Distortion Product Otoacoustic Emissions and High Frequency Audiometry for Early Detection of Cisplatin Induced Ototoxicity

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ABSTRACT

Introduction: Ototoxicity is chemical injury to the labyrinth occurring as a side effect of pharmacotherapy.The most frequent pattern of hearing loss in cisplatin ototoxicity is a bilateral, symmetric, progressive, high frequency, sensoneural hearing loss, caused by loss of cochlear outerhair cells. The aim of this research was to study the pattern of changes in hearing status of patients undergoing cisplatin chemotherapy and to study the distortion product otoacoustic emissions and high frequency audiometry for early detection of ototoxicity in terms of hearing loss.

Material and Methods: This study was conducted in the tertiary care teaching institute from January 2015 to June 2016. Total 63 patients were included in the study. After clinical examination all patients underwent Pure tone Audiometry (PTA), Distortion product otoacoustic emissions (DPOAEs) and baseline haematological investigations. A baseline PTA was done in all patients prior to the initiation of the cisplatin chemotherapy to detect any hearing loss before further evaluation of the patient.

Results: In the present study30 (47.6%) patients were detected with significant ototoxic changes. Significant ototoxic changes were found in 27 (90.0%) patients by both the high frequency audiometry and Distortion product otoacoustic emissions at the same time. 3(10%) patients were picked up earliest by high frequency audiometry.

Conclusion: We concluded that both the tests are equivalent and complementary in detection of cisplatin induced ototoxicity.

Keywords: Ototoxicity, Cisplatin, Pure Tone Audiometry, High Frequency Audiometry, Distortion Product Otoacoustic Emissions

INTRODUCTION

Ototoxicity is chemical injury to the labyrinth occurring as a side effect of pharmacotherapy. These ototoxic drugs may be vestibulotoxic, cochleotoxic or both.Cisplatin used in many chemotherapy regimens, causes permanent hearing loss by degenerating outer hair cells. Clinical presentation in cisplatin ototoxicity is permanent and usually irreversible hearing loss.[1] Tinnitus and fullness in ear are usually early symptoms of cochlear toxicity, while vestibular toxicity may present as vertigo, nausea, ataxia or nystagmus. The cellular mechanism for ototoxicity is oxidative stress, via an increased production of reactive oxygen species and free radicles.These interact with cell membrane phospholipids to create aldehydes lipid peroxidation products that promote programmed cell death. Factors affecting the severity of ototoxic reaction to cisplatin are a high cumulative dose, age extremes, preexisting hearing loss, anemia, co-administration of other ototraumatic agents or high dose vinca alkaloids, and prior cranial irradiation. The most frequent pattern of hearing loss in cisplatin ototoxicity is a bilateral, symmetric, progressive, high frequency, SNHL, caused by loss of cochlear outer hair cells. Following intravenous administration, cisplatin has an initial plasma half-life (t1/2) of 20-30 minutes. The variability of the terminal t1/2 of 6 to 47 days is related to the extensive (>90%) plasma protein binding displayed by cisplatin. Cisplatin undergoes incomplete urinary excretion via renal tubule secretion and glomerular filtration, with detectability in tissue samples for as long as 4 months post administration. Cisplatin preferentially concentrates in the liver, kidneys, and large and small intestines, with low penetration of the central nervous system. High frequency audiometry and OAEs are used for early detection of hearing loss due to cochleotoxic substances. This study was conducted with the aim of early detection of changes in hearing status presumably attributed to cisplatin so that changes in the treatment regimen may be considered, and adequate audiologic intervention can be considered when handicapping hearing impairment has occurred.

MATERIAL AND METHODS

This study was conducted in the tertiary care teaching institute from January 2015 to June 2016. Patients who have received prior chemotherapy and those who complaint of hearing loss prior to undertaking cisplatin chemotherapy were excluded from the study.Total 63 patients were included in the study. After clinical examination all patients underwent Pure tone Audiometry (PTA), HFA, Distortion product otoacoustic emissions (DPOAEs) and baseline haematological investigations. Histopathology (HPE) of all patients was recorded. A baseline PTA was done in all patients prior to the initiation of the cisplatin chemotherapy to detect any hearing loss before further evaluation of the patient. Ethical clearance and informed consent was taken before the start of study.

Cisplatin administration

The patients were followed for 3-4 cycles of cisplatin administration. Each patient received cisplatin dosage as per the own protocol of the department of radiotherapy based on the cell type of the tumor and body surface area. All the patients in our study underwent weekly cisplatin administration on day care basis with concurrent radiotherapy.

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How to cite this article: Manika Teotia, Sampan Singh Bist, Vinish Kumar Agarwal, Meenu Gupta. Distortion product otoacoustic emissions and high frequency audiometry for early detection of cisplatin induced ototoxicity. International Journal of Contemporary Medical Research 2017;4(6):1315-1318.

Testing method

A baseline audiogram was taken 1 week prior for each patient before commencing the study including the high frequency audiometry to rule out any pre-existing hearing loss. HFA and DPOAEs were done after 1 day of cisplatin administration for 3 to 4 cycles.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS 17.The Pearson's chi-square test or Fisher's exact test was used to determine the relationship between two categorical variables. One-way analysis of variance (ANOVA) was used to evaluate the significance of the differences in cisplatin dose and cisplatin cumulative dose at last test (mg/m^2) among different diagnosis. P<0.05 was considered statistically significant.

