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Risk of hearing loss in children exposed to gentamicin for the treatment of sepsis in young infancy: A community based cohort study in Pakistan

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Abstract

Objective: To determine the safety of gentamicin when used in a community setting to treat neonatal sepsis.

Methods: The study was conducted in peri-urban areas of Karachi from September 2009 to April 2010. The exposed group consisted of children 6 months to 3 years of age who were treated for sepsis during 0-2 months of age in the community, with a regimen that included gentamicin for at least five days. The control group included children from the same area who never received gentamicin. The outcome measure was hearing loss, which was assessed by Brainstem Evoked Response Audiometry.

Results: Of the 255 children enrolled, 125 (49%) received gentamicin, while 130 (51%) were not exposed to gentamicin. Children in the gentamicin exposed group were not at increased risk for hearing loss compared to controls (n=30; 30.9% vs. n=33; 31.4%, RR 0.98; 95% CI: 0.60-1.61). Children with history of ear discharge (RR 1.7) and children with family history of deafness (RR 2.0) were more at risk for having hearing loss.

Conclusion: No association was found between hearing loss and gentamicin exposure in a community setting for the management of sepsis in the first two months of life.

Keywords: Aminoglycoside, Gentamicin, Ototoxicity, Community management, Sepsis, Neonate. (JPMA 63: 1226; 2013)

Introduction

Infections account for 26-36% of all neonatal deaths worldwide.^{1,2} Current World Health Organisation (WHO) recommendation for the treatment for sepsis in infants younger than two months include hospitalisation and parenteral therapy with antibiotic regimens containing penicillin or ampicillin combined with an aminoglycoside.³ These recommendations are inadequately followed in developing countries as most births take place at home, and families of sick newborns are unable to access hospital care because of inefficient health systems, socioeconomic, logistic and cultural constraints.⁴⁻⁷ Many of these infants die at home without receiving any therapy. The Millennium Development Goal (MGD) for child survival cannot be attained without substantial decrease in infection-specific neonatal mortality.⁸ Thus approaches for detecting and managing serious infections within the community, at home or first-level health facilities are increasingly being explored in settings where there are delays, reluctance and constraints in seeking secondary or tertiary level care.⁹

The evidence for effectiveness of community-based treatment of neonatal sepsis is accumulating.¹⁰ Bang et al showed a 29% decline in the neonatal mortality in rural India by administering home-based oral cotrimoxazole,

and intramuscular gentamicin to newborns with sepsis by village health workers.¹¹ A 34% reduction in neonatal mortality was observed in Bangladesh by treatment of neonatal sepsis with procaine penicillin and injection gentamicin at home by community health workers.¹² A study of community management of suspected neonatal sepsis in Pakistan showed almost 86% success rate using 3 different antibiotic regimens, two of which included injection gentamicin.⁹

Although community use of injection gentamicin is effective for neonatal sepsis, its safety in these settings has not been clearly established. Moreover, there are concerns that indiscriminate use could lead to serious ototoxicity in such environments, especially if minimally-trained health workers are responsible for treatment decisions and drug administration. A Cochrane review compared the results of four studies which assessed hearing impairment caused by gentamicin use in neonates in hospital settings. Three of these studies showed no hearing impairment, but in one study, two out of 13 neonates developed hearing impairment.¹³ However, all the studies regarding safety of gentamicin in neonates were conducted in hospitalised children and the question of its safety when used at large scale in community settings remains unanswered. The current study sought to determine the risk of hearing loss associated with gentamicin exposure in the first 60 days of life when gentamicin was used for community-based management of sepsis where referral had failed.

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Patients and Methods

The retrospective cohort study was conducted from September 2009 to April 2010 in peri-urban coastal areas of Karachi. These are socio-economically depressed areas with fishing and livestock rearing as the major income-generating activities. The Aga Khan University's (AKU) primary healthcare centre is the major healthcare provider for children.

The primary objective was to determine the risk of hearing loss associated with gentamicin exposure in the first 60 days of life in children compared to those who had never received gentamicin. The exposed study population consisted of children who had previously been treated for sepsis at the area primary care clinics run by the AKU's Department of Paediatrics and Child Health with a regimen that included gentamicin. Sepsis had been diagnosed by study physicians using pre-defined clinical criteria¹⁴ and the infants received injectable procaine penicillin and gentamicin (dose 5 mg/kg once daily) for 7 days if the family refused facilitated referral. Antibiotics were administered by study physicians. Young infants with meningitis had been treated with ceftriaxone, and these children were excluded from the exposed population as they had not received gentamicin.

