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Research Article

Screening for Possible Nevirapine Induced Ototoxicity in Neonates, when Administered as Part of the Prevention of Mother-to-Child Transmission at Dr. George Mukhari Academic Hospital, Gauteng, South Africa Programme: A Pilot Study

Johani Fourie[1]*, Natalie Schellack[1], Deirdre Engler[1], Katerina Ehlert[2], Anna-Marie Wium[2], and Thato Moagi[3]

[1]*Department of Pharmacy, Sefako Makgatho Health Sciences University, South Africa*
[2]*Discipline of Speech and Language Pathology and Audiology, Sefako Makgatho Health Sciences University, South Africa*
[3]*Department of Speech Therapy and Audiology, Dr. George Mukhari Academic Hospital, South Africa*

***Corresponding author**
Johani Fourie, Department of Pharmacy, Sefako Makgatho Health Sciences University, BMS Building, N310, Molotlegi Street, Ga-Rankuwa, 0208, South Africa; Tel: 082-453-3501; Email: johanifourie@yahoo.com

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Abstract

Background: Drugs that are included in treatment regimens, including prevention programmes for the Human Immunodeficiency Virus (HIV), may place patients at risk of ototoxicity due to their side-effect profiles. Ototoxicity is part of this side-effect profile but is comparatively understudied in HIV-positive patients receiving antiretroviral (ARVs) agents. Patient safety has been identified as a part of the National Core Standards from the National Department of Health. As part of this strategy and due to the limited information available on the possible ototoxicity of nevirapine (NVP) as part of the prevention of mother-to-child transmission (PMTCT) in neonates, the study was conducted.

Method: The study aimed to determine if there was a possible association between neonates receiving NVP as part of PMTCT and ototoxicity at Dr George Mukhari Academic Hospital (DGMAH). A descriptive, quantitative cohort study was conducted prospectively. Participants were allocated purposively to either an experimental (received NVP) or control (NVP not received) group. The research team consisted of pharmacists, who performed the screening for eligible participants, and audiologists, who conducted all audiological assessments.

Results: A total of 165 participants were enrolled over a period of ten months; however, only 40 participants (24%) completed the study. The two study arms were comparable in terms of demographic variables. All of the participants that received NVP (n=20) were adherent. Both study arms (n=40) failed to pass the distortion product otoacoustic emission (DPOAE) assessments at baseline (day 0). There were no statistically significant differences between the two study arms in terms of the DPOAE results ($p>0.05$) tested at both two and six weeks.

Conclusion: Contrary to available literature, the results from this study showed that NVP administered as part of PMTCT was not associated with hearing loss in neonates who participated in this study. Future monitoring is strongly suggested as possible insults to the cochlea cannot be excluded at such an early age.

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ABBREVIATIONS

AABR: Automated Auditory Brainstem Response; AIDS: Acquired Immune Deficiency Syndrome; ARV: Antiretroviral; CEO: Chief Executive Officer; DGMAH: Dr George Mukhari Academic Hospital; DNA: Deoxyribonucleic acid; DPOAE: Distortion product otoacoustic emission; HIV: Human Immunodeficiency Virus; ICU: Intensive Care Unit; MREC: Medunsa Research and Ethics Committees; MSH: Management Sciences for Health; MTCT: Mother-to-child transmission; NDoH: National Department of Health; NIAID: National Institute of Allergy and Infectious Diseases; NICU: Neonatal Intensive Care Unit; NNRTIs: Non-Nucleoside Reverse Transcriptase Inhibitors; NVP: Nevirapine; OAE: Otoacoustic Emissions; PMTCT: Prevention of mother-to-child transmission; PNW: Postnatal ward; RNA: Ribonucleic acid; SMU: SefakoMakgatho Health Sciences University; SREC: School Research Ethics Committee; TEOAE: Transient-evoked otoacustic emissions; TYMP: Tympanometry; WHO: World Health Organization

INTRODUCTION

Limited information is available on the possible ototoxicity in neonates due to nevirapine (NVP). Further to this evidence on ototoxicity related to antiretroviral (ARV) therapy is not readily available. However, in a country like South Africa, there is a substantial need for intensified research in this area. Sub-Saharan Africa has been hit the hardest by the Human Immunodeficiency Virus (HIV) pandemic with exposure to ARV therapy being an increasing phenomenon [1]. The aim and main outcome of ARV therapy is to improve survival, but the side-effects associated with this therapy receive little attention [2]. One such important side-effect is ototoxicity [3].

