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Early View

Research letter

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Hearing loss with Kanamycin treatment for multidrug-resistant tuberculosis in Bangladesh

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Take home message for social media publicity: High frequency hearing loss from Kanamycin in MDR TB treatment: not if, but when?

Key words: MDR TB, Bangladesh, Ototoxicity, Kanamycin

Background

World Health Organization (WHO) recommendations for multidrug-resistant tuberculosis (MDR-TB) include 8+ months of an aminoglycoside such as kanamycin or amikacin or capreomycin, or a shorter course of 4+ months depending on the susceptibility of the patient's *Mycobacterium tuberculosis* isolate to other drugs in the regimen [1]. Aminoglycosides can produce significant side effects including irreversible ototoxicity, estimated to occur in 25-60% of patients treated for MDR-TB, depending on methods of measurement [2-5]. Even if surviving to cure, MDR-TB treatment itself is impoverishing [6] while ototoxicity further limits a patient's ability to regain employment and may compound social isolation.

Clinical trials are underway with regimens that exclude aminoglycosides, but depend upon the activity of oral drugs including fluoroquinolones [7]. Yet in prior studies of MDR-TB in Bangladesh, we found high proportions of patients with *M. tuberculosis* isolates with resistance or borderline susceptibility to fluoroquinolones, while susceptibility to an aminoglycoside was retained [8]. Thus, we aimed to measure pure tone hearing thresholds at a wide range of frequencies prior to and during kanamycin treatment among MDR-TB patients in Bangladesh with a view to inform the development of an accurate effect size for interventional trials of kanamycin dose or duration reduction, or the future use of adjunct agents to prevent ototoxicity.

Methods

A prospective cohort of consecutive adults referred to the national MDR-TB hospital in Dhaka, Bangladesh, the National Institute of Diseases of the Chest and Hospital (NIDCH), were enrolled if initiating kanamycin for MDR-TB treatment from October 2015 to February 2016. The prospective participants were counseled regarding the follow-up schedule and the consenting participants were enrolled. All patients signed written informed consent and the protocol was approved by the NIDCH administration and the ethical review committees at the International Centre for Diarrheal Diseases Research, Bangladesh and the University of Virginia.

Patients initially received daily injectable kanamycin as part of a standardized WHO recommended second-line regimen for MDR-TB. Pure tone hearing threshold testing was performed by an audiologist in a dedicated room at baseline (i.e., prior to kanamycin treatment) in all patients, and at 2, 3, 6 and 8 months after treatment initiation. Threshold measurements for pure tones presented to each ear via air conduction were performed at 250, 500, 1000, 2000, 4000, 6000 and 8000 Hz, while those presented via bone conduction were at 500, 1000, 2000 and 4000 Hz. Baseline hearing loss (HL) was defined as threshold >25 decibels (dB) at any frequency. Acquired HL (ototoxicity) was defined as: 1) pure tone threshold change (loss) >20dB compared to baseline at any frequency, 2) >10 dB loss at 2 adjacent frequencies, or 3) any worsening of pure tone threshold at 3 consecutive frequencies in either ear [9]. Acquired HL was further categorized as severe if > 70 dB loss at any frequency. Clinicians and patients were informed of pure tone test results for consideration of treatment alteration.

Pretreatment characteristics were compared among those with and without baseline HL by chi-square or Fisher's exact tests for categorical variables, and student's t-test for means of continuous variables. Kaplan-Meier survival analysis plotted acquired HL as the event against the month of pure tone testing and right-censored at 8 months or the month of last testing.

Results

Forty patients had baseline pure tone threshold testing, the mean age was 29 ±11 years, 22 (55%) were male and 6 (13%) had diabetes. Of 18 patients with prior TB treatment, 5 (28%) received streptomycin for a prior re-treatment regimen (formerly known as category II). Baseline HL was present in 18 (45%) and while older mean age and prior TB treatment were more common among those with baseline hearing loss, these proportions were not statistically significant. The median kanamycin mg/kg daily dose was 18.9 (minimum 13.0-maximum 25.0 mg/kg) and those with the lowest body mass index (BMI) receiving the highest daily mg/kg doses (R^2=0.46, $p<0.001$).

Thirty-six patients had follow-up pure tone testing and 28 (77.8%) acquired new HL, including 10 with baseline HL. Acquired HL was more common at higher frequencies, but in 11 patients (30.5%) HL occurred at or below 2000 Hz. All patients with HL below 2000 Hz also demonstrated acquired loss above 2000 Hz. As early as 2 months after treatment, 8 patients (22%) acquired HL. All patients with diabetes acquired HL, and were significantly more likely to acquire loss early, with a mean event free survival of 2.8 months (95% CI 1.2-4.4) compared to those without known diabetes, mean 4.7 months (95% CI 3.9-5.4) (p=0.006, Wilcoxon test equality of survival distribution) [Figure 1].

Discussion

Hearing loss during treatment for MDR-TB with kanamycin occurred in more than three quarters of all patients in this prospective cohort, one of the highest incidences reported to date. At the highest frequencies HL was severe and progressed stepwise to involve frequencies considered critical for perception of conversational speech in nearly a third of patients.

While this increased frequency of monitoring at a wide range of thresholds may have detected cases missed by a less intensive approach [3-5], daily dosing strategies in this cohort were aggressive, in excess of WHO recommended daily dose of 15 mg/kg in 35 (87.5%) of the initial 40 patients, and particularly so for those with the lowest BMI. Kanamycin is concentration dependent in activity and the mg/kg dose often correlates with the peak serum concentration, C_{max}, and the total serum exposure or area under the concentration curve (AUC) [10]. One MDR-TB treatment center in the Netherlands that routinely uses serum therapeutic drug monitoring (TDM) to estimate C_{max} and AUC has recently reported median doses as low as 6.5 mg/kg of kanamycin or amikacin that have prevented ototoxicity and preserved treatment efficacy [11].