Data for gentamicin exposed and non-exposed groups of infants were taken from the records of these clinics. Inclusion criteria in the gentamicin exposed group comprised infants who were given injection gentamicin in the dose of 5mg/kg in the first 60 days of life for at least 5 days, at least 6 months prior to enrollment in the study. Inclusion criteria in the gentamicin non-exposed group comprised infants who had never received gentamicin, and in whom complete records of treatment received at the relevant health centres were available. Children were excluded if they had any congenital anomaly, were having ear discharge at the time of study, or if they had received injection gentamicin outside the neonatal sepsis management programme. Crude relative risks (RR) with 95% confidence intervals (CI) were calculated using Cox proportional hazard regression algorithm in order to observe associations between outcome and other independent variables at univariate level. Multivariable analysis was done using the same algorithms by calculating adjusted relative risks (ARR) with 95% CI.

After informed consent, baseline characteristics of the participants were recorded using standard questionnaires, and hearing was assessed using Brainstem Evoked Response Audiometry (BERA) test. BERA was conducted at the neurophysiology laboratory at the Aga Khan University Hospital (AKUH), where it was interpreted by trained neurophysiologists. The hearing

loss, if present, was classified as mild (15-30 db), moderate (31-60 db) or severe (>61 db). The study was approved by the institutional ethics review committee.

The risk of hearing loss in children in Asia is reported as 4.64/1000.¹⁵ It was hypothesised that gentamicin exposure in the first 60 days of life causes hearing loss in 10% of exposed Pakistani children. Assuming the risk of hearing loss in gentamicin exposed and non-exposed children as 10% and 0.46% respectively, with level of significance of 0.05 achieved a power of 80 per cent for a minimum of 104 children in each of the exposed and non-exposed group. An anticipated non-response rate in each group was assumed as 10%, so we planned to enroll 115 children in each group.

Results

A total of 255 children were enrolled; 125 (49%) in the gentamicin exposed group, and 130 (51%) in the non-exposed group to account for the higher than expected refusal rate for BERA. BERA was done in 97 (77.6%) gentamicin exposed children, and in 105 (80.7%) non-exposed children. The baseline socio-demographic and clinical characteristics in the two groups were noted (Table-1).

Some degree of hearing loss was detected in 30 (30.9%) children in gentamicin exposed group and in 33 (31.4%) children in the non-exposed group. In the former group, 15 (15.4%) of the 97 children had mild hearing loss, 14(14.4%) had moderate, and 1(1.0%) child had severe

Table-1: Baseline socio-demographic and clinical factors in children of gentamicin exposed and non-exposed group.

	Gentamicin exposed (n=97)	Gentamicin non-exposed (n=105)
Age in months (mean±SD)	14.0 ± 7.0	18.0 ± 7.0
Male (n, %)	56 (57.7)	55(52.4)
Consanguinity (n,%)	47(48.5)	47(44.8)
Family history of hearing loss (n, %)	28(28.9)	24(22.9)
Relative with history of hearing loss		
- Immediate relative (n, %)	8(28.6)	13(54.2)
- Maternal relative (n, %)	7(25.0)	4(16.6)
- Paternal relative (n, %)	13(46.4)	7(29.2)
Preterm Birth (n,%)	3(3.1)	1(1.0)
History of delayed cry after birth (n, %)	10(10.3)	10(9.5)
History of neonatal jaundice (n, %)	35(36.1)	33(31.4)
History of ear discharge (n, %)	22(22.7)	31 (29.5)
Care taker's perception of hearing loss (n, %)	5(5.2)	4(3.8)
Age (in months) at which child started startling (median(IQR))	6(5,6)	6(5,6)
Age (in months) at which child started recognizing voice (median (IQR))	6(5,6)	6(6,6)

IQR: Interquartile range.

Table-2: Multivariable analysis showing association of variables with hearing loss in gentamicin exposed and non-exposed children.

Model variable	Adjusted Relative Risk (ARR)	95% confidence interval
Gentamicin exposure	1.05	0.63 - 1.75
Previous history of ear discharge	1.79	1.08- 2.98
Hearing loss in immediate relatives	2	1.02- 3.95
Hearing loss in maternal relatives	2.73	1.27 - 5.87
Hearing loss in paternal relatives	0.89	0.35 -2.28

hearing loss. In the non-exposed group, 17(16.1%) of the 105 children had mild, 13(12.3%) had moderate, and 3(2.8%) had severe hearing loss.