Ototoxicity can be defined as the tendency of certain substances to cause functional impairment and cellular damage to tissues of the inner ear, especially to the end organs of the cochlea (which can lead to hearing loss, tinnitus and hyperacusis), vestibular system (which can lead to vertigo, disequilibrium and instability of visual field) and divisions of the eighth cranial nerve that can occur from systemic or topical administration [4]. Hearing loss has become one of a number of sensory disabilities associated with HIV that must now compete for attention by the research and medical community [1].

Neonates are classified as a vulnerable population. Medicine causing potential ototoxicity in the neonatal population requires careful monitoring by health care professionals because of the characteristics and special needs of this population [5]. The earlier a hearing loss occurs in a child's life, the more serious the effects on the child's speech and language development that is in the process of development [6]. Similarly, the earlier the problem is identified and intervention begun, the less serious the ultimate impact [6]. Children who present with mid-to high-frequency hearing loss which is typical in ototoxicity experience difficulty to hear in certain situations (e.g. noisy environments in class rooms, soft speakers).

Considering the lipophilic properties of NVP, this substance penetrates deep into the cochlea where it could affect both the basal and apex regions of the cochlea [6].

Mid-or high-frequency hearing loss could result in the child missing approximately 30% of speech information in natural contexts causing a speech and language delay with eventual reduced academic achievement [6]. Hearing loss will potentially impact on social relationships, result in poor self-esteem and cause frustration and fatigue in classroom settings [6]. Depending on the degree and the configuration of the hearing loss, such children could show delayed language development and articulation problems [6].

NVP is widely used as an ARV agent, especially as part of PMTCT [7]. Claims of high rates of toxicity have not been confirmed in clinical trials in the use of NVP as part of PMTCT [8]. Clinical trials to determine the safety (for the purpose of this study, ototoxicity); pharmacokinetics and optimal dosing of ARVs in neonates are urgently needed [9].

Claims of ototoxicity induced by ARV agents have been made in literature [1]. South Africa, as a country, is still facing a large number of paediatric patients infected with HIV. HIV itself can cause alterations in the auditory system, directly through the action of the virus upon the auditory system [10]. To exclude this variable, the study was conducted in healthy newborns, to examine possible ototoxic effects due to NVP used as part of the PMTCT in HIV-exposed neonates.

MATERIALS AND METHODS

Study design and study site

A descriptive quantitative, cohort study was conducted prospectively. The study was conducted at Dr George Mukhari Academic Hospital (DGMAH), a 1,650-bed tertiary academic hospital, situated in a peri-urban context known as Ga-Rankuwa, which is in Gauteng Province, South Africa. The research team consisted of pharmacists and audiologists. Screening for eligible participants was done by the pharmacists and all audiological assessments were done by the audiologists. The baseline visit took place in the postnatal wards (PNW), which are the obstetrics wards (wards 30 and 31). Two- and six-week visits took place in the Discipline of Speech and Language Pathology and Audiology and the Department Speech Therapy and Audiology.

Study population and sampling

All full-term neonates exposed to HIV, whom received NVP for the PMTCT and admitted to ward 30 and 31, the PNW and obstetric wards after birth, were considered for the experimental group of the study. All full-term neonates not exposed to HIV and therefore not on NVP therapy were considered for the control group. They were only enrolled as study participants once consent was obtained from the mothers. A total of 165 neonates were screened for eligibility. Eventually only 40 neonates (20 in the control group and 20 in the experimental group) completed the six week study period with associated tests and assessments. Therefore, the final sample size was 40 neonates, with 125 neonates that never followed up. The study adopted a pilot study approach due to the low numbers of neonates that were recruited and finished the final study. Purposive sampling was done to include all neonates that met the inclusion criteria. The following inclusion criteria were applied: Neonates that received NVP as part of PMTCT (experimental group), neonates who were

not initiated on NVP (control group) and mothers that provided consent.

