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ORIGINAL ARTICLE

Serum Amikacin Levels And Hearing In Very Low Birth Weight (VLBW) Infants

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ABSTRACT

Objectives: To assess hearing in the very low birth weight infants receiving amikacin for 7 and 14 days; and to study the relationship of serum amikacin levels with hearing. **Study design**: Single Centre, Non Randomized Prospective Parallel Group, Assessor Blind Study. **Setting**: Tertiary care neonatal unit of a teaching hospital. **Participants**: 30 VLBW infants who received amikacin for 7 days, 30 VLBW infants who received amikacin for 14 days and 30 VLBW infants who did not receive amikacin. None had any other risk factor for hearing impairment. **Intervention**: Amikacin administration as per their setting of indication. **Outcome measures**: Serum amikacin levels and hearing assessment. **Results:** Mean trough serum amikacin level (µg/ml) was 6.85±2.49 in 7 days amikacin group; and 15.2±3.41 in 14 days amikacin group. Mean peak serum amikacin level (µg/mL) was 14.5±3.16 in 7 days amikacin group; and 24.8±3.95 in 14 days amikacin group. All were normal on hearing assessment. **Conclusion:** Use of amikacin is safe in VLBW infants in therapeutic dosages in the absence of any other risk factors for hearing impairment and the monitoring of serum amikacin levels is advisable but not mandatory.

Key Words: Hearing assessment, Amikacin, VLBW infants.

Key Message:
Administration of Amikacin to the Very Low Birth Weight Babies in Therapeutic Dosages is Safe in the Absence of Any Other Risk Factors of Hearing Impairment.

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Introduction

With the modernization and advances in NICU care, more and more low birth weight babies are surviving. Various centers in the country report survival of Very Low Birth Weight (VLBW) babies up to 80% and survival of Extremely Low Birth Weight (ELBW) babies up to 50%. These babies are frequently exposed to aminoglycosides such as amikacin which is not completely metabolized in the body and may cause irreversible ototoxicity, including sensory neural hearing loss (SNHL) [1]. Monitoring of serum amikacin levels is not a priority and also not practically feasible. There is scarcity of data published on hearing evaluation in babies receiving amikacin.

Methods

The study was carried out in a major teaching institution and general hospital which is a major referral center for high risk deliveries with a tertiary level Neonatal Intensive Care

Unit in collaboration with National Institute for Hearing Impaired, from November 2006 to October 2007. The approval from the institutional Human Ethics Committee was obtained prior to the study. Informed consent from parents of the infants was taken.

It was a Single Centre, Non Randomized Prospective Parallel Groups, Assessor Blind Study. VLBW infants admitted in NICU who received amikacin for a period of >5 days during neonatal period were included. Those with family history of hereditary childhood sensorineural hearing loss; In utero infection, such as cytomegalovirus, rubella, syphilis, herpes, or toxoplasmosis; craniofacial anomalies, including those with morphological abnormalities of the pinna and ear canal; hyperbilirubinemia at a serum level requiring exchange transfusion; ototoxic medications, other than amikacin; bacterial meningitis; APGAR scores of 0- 4 at 1 minute or 0 - 6 at 5 minutes; mechanical ventilation lasting 5 days or longer; and stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss, were excluded. [2],[3].

Sample size: We included 30 VLBW infants in each of the 3 groups. This estimate was based on the hypothesis that amikacin exposure increases the risk of hearing impairment by 10 times. Taking background incidence of hearing impairment as 3% based on the result of previous study in our unit, α error of 0.05, β error of 0.2 and power of 80%, the sample size was calculated as 26 for each group. For statistical significance, the sample size of 30 in each group was felt adequate.

