ORIGINAL ARTICLES

DOES VINCRISTINE AFFECT COCHLEAR FUNCTION IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKAEMIA?

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Abstract:

Context: *Vincristine chemotherapy has dose dependent ototoxicity. Early detection of ototoxicity is better with otoacoustic emissions and high frequency audiometry than conventional pure tone audiometry. The study was done to see if vincristine treatment interferes with hearing sensitivity in children.*

Methods and Material: *A prospective study was conducted on twenty-three children with acute lymphoblastic leukemia (ALL) on Multi Center Protocol (MCP 841).These were subjected to conventional audiometry, high frequency audiometry and distortion product otoacoustic emissions (DPOAEs) before starting chemotherapy. The follow up audiological evaluation after early intensive phase chemotherapy (approximately 6 months) was conducted in thirteen children, who received 12 doses of vincristine (1.4 mg/m^2), cranial irradiation of 1800cGy (>3 years) as per protocol and antibiotics as per clinical demands.*

Results: *Baseline audiological evaluation was normal. Follow-up evaluation DPOAEs showed a declining tendency, however changes did not reach statistical significance. Differences in median hearing thresholds prior and post treatment in higher frequency audiometry were also minimal which was not statistically significant. Conventional audiometric thresholds were not altered.*

Conclusions: T*he reduction in the signal noise ratio of DPOAE, and reduced hearing sensitivity in high frequencies in post chemotherapy in comparison with baseline measures cannot be ignored though it has failed to reach the level of statistical significance. children on vincristine should have a pre chemotherapy and follow up audiological evaluation with DPOAE The results of the present study needs to be strengthened by including larger sample and long term follow up.*

Key-words: *leukemia, children, Vincristine, ototoxicity, otoacoustic emissions*

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Introduction:

Acute Lymphoblastic Leukemia (ALL) has current event -free- survival rates of approximately 80%, increasing concerns about late effects of treatment[1,2]

Leukemic infiltration, hyperleukocytosis, infection and hemorrhage are proposed mechanisms for deafness in leukemia.[3,4] Myelosuppression and infections often induce addition of drugs with potential for ototoxicity.[5]

Ototoxicity manifests initially as high frequency hearing loss (> 8000 Hz.)[6] which has implications on academic achievement and communication in young children.

Present study was designed to determine effects of Vincristine on cochlear function in children with ALL

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by using conventional pure tone audiometry, high frequency audiometry, and distortion product otoacoustic emissions (DPOAEs).

Subjects and Methods:

Study design & subjects: This study followed a prospective, convenient sampling method. The audiological evaluation of children diagnosed with ALL before starting chemotherapy and after completion of consolidation phase or early intensive phase of MCP841 protocol was determined in a tertiary referral hospital affiliated to a medical college . Institutional Ethics Committee approval was obtained before conducting the study. The inclusion criteria was normal otoscopic findings, with A type tympanogram , stapedial reflex being normal in bilateral ears and renal function , liver function and serum electrolytes within reference range. All new cases of ALL between 1 and 15 years with history of otologic disease/ surgery, major head trauma, central nervous system infections, exposure to neurotoxic/ototoxic drugs or radiotherapy and family history of hereditary hearing loss were excluded from the study. Children who failed to go into bone marrow remission (<5% lymphoblasts on bone marrow cytology) at the end of I_1 phase of MCP841 protocol were also excluded. Children were included after an informed consent from the parents.

Procedure: All children who fulfilled the entry criteria were subjected to baseline audiological evaluation comprising of conventional pure tone audiometry (PTA; using GSI 61clinical audiometer), high frequency audiometry (using GSI 61 clinical audiometer) and Distortion product otoacoustic emissions (DPOAE; using GSI Audera) measurement before starting chemotherapy. PTA and high frequency audiometry are subjective tests requiring active participation of the child and DPOAE is an objective measure conducted with the child being immobile/sleeping. Follow up audiological evaluation was done by using the same protocol after an early intensive phase (after consolidation phase) chemotherapy of MCP841 protocol. All testing was carried out in an acoustically treated air conditioned room. For pure tone audiometry, hearing thresholds dŠ25 dB was taken as normal as per Goodman classification.[7]

Statistical analysis: comparison of the baseline responses by frequency with the respective results after an early intensive phase of chemotherapy was done by Wilcoxon signed rank sum test. Data were coded and entered into SPSS version 16. A *p* value less than or equal to 0.05 was considered as significant.