Study procedure and duration

Data collection took place on day 0 (baseline), week two and week six of life. Ethical consent was obtained if a subject was identified, subsequent to this, screening and allocation was done. The audiologist performed a baseline diagnostic distortion product otoacoustic emission (DPOAE) assessment for all participants within 24 hours. All participants that were exposed to HIV, received NVP within 72 hours after birth, according to the South African Antiretroviral Treatment Guidelines (2014) [11]. At each study visit (at two and six weeks of life) follow-up diagnostic DPOAE assessments were performed for both study arms and were repeated. If the DPOAE failed at the six-week visit, the participant was referred to the audiologist for further management, e.g. Tympanometry (TYMP) and Automated Auditory Brainstem Response (AABR) and interventions made when and if needed (Figure 1).

Adherence to NVP was calculated for each participant in the experimental group at follow-up visits.

Adherence to NVP

Patient adherence to NVP was determined using volumetric measurement. NVP medication returned by the mother with each follow-up visit was measured and adherence was calculated using the following formula [12].

% Adherence = (Previous quantity taken home in millilitres) – (Quantity returned in millilitres) x 100

Quantity should have taken

To categorise adherence a rating scale was used, ranging from very poor to excellent. Adherence is presented as a percentage for each participant at each visit (Table 1).

Audiology

The Otoport Advance® was used for all the screening applications as well as advanced diagnostic testing. Regular calibration ensures reliable results and was performed during June 2014 and September 2015. This instrument is an all-purpose DPOAE instrument with customisable protocols including optimised paediatric modes. An option exists for simple pass and refers results, however, this study made use of the option for detailed data display and diagnostic testing. Infant probes were used and the probe fit is shown graphically. A constant display of

Figure 1 Study procedure.

Table 1: Rating scale categories converted to adherence percentage [12].

Rating scale category	Adherence percentage
Excellent	100%
Very good	95%
Good	90%
Fair	80%
Poor	70%
Very poor	60%

signal-to-noise ratio ensures reliability of the data. The protocol used for diagnostic purposes consisted of a 13-frequency clinical DPOAE. This protocol is frequency-specific and starts at 1000Hz and ends at 8000Hz.The research used a binary scale (refer/pass). In order to qualify as a pass outcome, the signal to noise ratio was > 6db. For a DPOAE to be considered a pass, nine or more out of the 13 frequencies should pass, whereas a fail is considered when less than nine of 13 frequencies pass. The results obtained are more effective and reliable while a neonate is sleeping or is in a content state and in a quite environment.

Data analysis

All data was captured on Microsoft Excel™ spread sheets and were checked for accuracy and completeness by a second person. Corrections were made prior to data analysis. Data was statistically analysed in consultation with a statistician via a Statistical Analysis System® using SAS® Release 9.3. Demographic and clinical data were expressed as frequency percentages, with confidence intervals, where feasible, and as means, medians, inter-quartile ranges, minimum and maximum values, where appropriate.

The following statistical tests were used for comparisons of the experimental and control groups:

- Parametric t tests for the comparison of mean values (normality assumption satisfied)
- Nonparametric Wilcoxon tests for the comparison of median values
- Fisher Exact tests for the comparison of percentages.

Ethical considerations

DGMAH is affiliated to Sefako Makgatho Health Sciences University (SMU) and approval to conduct the study was obtained from the Research and Ethics Committee (MREC/H/240/2014) before commencement of the study. Permission to conduct the study was requested and obtained from the Chief Executive Officer (CEO) of DGMAH and the Head of the Paediatrics Department. The mothers of the participants were provided with a study information leaflet and the information was also verbally transferred. Written informed consent, which was translated into the local language, was obtained. Confidentiality and anonymity of patient information were maintained throughout the study. Participants were allocated study numbers to ensure confidentiality and anonymity.

Ethical guidelines for a vulnerable population

The research team ensured that all potential benefits and risks were reasonably balanced and risks were minimised. Interventions or procedures that hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual subject were justified by the expectation that they were at least as advantageous to the individual subject, in the light of foreseeable risks and benefits, as any available alternative. Risks of such *'beneficial'* interventions or procedures were justified in relation to expected benefits to the individual subject. Risks of interventions that do not hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual were justified in relation to the expected benefits to society (generalisable knowledge). The risks presented by such interventions were reasonable in this study in relation to the importance of the knowledge gained [13].