Given the complexities of TDM, adjunct agents that may prevent toxicity also warrant study. Aminoglycosides form complexes with iron catalyzing reactive oxygen species that result in basal hair cell destruction and basilar membrane apoptosis [12]. N-acetylcysteine (NAC) has been used by some experts in co-administration with aminoglycosides for MDR-TB and in at least one meta-analysis has been found to prevent ototoxicity without additional harm [13]. Patients with diabetes progressed to HL earlier than those without known diabetes and represent a subgroup which may be ideal for studying agents such as NAC. Prior age-matched retrospective studies in non-TB populations have found an association with diabetes and sensorineural HL which correlated with worsening kidney function, leading to postulates of microangiopathic inner-ear processes [14]. Screening for diabetes at TB diagnosis is now a broadly endorsed programmatic recommendation, but well-characterized studies of MDR-TB drug toxicities and pharmacodynamics across the diabetes disease spectrum are lacking [15]. Nevertheless, pending the results of new clinical trials, baseline audiometry and frequent follow-up monitoring appears warranted and can be dose tailored based on patient characteristics and preferrably guided by TDM, while careful attention to not exceeding the maximum WHO recommended dosage.

This study did not test for known, albeit rare, pharmacogenetic risk factors for aminoglycoside induced ototoxicity [3]. In addition, the pattern of ototoxicity was not always definitively sensorineural as would be expected for kanamycin, and differences in air and bone thresholds of more than 25 dB were suggestive of other middle ear pathology.

In conclusion, these findings provide a more accurate effect size of HL in a high-risk cohort, and compel trials of reduced kanamycin exposure and/or adjunct agents to reduce ototoxicity.

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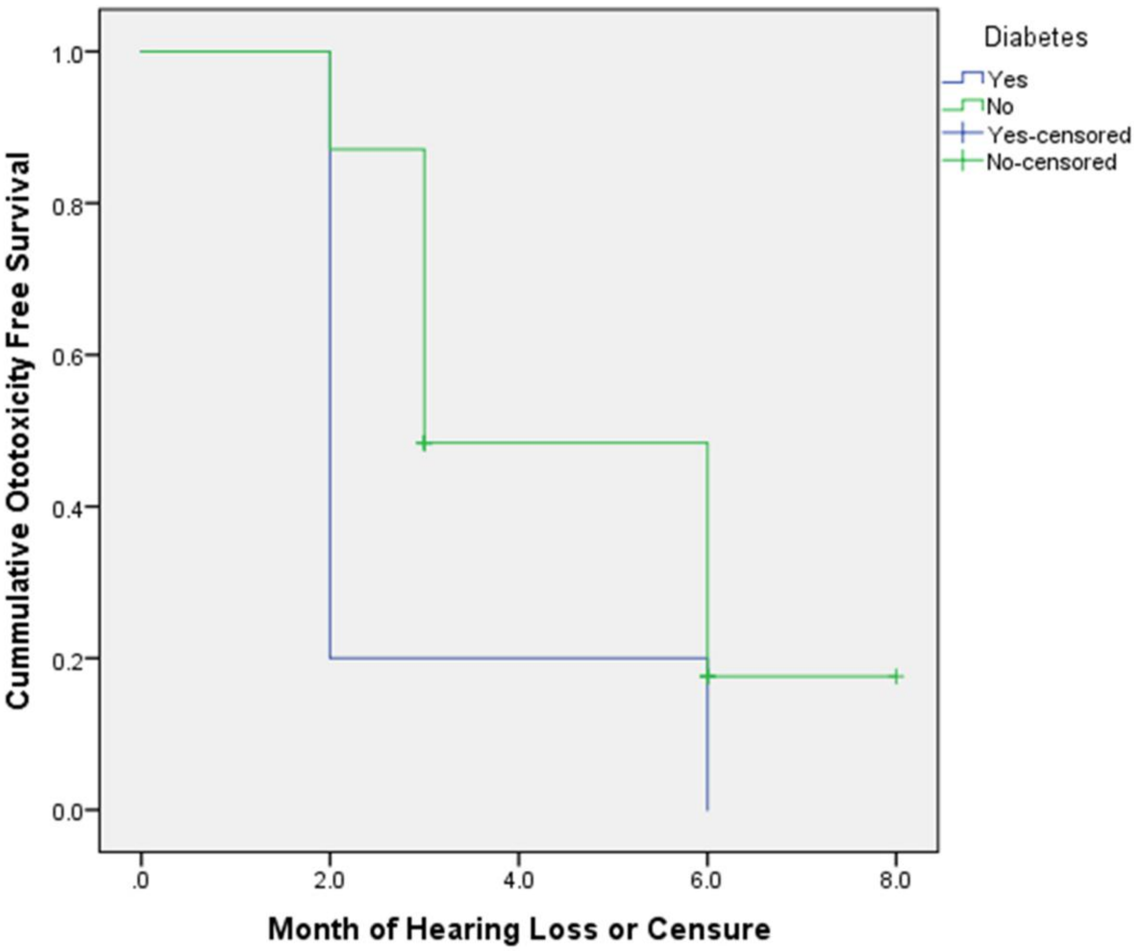
Diabetes
Yes
No
Yes-censored
No-censored
Cummulative Ototoxicity Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
.0
2.0
4.0
6.0
8.0
Month of Hearing Loss or Censure