Results:

A total of 23 children, 10 male and 13 female who fulfilled entry criteria were included in the study. There were 15 children in the age group of 1 and 5 years, 5 between 6 and 10 years and 3 between 10 and 16 years. Out of this 13 children completed follow up evaluation.. Remaining 10 children were lost for follow up due to discontinuation of treatment in 3 children, failure to go into bone marrow remission at the end of I_1 phase of chemotherapy in 2, transfer to a different hospital for continuation of chemotherapy in 2, death in 2 children and failure to obtain consent for follow up audiological evaluation in one child.

(a) Conventional Audiometry: It was observed that median hearing thresholds before and after chemotherapy were within normal limits in both ears in 13 children who completed follow up evaluation and the difference was not statistically significant (*p>0.05).*

Table-I

Hearing thresholds with conventional audiometry before and after chemotherapy

Frequency (Hz)	No of subjects (n)	Pre chemotherapy threshold (dB)±SD Median	Post Chemotherapy threshold (dB)±SD Median	*p*
Right Ear				
500	13	20±7.53	15±8.20	0.79
1000	13	15±5.54	15±8.02	0.35
2000	13	15±5.93	10±7.36	0.71
4000	13	10±10.51	15±6.60	0.29
8000	13	15±11.69	15±6.77	0.31
Left Ear				
500	13	20±6.81	15±7.48	0.67
1000	13	20±11.25	15±6.40	0.61
2000	13	20±10.31	15±7.20	0.39
4000	13	15±8.02	10±6.33	0.38
8000	13	20±12.22	15±8.16	0.32

Table-II

Hearing thresholds with high frequency audiometry before and after chemotherapy

Frequency (Hz)	No of subjects (n)	Pre chemotherapy threshold (dB)±SD Median	Post Chemotherapy threshold (dB)±SD Median	*p*
Right Ear				
10000	11	25±14.46	20±11.20	0.28
12000	11	30±10.78	25±12.89	0.67
16000	11	30±16.44	25±21.96	0.52
Left Ear				
10000	11	25±13.98	25±17.04	0.83
12000	11	30±14.83	30±19.47	0.48
16000	11	35±19.52	35±21.57	1.00

Table-III

SNR (Signal Noise Ratio) amplitudes before and after chemotherapy

Frequency (Hz)	No of subjects (n)	Pre chemotherapy threshold (dB)±SD Median	Post Chemotherapy threshold (dB)±SD Median	*p*
Right Ear				
1000	13	10.6±5.57	10.08±5.82	0.70
2000	12	13.31±7.65	14.70±4.98	0.43
4000	13	18.59±12.3	12.70±12.41	0.80
8000	8	10.15±7.68	11.99±7.42	**0.017**
Left Ear				
1000	11	11.62±4.79	9.80±4.84	0.62
2000	11	16.06±7.03	12.12±10.57	0.85
4000	11	23.60±11.27	21.69±13.93	0.28
8000	7	12.13±6.42	12.76±6.70	0.61

(b) High frequency audiometry: It was observed that changes in median hearing thresholds prior and after treatment at higher frequencies were minimal which was not statistically significant (*p>0.05).* (Table-II)

(c) DPOAEs: Signal Noise Ratio (SNR) was measured at frequencies of 1 kHz, 2 kHz, 4 kHz and 8 kHz and Median SNR amplitudes obtained are depicted in table 3. Median SNR amplitudes were within acceptable limits (SNR>6 dB) at all frequencies in both ears before and after chemotherapy except in right ear at 8k (*p=0.017).* There was no significant change in SNR amplitudes at baseline evaluation and after chemotherapy (*p>0.05).*

Discussion:

With increased effectiveness of treatments for cancer, focus has been also to minimize the impact of treatment. Early or delayed onset hearing loss can be seen in survivors of childhood malignancies. Hearing loss may interfere with communication, social interaction, school performance and finally quality of life (QOL).[8] MCP841 protocol is a chemotherapeutic protocol commonly used for the treatment of childhood ALL. This protocol was designed in collaboration with the National Cancer Institute (USA) at Tata Memorial Hospital, Mumbai.[9]

Ototoxicity can be divided into cochleotoxicity and vestibulotoxicity. Cochleotoxicity associated with the use of vincristine, [10, 11] aminoglycosides, macrolides, diuretics, NSAIDs has been reported in the literature .[12-18] Ototoxicity causes hearing loss primarily by damaging the outer hair cells within the organ of Corti, and the stria vascularis, which provides the electrical

drive to the outer hair cells. The damage starts at high-frequency coding cochlear base and progresses towards the apex.[19, 20]

In our study all children received treatment as per MCP841 protocol which include 12 doses of vincristine at a dose of 1.4 mg/m^2 between baseline and follow up evaluation and cranial irradiation of 1800cGy in those aged above 3 years. Antibiotics were selected at recommended doses depending on the clinical demands.