RESULTS AND DISCUSSION

Results

Patient enrolment: During the ten-month study period, 165 study participants were enrolled (83 patients were assigned to the control group and 82 to the experimental group). Despite the fact that participants were encouraged and motivated to return for follow-up visits, only 40 participants (20 experimental and 20 controls) completed the study. Although transport cost reimbursements were given to the mothers of the participants (as per the Medicine Control Council (MCC) guidelines), this was still cited by the mothers as being insufficient and therefore resulted in a high dropout rate. A higher dropout rate was also noted during the winter months, more than likely due to adverse weather conditions. Figure (2) illustrates the participants' enrolment during the ten month study period.

Patient demographics: Participants in the experimental and control groups were similar in terms of gestational age, birth weight, gender and method of delivery (Table 2).

Breastfeeding and antiretroviral therapy: All participants in the experimental group were breastfed by their mothers, who all used highly active antiretroviral therapy (HAART). More than 90% of these mothers used Tribuss®, a fixed-dose combination consisting of two nucleotide/nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor (tenofovir, emtricitabine and efavirenz). The remaining 10% received ART, but could not state the name/regimen of their medication. The majority (90%) of participants did not receive extra NVP through the breast milk of the mothers.

NVP Dosing and Adherence: The NVP dose for each participant was 1.5 ml per day, thus 15 mg per day, for up to six weeks after birth, which is in accordance with the South African National Department of Health Guidelines (2014) [11].

Adherence was measured to ascertain compliance to NVP and the probable cause of ototoxicity. All participants that received NVP were adherent, with a mean percentage adherence rate of 98.8% (SD; ±2.22) and 97.4% (SD; ±3.98) at the two- and six-week visits respectively. There was no statistically significant differences (p=0.178; t-test) between the mean adherence of NVP for both these visits. Participants scored between good, very good and excellent.

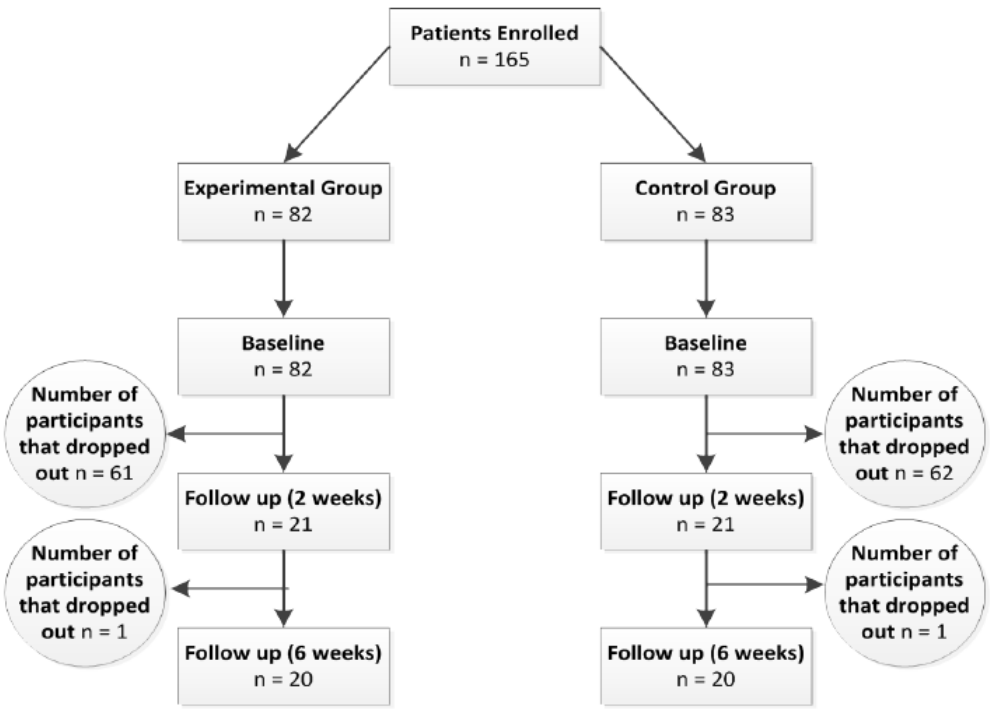

Figure 2 Participants enrolled into the study.