At the univariate level of analysis, children with exposure to gentamicin during early infancy were not at increased risk for hearing loss (RR 0.98; 95% CI: 0.60-1.61). Children with a family history of hearing loss ($p < 0.008$; RR: 1.78; 95% CI: 1.07- 2.95), history of previous ear discharge ($p < 0.004$; RR: 1.85; 95% CI: 1.12=3.06), and whose caretakers perceived that their child had difficulty in hearing ($p < 0.03$; RR: 2.26; 95% CI: 0.97=5.24) were more likely to have hearing loss compared to the comparison group. Risk of hearing loss was also higher in children who had history of neonatal jaundice ($p < 0.06$; RR: 1.48; 95% CI: 0.89=2.43), but was not statistically significant. None of the other variables such as age, gender, mothers' education, consanguinity etc. showed significant association with hearing loss at univariate level. Therefore, the final model describing the risk of hearing loss in children comprised gentamicin exposure, history of ear discharge and relative with hearing loss (Table-2). Using a multiple logistic regression model controlling for confounders, history of ear discharge (RR 1.79; 95% CI: 1.06=2.98), history of hearing loss in immediate relatives (RR 2.0; 95% CI: 1.09=4.16) and children having history of hearing loss in maternal relatives (RR 2.7; 95% CI: 1.23=5.87) retained their significance as independent risk factors for hearing loss, while exposure to gentamicin (RR 1.05; 95% CI: 0.63=1.75) continued to be non-significant risk factor for hearing loss.

Discussion

The study did not find an association between hearing loss and gentamicin exposure for the management of sepsis in the first two months of life. This finding was consistent with results of other studies conducted in hospitalised children.¹⁶ In a four-year randomised controlled trial comparing the hearing ability in neonates treated with gentamicin or kanamycin, no difference was found in auditory function between gentamicin or kanamycin treatment and control group.¹⁷ However, these prior studies were hospital-based, and their results may not be applicable for community level use of

gentamicin. Our study is the first to show safety of gentamicin with regards to ototoxicity when gentamicin is used in community settings to treat neonatal sepsis.

A striking 31% of study participants were found to have hearing loss. While there are no national estimates from Pakistan, investigators in the UK have reported a 3.5 times higher prevalence of hearing loss in Asian children (Pakistani, Indian and Bangladeshi) compared to non-Asian children (4.64/1000 vs. 1.33/1000 live births).¹⁵ Elahi et al showed 7.9% prevalence of hearing loss in children of rural Pakistan, but hearing loss was determined by audiometry, not BERA which is a more sensitive tool to detect sensorineural hearing loss.^{18,19} To the best of our knowledge, this is the first community-based study in Pakistan to measure hearing loss with the help of BERA.

The etiology of hearing loss in children could be genetic, acquired or a combination of the two. Untreated middle ear infections are an important cause of acquired hearing loss, and the study found that children with history of ear discharge, presumed to be most likely due to middle ear infections, were 1.85 times more likely to have hearing loss compared to other children. Genetics is also likely to be playing a major role in the high prevalence of hearing loss seen in the study. Children whose parents or sibling had hearing loss were at 1.78 fold increased risk (95% CI: 1.07, 2.95) of having hearing loss. A study in UK also found that positive family history of deafness was more common in Pakistani children with deafness compared to white children (66.4% vs. 38.8%).²⁰ Genetically transmitted hearing loss can be syndromic, i.e., combined with other conditions, or non-syndromic. In non-syndromic forms, which occur in about 70% of cases of hereditary hearing loss, deafness can be inherited by mitochondrial transmission, i.e., via the mother lineage.²¹ We observed that children whose maternal relative had hearing loss were at highest risk (2.82 fold) for having hearing loss. This might be due to the fact that the majority of the respondents in our study were children's mothers who may have had better recall for their relatives with hearing loss compared to paternal relatives, and so hearing loss in paternal relatives did not come out as a risk factor. Alternatively, this could be due to mutations in mitochondrial genome, which is maternally inherited. There is a need for better understanding of the genetic causes of hearing loss in children in Pakistan so that appropriate genetic counselling could be done, especially given the high rate of consanguinity.²²

The study assessed hearing impairment in children by BERA, which has 100% sensitivity and 88% specificity.¹⁹ Results of BERA were interpreted by neurophysiologists

who were not aware of gentamicin exposure status of the children. We used the data of neonatal sepsis management programme for the identification of gentamicin exposed and non-exposed groups. Thus, the ascertainment of exposure was reliable as it was not self-reported. Gentamicin dosage given to study participants was the WHO recommended dose.

Although gentamicin use was not associated with hearing loss in our study, but we would be cautious in assuming generalisability of these findings. Our study was conducted in a research setting, where accurate dosing of gentamicin was ensured by physicians. In programmatic settings, if workers are not trained and monitored, newborns may be exposed to inadvertent high doses which may result in ototoxicity. High prevalence of hearing loss in South Asian population makes it advisable to develop sensitive and specific diagnostic tools for the diagnosis of sepsis by minimally trained health workers so that unnecessary gentamicin use can be avoided. The other important finding is the presence of hearing loss in 31% of the children studied. Further research is recommended to find and address the causes behind this high prevalence, as hearing loss in early childhood often remains undiagnosed and affects children's milestones and cognitive development.

