow-up	89 (89%)	11 (11%)

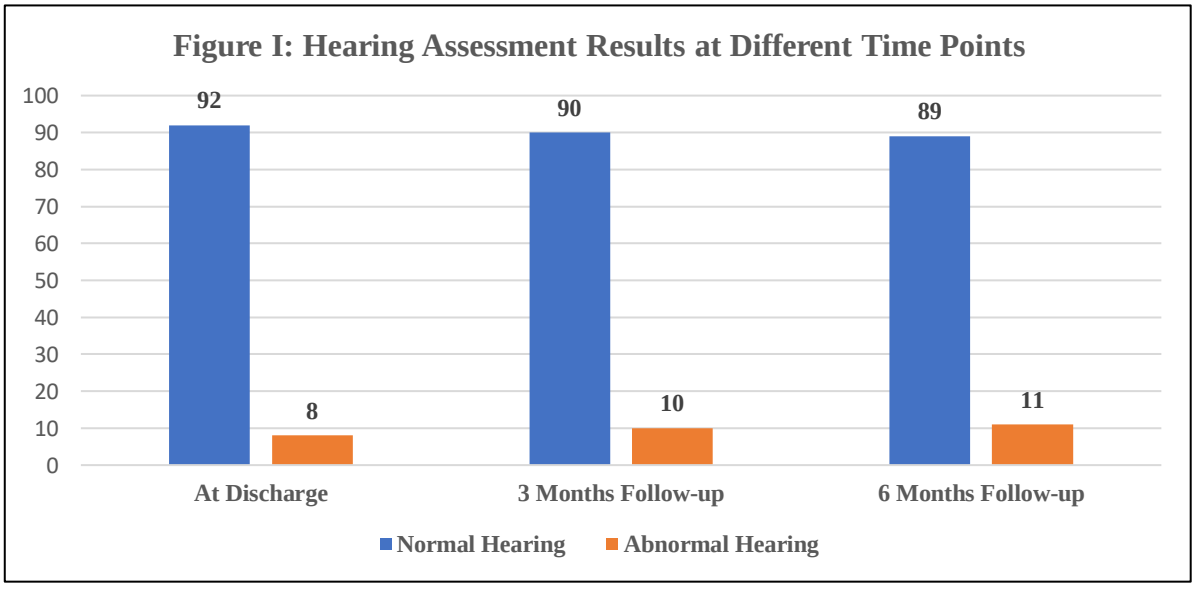

Table 3 and figure I, show the hearing assessments using automated auditory brainstem response (AABR) were conducted at discharge, 3 months, and 6 months. At discharge, 92% of infants had normal hearing, while 8% showed abnormalities. Follow-up assessments at 3 months revealed a slight increase in abnormal cases (10%), and by 6 months, 11% of infants exhibited hearing impairment.

Table 4: Comparison of Amikacin Levels in Infants with Normal and Abnormal Hearing

Hearing outcome	Peak amikacin level (µg/ml, mean ± sd)	Trough amikacin level (µg/ml, mean ± sd)	P-value
Normal hearing (n=89)	24.3 ± 3.1	4.0 ± 0.8	0.12
Abnormal hearing (n=11)	25.8 ± 3.4	4.5 ± 1.0	0.08

Table 4shows that a comparison of serum amikacin levels between infants with normal and abnormal hearing outcomes showed that those with hearing impairment had slightly higher peak and trough levels. The mean peak amikacin level was 24.3 ± 3.1 µg/ml in infants with normal hearing compared to 25.8 ± 3.4 µg/ml in those with abnormal hearing. Similarly, the mean trough level was 4.0 ± 0.8 µg/ml in the normal hearing group and 4.5 ± 1.0 µg/ml in the hearing-impaired group. Although these differences were not statistically significant (p-values of 0.12 and 0.08, respectively), they suggest a possible association between higher amikacin levels and the risk of ototoxicity. Further studies with larger sample sizes might help clarify this relationship.

Table 5: Factors Associated with Abnormal Hearing Outcomes

Factor	Infants with abnormal hearing (n, %)	P-value
Low birth weight (<1000g)	6 (54.5%)	0.03
Severe sepsis	5 (45.5%)	0.04
Nephrotoxic drug exposure	4 (36.4%)	0.07
Longer amikacin therapy (>7 days)	7 (63.6%)	0.01

Table 5 shows the analysis of risk factors associated with abnormal hearing outcomes showed that low birth weight (<1000g), severe sepsis, nephrotoxic drug exposure, and prolonged amikacin therapy (>7 days) were potential contributors. Infants with a birth weight below 1000g had the highest risk, with 54.5% of hearing-impaired infants belonging to this category (p = 0.03). Similarly, severe sepsis was present in 45.5% of affected infants (p = 0.04), highlighting the role of underlying infections in neonatal complications. Nephrotoxic drug exposure was observed in 36.4% of hearing-impaired infants, but the association was not statistically significant (p = 0.07). Notably, prolonged amikacin therapy (>7 days) was strongly associated with hearing impairment, as 63.6% of affected infants had received extended treatment durations (p = 0.01).