An existing practice in many clinics for monitoring ototoxicity in children is conventional audiometry. It is well established that Ototoxicity manifests initially as high frequency hearing loss above 8000 Hz, gradually involving lower frequencies. The fact that MCP841 treatment protocol did not cause any appreciable hearing threshold shift at follow up evaluation in conventional audiometry may be interpreted as the lack of any ototoxic effect of the chemotherapy regimen at these frequencies in our study sample.

It was also noted that the median hearing thresholds on conventional audiometry in our study at follow up were 5dB better than that of baseline measures. This can be due to test-retest variability which is a known entity with respect to conventional audiometry testing especially in children. More over the better clinical condition of the child at the completion of early intensive phase of chemotherapy than at baseline evaluation could have also resulted in better thresholds post therapy. Riga et al [21] have reported a similar study on ten children with leukemia receiving chemotherapy as per BFM-95 protocol in which DPOAEs revealed a declining tendency, however changes did not reach statistical significance. Pure tone audiometry and stapedial reflex thresholds were not altered. The possibility of having the higher frequencies involved in ototoxicity cannot be ruled out even when the thresholds are within normal limits for conventional audiometry. In the present study comparison of high frequency audiometry thresholds before and after chemotherapy did show increase in the thresholds though it was not statistically significant. Hearing loss is first noticed in high frequency range which progresses to lower frequencies. Early detection of hearing loss above 8 kHz and prompt initiation of preventive measures can stop the hearing loss from "spreading" into lower frequencies. Hearing loss at lower frequencies is much more noticeable to the patient and can negatively impact communication and quality of life. American Academy of Audiology "Position Statement and Clinical Practice Guidelines for Ototoxicity Monitoring" (AAA 2009) advocate the use of extended high-frequency testing when possible to improve test sensitivity

DPOAEs are considered to be sensitive to ototoxic damage coincident with, or that might lead to, hearing changes. DPOAEs depend on the physiological status of the outer hair cells (OHC) which are typically affected first by most ototoxic medications and therefore should be a sensitive and specific measure of hearing change. DPOAEs provide frequency specific information on OHC dysfunction and hence are considered ideal measures of ototoxicity. Our study found that changes observed in DPOAE amplitudes were not statistically significant at all frequencies in both ears except in right ear at 8k (p=0.017). However the reduction in the SNR (Signal Noise Ratio) in post chemotherapy in comparison with baseline measures cannot be ignored though it has failed to reach the level of statistical significance. Earlier studies done by Ress et al [13] and Lonsbury et al [22] have shown that OAE detects damage to high frequency region before it affects speech frequency. Study by Lisowska et al [11] compared DPOAEs with conventional audiometry in 10 children with ALL on IC-BFM 2002 protocol. The results of the study were in favor of using DPOAE as a more sensitive technique for the assessment of chemotherapy induced ototoxicity than conventional audiometry. The study found a significant decrease in DPOAE amplitude at all frequencies studied in 50% children with leukemia which was evident only during and after first protocol of ALL IC-BFM 2002, which was found reversible on long term follow up. Lisowska has also documented a large individual variability in DPOAE response following chemotherapy and in few cases a transient increase in DPOAE amplitude had been observed before it was reduced. This is similar to the findings in our study where median SNR was increased in the right ear at 8k ($p=0.017$) at follow up after 6 months .This could be the transient rise in SNR before it reduces, and requires long term follow up evaluation to find whether there is reduction in SNR amplitudes. Hence, DPOAE is observed to be a more sensitive technique for the assessment of chemotherapy-induced ototoxicity than conventional audiometry.

Conclusion

We observed that changes in hearing thresholds for high frequencies and DPOAE amplitudes were observed in children exposed to MCP841 protocol, though it failed to reach a statistically significant level. This difference was not seen in conventional audiometric thresholds. Hence it is concluded that extended frequency audiometry as well as DPOAES

may reveal ototoxic effect in children better than conventional audiometry. The MCP841 protocol did not adversely affect the hearing in children with ALL at the end of early intensive phase of chemotherapy. However the results of the present study needs to be strengthened by including larger sample and long term follow up. Ototoxicity monitoring programs should be joint initiative of clinicians and audiologists, aimed to prevent or minimize the hearing loss in order to maintain effective communication and quality of life.

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