Table 2: Comparative demographics between two study groups.

Parameters	Experimental (n=20)	Control (*n*=20)	*p*	Test
Gestational age (weeks)				
Mean (±SD)	37.1 (±1.68)	37.6 (±1.50)	0.328	t-test
Median (IQR)	37.5 (36-38)	38.0 (37-38)	0.364	Wilcoxon test
Birth weight (kg)				
Mean (±SD)	3.0 (±0.44)	3.1 (±0.48)	0.513	t-test
Median (IQR)	2.98 (2.7-3.2)	3.07 (2.8-3.5)	0.433	Wilcoxon test
Gender	7F; 13M	12F; 8M	0.205	Fisher exact test
Delivery Number (%)				
Caesarean Section	9 (45%)	6 (30%)	0.515	
Normal vaginal	11 (55%)	14 (70%)	0.515	Fisher exact test

Nine (45%) participants from the experimental group (n=20) rated excellent (Table 1) on adherence. Another nine (45%) participants had an adherence rating of very good and two (10%) of good.

Measurement of cochlear function using comparative distortion product otoacoustic Emissions (DPOAE):

Baseline Visit: All participants in both study arms failed to pass at least nine of the 13 frequencies in both ears, as measured using DPOAE at baseline. Repeated DPOAE assessments confirmed the results. Reliability of the baseline results were also ensured by the machine constantly monitoring background noise which was considered during the analysis of the results.

Two-week follow-up visit: Fifteen (75%; n=20) of the study participants in the experimental group subsequently passed the DPOAE assessments. The control group had a slightly higher pass rate with 85% (17; *n*=20) of the participants that passed. The Fisher Exact test was done to determine if there was any significant hearing loss in either study arms, or the variable was nevirapine. Subsequently no statistical significant difference (p=0.695) was found between the two study arms (Table 3).

Six-week follow-up visit: In the experimental group, 18 (90%; n=20) of the participants passed the DPOAE assessment and all of the participants in the control group passed. There was no statistically significant difference (Fisher Exact test; p=0.487) between the two study arms (Table 3).

Baseline to six-weeks: Of all participants that failed the baseline and two-week DPOAE assessments for both study arms, 18 participants (90%; n=20) in the experimental group passed the six-week and all participants in the control group. As illustrated in Table (3) there was no statistically significant difference between the two groups (Fisher Exact test; p=0.487). The two participants of the experimental group that failed are outlined in the subsequent section.

Outliers (participants that failed DPOAE assessments at the two follow-up visits): As evident in Tables (4 and 5) the frequencies, affected by the participants that failed the DPOAE assessments for both study arms at two and six weeks, was evenly distributed, between low (1000-1682 Hz), middle (2000-4000 Hz) and high (4757-8000 Hz).

Two-week follow-up visit: In the experimental group, five (25%; n=20) participants failed to pass at least nine of the thirteen frequencies at the two-week visit.

The control group had three (15%) participants that failed their DPOAE assessments at the two-week visit, which was 10% less than the experimental group. All of the participants that failed at the two-week visit, passed at the six-week visit. The Fisher Exact test was done (p=0.695) and no statistical significant difference.

Six-week follow-up visit: The two participants (10%; n=20) that failed the six-week DPOAE assessments in the experimental group passed the two-week assessments, but were referred for further investigation. At these assessments, one of the participants passed the tympanometry (TYMP) and the AABR, the remaining participant failed the DPOAE, TYMP and the AABR. This participant was referred for further investigation and management. The final outcome was that this participant passed all three assessments. There were no statistically significant differences between the two study arms in terms of the DPOAE results (p>0.05) (Table5).

DISCUSSION

This study evaluated a possible association between NVP used in neonates as part of PMTCT and ototoxicity. To the best of our knowledge this study is the first to assess this association. The attrition rate for this study was relatively high, despite continued efforts over the ten month study period to retain participants for follow-up visits. From the initial eligible participants, only 24% of the participants completed the study. The Wilcoxon two-sample test was performed and the two study arms showed no statistically significant difference in respect to the demographics. The experimental group could therefore be compared to the control group, with regards to diagnostic DPOAE assessments.