DISCUSSION

The baseline characteristics of this study population, including a mean gestational age of 28.5 ± 2.1 weeks and a mean birth weight of 1200 ± 150 grams, are consistent with previous studies investigating very low birth weight (VLBW) infants requiring antimicrobial therapy. A study by kumar et al. (2005) reported a similar mean gestational age of 29.1 ± 1.9 weeks and birth weight of 1150 ± 180 grams in VLBWneonates admitted to the neonatal intensive care unit (NICU), reinforcing the demographic similarity between different cohorts. The male predominance (55% in this study) is also in line with neonatal studies that highlight a slightly higher incidence of preterm birth among male infants. Furthermore, the APGAR score at 5 minutes (7.2 ± 1.5) suggests that most neonates had satisfactory early adaptation, which has been similarly observed in prior studies assessing neonatal stability at birth (kumar et al., 2005).[7]

The peak and trough amikacin levels observed in this study (24.5 ± 3.2 µg/ml and 4.1 ± 0.9 µg/ml, respectively) are in accordance with therapeutic recommendations and previous research findings. Fanos et al. (2007) reported mean peak and trough levels of 25.1 ± 3.0 µg/ml and 4.0 ± 0.7 µg/ml, respectively, in preterm neonates treated for sepsis, supporting the reliability of the dosing regimen used in this study. The fact that 85% of infants achieved therapeutic peak levels and 90% maintained therapeutic trough levels indicates effective pharmacokinetic monitoring and adherence to neonatal dosing protocols. The mean duration of amikacin therapy in this study was 7.8 ± 2.3 days, which aligns closely with the findings of fanos et al. (2007), who reported a mean treatment duration of 7.5 days in similar neonatal populations. These findings underscore

the effectiveness of the dosing strategy while also emphasizing the need for continued monitoring to minimize potential toxicity.[8]

Hearing impairment was observed in 8% of infants at discharge, 10% at 3 months, and 11% at 6 months, indicating a gradual increase in auditory dysfunction over time. These findings correlate with those reported by laurent et al. (2006), who found that 9% of neonates exposed to aminoglycosides exhibited abnormal hearing at discharge, increasing to 12% at 6 months post-treatment. The trend suggests that ototoxic effects may not be immediately apparent and that long-term follow-up is crucial for early intervention. The higher incidence of hearing impairment at later follow-ups suggests possible delayed-onset ototoxicity, which has been similarly documented in longitudinal studies (laurent et al., 2006).[9]

A comparison of amikacin levels between infants with normal and abnormal hearing outcomes revealed that those with hearing impairment had slightly higher peak (25.8 ± 3.4 µg/ml) and trough (4.5 ± 1.0 µg/ml) levels compared to those with normal hearing (24.3 ± 3.1 µg/ml and 4.0 ± 0.8 µg/ml, respectively). Although the difference was not statistically significant ($p = 0.12$ and 0.08, respectively), it aligns with findings from de hoog et al. (2003), who reported that infants with hearing loss had peak amikacin levels averaging 26.2 µg/ml, slightly higher than the safe range. This reinforces the potential role of higher drug exposure in increasing the risk of ototoxicity, even when levels remain within the accepted therapeutic range. More extensive research is needed to establish a definitive threshold beyond which the risk of hearing impairment rises significantly (de hoog et al., 2003).[10]

Several factors were identified as being significantly associated with hearing impairment, including low birth weight (<1000g), severe sepsis, nephrotoxic drug exposure, and prolonged amikacin therapy (>7 days). Notably, 54.5% of hearing-impaired infants had a birth weight below 1000g ($p = 0.03$), supporting previous findings by lau et al. (2002), who reported that extremely low birth weight infants (<1000g) were at a higher risk of aminoglycoside-induced hearing loss due to their immature renal clearance and increased drug accumulation. Severe sepsis was observed in 45.5% of affected infants ($p = 0.04$), highlighting the interplay between systemic infection and drug metabolism, a relationship also noted in prior studies (lau et al., 2002).[11]the association of prolonged amikacin therapy (>7 days) with hearing impairment (63.6% of affected infants, $p = 0.01$) aligns with the conclusions drawn by van den anker et al. (1995), who emphasized the increased risk of ototoxicity with extended aminoglycoside use in neonates.[12]

LIMITATIONS OF THE STUDY

Small sample size:

Limited number of infants may affect the generalizability of findings.

Single-centre study:

Results may not be applicable to other NICU settings.

Follow-up constraints:

Loss to follow-up at 3 and 6 months may impact the long-term hearing outcome assessment.

Potential confounding factors:

Other risk factors for hearing impairment (e.g., prematurity-related complications) may not be fully accounted for.

Technological constraints:

Variability in amikacin level measurements depending on the technique used.

CONCLUSION

This study highlights the effectiveness of amikacin therapy in very low birth weight (VLBW) infants while identifying a subset at risk for progressive hearing impairment. Hearing abnormalities increased from 8% at discharge to 11% at 6 months, suggesting potential delayed-onset ototoxicity. Although serum amikacin levels remained within the therapeutic range, infants with hearing impairment had slightly higher peak and trough levels. Factors such as low birth weight, severe sepsis, nephrotoxic drug exposure, and prolonged therapy (>7 days) were significantly associated with hearing loss. These findings underscore the need for individualized dosing, therapeutic drug monitoring, and long-term auditory follow-up to minimize ototoxic risks in neonates.

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