Conclusion

No association was found between gentamicin exposure and hearing loss in a community setting for the management of sepsis in the first two months of life.

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References

- Jehan I, Harris H, Salat S, Zeb A, Mobeen N, Pasha O, et al. Neonatal mortality, risk factors and causes: a prospective population-based cohort study in urban Pakistan. *Bull World Health Organ* 2009; 87: 130-8.
- Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: When? Where? Why? *Lancet* 2005; 365: 891-900.
- Department of Child and Adolescent Health and Development, World Health Organization. *Explore Simplified Antimicrobial Regimens for the Treatment of Neonatal Sepsis: Meeting Report*. Geneva, Switzerland: WHO; 2003.
- Thaver D, Zaidi AKM. Burden of neonatal infections in developing countries: a review of evidence from community-based studies. *Pediatr Infect Dis J* 2009; 28 (Suppl 1): S3-9.
- Shaikh BT, Hatcher J. Health seeking behaviour and health services utilization trends in National Health Survey of Pakistan: what needs to be done? *J Pak Med Assoc* 2007; 57: 411-4.
- National Institute of Population Studies (NIPS) [Pakistan], Macro International Inc. *Pakistan Demographic and Health Survey 2006-07*. Islamabad: National Institute of Population Studies, Macro Internal Inc.; 2008.
- Owais A, Sultana S, Stein AD, Bashir NH, Awaldad R, Zaidi AK. Why do families of sick newborns accept hospital care? A community-based cohort study in Karachi, Pakistan. *J Perinatol* 2011; 31: 586-92.
- Millennium Development Goals. (Online) World Health Organization (Cited 2010 August 12). Available from URL: http://www.who.int/topics/millennium_development_goals/about/en/index.html.
- Bhutta ZA, Zaidi AK, Thaver D, Humayun Q, Ali S, Darmstadt GL. Management of newborn infections in primary care settings: A review of the evidence and implications for policy? *Pediatr Infect Dis J* 2009; 28 (Suppl 1): S22-30.
- Zaidi AK, Ganatra HA, Syed S, Cousens S, Lee AC, Black R, et al. Effect of case management on neonatal mortality due to sepsis and pneumonia. *BMC Public Health* 2011; (11 Suppl 3): S13. doi: 10.1186/1471-2458-11-S3-S13.
- Bang AT, Reddy HM, Deshmukh MD, Baitule SB, Bang RA. Neonatal and infant mortality in the ten years (1993 to 2003) of the Gadchiroli field trial: effect of home-based neonatal care. *J Perinatol* 2005; 25 (Suppl 1): S92-S107.
- Baqui AH, El-Arifeen S, Darmstadt GL, Ahmed S, Williams EK, Seraji HR, et al. Effect of community-based newborn-care intervention package implemented through two service-delivery strategies in Sylhet district, Bangladesh: a cluster-randomised controlled trial. *Lancet* 2008; 371: 1936-44.
- McGlone A, Cranswick N. Evidence behind the WHO guidelines: Hospital care for children: what is the evidence of safety of gentamicin use in children? *J Trop Pediatr* 2008; 54: 291-3.
- Young Infants Clinical Signs Study Group. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. *Lancet* 2008; 371: 135-42.
- Mytton J, Mackenzie I. Observed and expected prevalence of permanent childhood hearing impairment in Oldham. *J Public Health (Oxf)* 2005; 27: 298-302.
- Rao 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; CD005091.
- Finitzo-Hieber T, McCracken Jr GH, Roeser RJ, Allen DA, Chrane DF, Morrow J. Ototoxicity in neonates treated with gentamicin and kanamycin: results of a four-year controlled follow-up study. *Pediatrics* 1979; 63: 443.
- Elahi MM, Elahi F, Elahi A, Elahi SB. Paediatric hearing loss in rural Pakistan. *J Otolaryngol* 1998; 27: 348-53.
- Pauwels HP, Vogeleer M, Clement PA, Rousseeuw PJ, Kaufman L. Brainstem electric response audiometry in newborns. *Int J Pediatr Otorhinolaryngol* 1982; 4: 317-23.
- Yoong SY, Feltbower R, Spencer N, McKinney PA. Families affected by deafness: hospital services uptake in a multiethnic population. *Arch Dis Child* 2005; 90: 454-9.
- Perletti G, Vral A, Patrosso MC, Marras E, Ceriani I, Willems P, et al. Prevention and modulation of aminoglycoside ototoxicity (Review). *Mol Med Report* 2008; 1: 3-13.
- Sajjad M, Khattak AA, Bunn JE, Mackenzie I. Causes of childhood deafness in Pukhtoonkhwa province of Pakistan and the role of consanguinity. *J Laryngol Otol* 2008; 122: 1057-63.