Ninety VLBW infants admitted in NICU were included in the study after taking informed written consent from the parents. A detailed clinical history and examination was recorded on a predesigned proforma. Three groups of 30 neonates each were formed. The first 2 groups included neonates who received amikacin for a period of 7 days and 14 days respectively. The third group which consisted of those VLBW infants who neither received amikacin nor had any risk factor for hearing impairment, served as control. The neonates received amikacin, being the first line antibiotic as per the unit policy with predefined dose and duration (7.5mg/kg/dose 12 hourly amongst 7days amikacin group and 7.5mg/kg/dose 12 hourly within 1st week then 8 hourly during 2nd week among 14 days amikacin group). The neonates born to mothers with intrapartum risk factors for sepsis, were started on antibiotics and subjected to sepsis work up. They were subsequently classified as probable sepsis and proved sepsis (blood culture reported positive) and were treated for 7 or 14 days amikacin groups respectively. No baby was given medication for the study purpose nor was the duration of medication changed. Amikacin recipients were subjected to estimation of serum amikacin levels. Samples for estimation were collected on day 7 or da714 of amikacin therapy from 7days and 14 days amikacin groups respectively. The babies in 7 days amikacin group were on 12 hourly dose and babies in 14 days amikacin group were on 8 hourly dose at the time of estimation of serum amikacin levels. Three ml of venous blood sample was drawn in heparinised container under all aseptic precautions, 1hr after administration of standard recommended dose (peak level) and within 30 min of expected next dose (trough level); and sent to Clinical Pharmacology Laboratory at 4-8°C, for estimation of serum amikacin level by HPLC (High Performance Liquid Chromatography). [4],[5] The infants were subjected to renal function assessment every 3rd day during amikacin treatment in both the groups, and only once in control group as routine work up.

Hearing assessment was done in NICU within 14 days following amikacin course completion and at 2 months follow up, by screening Brainstem Evoked Response Audiomentry (BERA) & screening Otoacoustic Emission (OAE)

Clinicians performing serum amikacin estimations and hearing assessment were blinded. Comparison of hearing assessment was done among the groups. Statistical tests used were paird t test, χ^2 test and ANOVA as applicable.

Results

There was no statistically significant difference between the 2 amikacin treated groups in terms of baseline neonatal & maternal characteristics [Table/Fig I], Both peak and trough mean serum amikacin levels, were significantly higher ($p<0.0001$) in 14 days amikacin group as compared to 7 days amikacin group who were on 12 hourly dose till day 7 of life.

[Table/Fig 1]: Comparison of Neonatal Topography among the 3 groups

Features	Control (%)	7days amikacin (%)	14days amikacin (%)	P value (ANOVA test)
Mean(SD) Birth Weight (g)	1304	1311	1313	0.96
Mean (SD) Gestational age (wk)	33.9	33.53	33.95	0.83
SGA	14(46.67)	12(40)	14(46.67)	0.83
Male	16(53.33)	12(40)	23(66.67)	0.01

[Table/Fig 2]: Comparison of Serum Amikacin levels between 7days and 14days amikacin groups

Serum Amikacin (µg/ml)	7days amikacin	14days amikacin	P value (t test)
Trough Levels:			
Mean (SD)	6.85 (2.49)	15.2	0.0001
Range	2.26-12.5	7.25-20.2	
Peak Levels:			
Mean (SD)	14.5	24.8	0.0001
Range	9.22-21.6	16.3-30.7	

(Normal range for trough levels of serum amikacin: 5-10µg/ml and normal range for peak levels of serum amikacin: 15-30µg/ml)

[Table/Fig 2] Infants of all the 3 groups had normal hearing screening with BERA and OAE at discharge and at 2 months. There was no statistically significant difference among the 3 groups in terms of renal function tests. (p>0.05 on ANOVA)

Discussion

The effect of aminoglycoside therapy on hearing (in NICU graduates) has been the area of interest over the years. The studies conducted by various researchers have shown positive correlation of aminoglycoside exposure and hearing impairment.[6],[7],[8] However these studies have not documented the serum drug levels and other risk factors for hearing impairment, which our study did. McDonald et al detected the incidence of hearing loss as 10.7% in neonates receiving streptomycin, 5.8% in those receiving other antibiotics and only 0.6% in whom the antibiotics were not given. [6] Bernard et al found higher latencies in aminoglycoside treated neonates. [7] Ito H reported statistically significant prolongation of I-V interpeak latency on ABR in those infants who received phototherapy and aminoglycoside antibiotics. [8]

However in the present study we had ruled out all the confounding factors in neonates to get the cleanest possible sample to study the effect of amikacin only. Our study brings out the fact that the use of amikacin in therapeutic dosages is safe in VLBW infants without any other risk factor for hearing impairment. But it was observed that in 14 days amikacin group the mean peak and trough serum amikacin levels were towards the upper limit of normal range as compared to 7 days amikacin group. This statistically significant difference in mean serum amikacin levels may be due to the difference in frequency of amikacin administration between the 2 groups at the time of serum amikacin estimation.

Conclusion

In VLBW infants in absence of any other risk factors for hearing impairment the use of amikacin in therapeutic dosages for 14 days is safe. Monitoring serum drug levels is advisable but not mandatory.

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