Participants were dosed according to the National Department of Health (2014); NVP is used as a prophylactic agent, administered as a single daily dose of 15 mg, thus 1.5 ml, in neonates for PMTCT [11]. Sub-Saharan Africa has the largest burden of paediatric HIV in the world [15]. A study concluded that a single dose of NVP given to infants may decrease infant mortality [16]. All participants that received NVP were adherent with 90% of the participants rated as between very good and excellent. This is an important factor as poor adherence can lead to inadequate drug levels (with a decrease in both efficacy, but

Table 3: DPOAE assessments from baseline to six weeks.

	Baseline to two-week follow-up		Baseline to six-week follow-up		Test
	Experimental Group	Control Group	Experimental Group	Control Group	Fisher exact test
Number of participants	15 (75%)	17 (85%)	18 (90%)	20 (100%)	

Table 4: Outliers at two weeks.

Participants (8: n=40)		Frequency A (1000-1682 Hz)				Frequency B (2000-4000 Hz)					Frequency C (4757-8000 Hz)				Fisher Exact test (p = 0.695)
Experimental Group (5; n=20)		**1000**	**1189**	**1414**	**1682**	**2000**	**2378**	**2828**	**3364**	**4000**	**4757**	**5657**	**6727**	**8000**	
0018	**R**	F	P	F	P	P	P	P	F	F	P	P	F	P	
	L	F	F	F	F	F	F	F	F	F	F	F	F	F	
0024	**R**	F	P	P	P	P	P	P	F	F	F	P	F	P	
	L	F	P	P	P	P	P	F	P	F	F	F	F	F	
0115	**R**	F	F	F	F	F	F	F	P	F	P	P	P	F	
	L	F	F	F	F	F	F	F	F	F	F	F	F	F	
0117	**R**	F	F	F	F	F	P	F	P	F	P	P	P	F	
	L	F	F	F	F	F	F	F	F	F	F	F	F	P	
0119	**R**	F	F	F	F	F	F	F	F	F	F	F	F	F	
	L	F	F	F	F	F	F	F	F	F	F	F	F	F	
Control Group (3; *n*=20)		**1000**	**1189**	**1414**	**1682**	**2000**	**2378**	**2828**	**3364**	**4000**	**4757**	**5657**	**6727**	**8000**	
0014	**R**	F	F	F	F	F	F	F	F	F	F	F	F	F	
	L	F	F	F	F	P	F	P	P	P	P	P	P	P	
0027	**R**	F	P	P	P	P	P	P	F	F	F	P	F	P	
	L	F	P	P	P	P	P	F	P	F	F	F	F	F	
0033	**R**	F	F	F	F	F	F	F	F	F	F	F	F	F	
	L	F	F	F	F	F	F	F	F	F	F	F	F	F	

F: Failed; P: Passed; R: Right; L: Left

Table 5: Outliers at six weeks.

Participants (2;n=40)		Frequency A (1000-1682 Hz)				Frequency B (2000-4000 Hz)					Frequency C (4757-8000 Hz)				Fisher Exact test (p = 0.487)
Experimental Group (2; n=20)		**1000**	**1189**	**1414**	**1682**	**2000**	**2378**	**2828**	**3364**	**4000**	**4757**	**5657**	**6727**	**8000**	
0010	**R**	F	P	P	P	P	P	P	F	F	F	P	F	P	
	L	F	P	P	P	P	P	F	P	F	F	F	F	F	
0113	**R**	F	F	F	F	F	F	F	F	F	F	F	F	F	
	L	F	F	F	F	F	F	F	F	F	F	F	F	F	

F: Failed; P: Passed; R: Right; L: Left

also toxicity) and development of drug resistance [17].

All participants in the experimental group were breastfed, most of the mothers (90%) were on an ARV regimen that did not include NVP; the majority of participants therefore did not receive extra NVP through breast milk.

Studies done previously in Malaysia on new-born hearing screening, reported that the age of the participants might affect the DPOAE result. All participants in the study population failed the baseline (day 0) DPOAE assessments conducted within 24 hours of birth, even after a repeat assessment. This may be explained by the fact that the vernix and amniotic fluid had not cleared up from the ear canal during the first day of life. It is recommended that DPOAE assessment should be done on a neonate after 24 hours of age, or the ears should be cleaned of the vernix before testing.[18]A study conducted by Priner *et al*, concluded that on the day of birth there were signs of conductive hearing loss due to absorption of amniotic fluid from the middle-ear cavity [19].

Although cochlear function measured at the two- and six-week visits for both groups did not differ significantly, studies

have not discounted the effect of HIV on hearing function, with an increasing trend in newborns that are exposed to the virus [20].

This study showed that although some neonates failed at the two-week follow-up, they all passed at the six-week follow-up. Audiologists should therefore follow the Health Professions Council of South Africa's Guidelines for Early Hearing, Detection and Intervention, which stipulate that follow-up screening for high risk infants should continue up to three months after baseline measurements were obtained at birth [21]. Pharmacists should facilitate the identification of potential ototoxic medicines, as such follow-up screening will facilitate adherence and identify early changes in hearing.

DPOAE's cannot be measured in the presence of middle ear pathology which is a possible cause of hearing loss in paediatrics. It can be caused by viral, bacterial or parasitic infections. Middle ear infections are important causes of hearing impairment for many children in the world. For example chronic supportive otitis media is the commonest cause of hearing loss in paediatrics in developing countries [22]. Furthermore, DPOAE's cannot be measured in a child who is crying, vocalizing, moving, and is highly sensitive to background noise [24]. These aspects could also have contributed to the findings in these participants.

Although this study could not confirm ototoxicity in infants on NVP, it is well recognised that hearing is critical to speech and language development, communication, and learning [6]. Paediatric hearing loss has a severe negative effect on the development of an infant's speech and language, as well as cognitive and social skills [14]. Children with listening difficulties due to hearing loss or auditory processing problems, continue to be an under-identified and under-served population. It cannot be excluded at this time that future insults to the cochlea due to ototoxic medications taken at a later stage, or continuous noise exposure may create an increased vulnerability to the development of hearing loss.

This particular treatment regime is treating HIV, so the cost to benefit ratio of the treatment outweighs the possibility for hearing loss, which is in accordance to the consequentialist view where the morality of the decision stems from the expected outcome or result (e.g. healing, avoidance of death) [23].

Neither the neonates initiated on NVP therapy, nor those who were not on treatment, developed hearing loss. There were also no association of hearing loss between neonates exposed to HIV that received NVP and their audiological results, from baseline to follow-up.

CONCLUSION

Limited information on the possible ototoxicity of NVP in neonates is available. The main aim of the study was to determine a possible association between neonates receiving NVP as part of PMTCT and ototoxicity. Adherence to NVP was confirmed and should be continuously promoted for the prevention of HIV transmission. Results obtained as part of this study points to the fact that no association could be made between treatment with nevirapine and loss of cochlear function in neonates who participated in this study. Variations in audiological assessments were seen in the study population, over the study period, but mostly returned to normal. This emphasises the importance of continuous communication within the multi-disciplinary team, which includes the audiologist, pharmacist and doctor, to ensure best treatment outcomes for neonates.

Limitations and challenges

The equipment used for DPOAE assessments in this study was very sensitive to noise. These assessments were very challenging, especially in the neonatal population where body movements and crying are unpredictable .It remains a challenge to obtain true baseline results within 24 hours after birth, due to the absorption of amniotic fluid in the neonates' ears. High attrition rates resulted in a small sample size and generalisation of the results cannot be done.

Recommendations

It is recommended to make use of equipment that is less sensitive to noise and to conduct baseline in a noise controlled area such as isolation rooms within the ward. Neonates should preferably be asleep while conducting audiological assessments. The sample size of future studies should be large enough to allow for deviations in data. Transient-evoked otoacoustic emissions (TEOAE) which tests lower frequencies, should be included in future ototoxicity studies and noise controlled environments, as TEOAE and DPOAE measurements are recommended in newborn hearing screening protocols. TEOAE measurements are recommended for the testing of well babies. However the design of each hearing screening protocol is unique to each setting [24].

Lastly, for this study we used HIV positive neonates as the experimental group to see if there was a possibility that the treatment itself could cause hearing loss. Future research may want to consider using HIV positive neonates that were not permitted the treatment (mother rejected treatment) as a secondary control for the possible influence of HIV-related hearing changes.

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