RESULTS

In the present study of 63 patients the median age was found to be 55 years. The mean age was 52.52± 12.80 years. Of the total 63 patients there were 41 (65.1%) males and 22 (34.9%) females with a male to female ratio of 1.8:1.Majority of the patients in our study i.e. 36(57.1%) patients were smokers as compared to 27(42.8%) patients which were non -smokers. In the present study the mean cisplatin dose per cycle was 62.22±26.61 with a minimum-maximum dose ranging from 30-120mg/m^2. The mean cisplatin cumulative dose at last test came out to be 188.89±95.58 with a minimum-maximum range between 60-400 mg/m^2.The cumulative dose of cisplatin received at the end of last test was found to be 150 mg/m^2 in 17 (27%) patients, followed by 120mg/m^2 in 10 (15.9%) patients. In our study out of 63 patients, 24 patients were of head and neck region malignancy and 39 patients were of non-head and neck malignancy (Table 1).

In the present study 30(47.6%) patients were detected with significant ototoxic changes. In the conventional frequency range 25 (39.7%) patients developed ototoxicity in both ears, 2 (3.2%) developed ototoxicity in left ear only whereas 36 (57.1%) patients had no significant changes in either ear. In high frequency audiometry, 29 (46%) patients developed ototoxic changes in both ears; only 1 (1.6%) patient had significant ototoxic change in left ear only while 33 (55.6%) patients had no significant ototoxic changes. Significant changes in DPOAEs were observed in 28 (44.4%) patients. No such patients were there in which the changes in DPOAEs were observed in an isolated ear. In 35(55.6%) patients DPOAEs came out to be normal at the end of the test. In our study 27 (42.9%) patients were those in whom the earliest ototoxic changes were observed simultaneously by both the DPOAE and HFA. There were 3 (4.8%) patients in whom earliest changes were observed by HFA and 33 (52.4%) patients were in which no changes were observed. There were no such patients in whom the earliest detection of ototoxicity was done by DPOAEs (Table 2).

DISCUSSION

In our study 56% (n=41) males and 31.8% (n=22) females developed ototoxicity. The possible reason for male preponderance could be due to larger number of male patients in our study group of which majority were of head and neck cancer which also received concurrent radiotherapy. The incidence of ototoxicity in our study was found to be 47.6%. Our study was in accordance with one in which audiometric monitoring of cisplatin ototoxicity was done in 37 patients and ototoxicity was noted to occur in 46% of the patients during cisplatin therapy.[2] In another study the incidence rate of ototoxicity detected with DPOAE was 77.3% in adult patients.[3] In our study 42.9% patients developed significant ototoxic changes in the conventional frequency range out of total 47.6% patients who had ototoxicity. Out of these 42.9% patients, 3.2% patients showed changes in the left ear only. This could be explained on the basis that PTA being a subjective test there could be either inconsistent response from the patient or examining methods could have faltered because as per the literature the hearing loss in cisplatin induced ototoxicity is bilateral and symmetric. Significant ototoxic changes were found in 44.4% patients by DPOAEs. In our study no such patient was there in whom earliest detection of ototoxic change was done by DPOAEs alone. However DPOAEs detected ototoxicity in conjunction with HFA. 2 patients were not picked up by DPOAEs who showed ototoxicity in HFA. Overall 47.6% patients were picked upon HFA. Earliest detection of ototoxicity by HFA was seen in 3 (4.8%) patients, but 1 of the patient developed changes in left ear only. Same patient also had changes in the conventional

Site of malignancy	Total	Patients with concurrent radiation	Patients without concurrent radiation	Patients who developed ototoxicity (n=24)	Patients who developed ototoxicity with concurrent radiation(n=22)
Head and neck	24(38.1%)	22(38.5%)	2(33.3%)	18(60%)	16(59.2%)
Non head and neck	39(61.9%)	35(61.40)	4(66.6%)	12(40%)	11(40.74%)
Total	63	57	6	30	27

Table-1: Correlation of radiation, ototoxicity and malignancy site

	Ototoxicity in conventional frequencies		Ototoxicity HFA		Significant change DPOAEs	
	No. of patients	Percentage	No. of patients	Percentage	No. of patients	Percentage
Both ear	25	39.7%	29	46.0%	28	44.4%
Left ear	2	3.2%	1	1.6%	0	0
No	36	57.1%	33	52.4%	35	55.6%
Total	63	100%	63	100%	63	**100%**

Table-2: Distribution of ototoxicity in individual tests (n=63)

frequency range but had normal DPOAEs. The ototoxicity detection rate of HFA was 47.6%, in our study. The probable reason why HFA based ototoxicity was found in these 3 (4.8%) patients could be explained on the basis that significant ototoxic change criteria for HFA are well established with excellent specificity and sensitivity while for DPOAEs the criteria was based on the studies of DPOAE variability in healthy young adults.[4-6] The second probable reason for the effectiveness of HFA is based on the fact that measurement of DPOAE was limited to the frequency of 8 kHz thus reducing its sensitivity whereas on the other hand in HFA, the highest frequency measured was 16 kHz. Conventional frequencies were subsequently involved in each cycle. The basic audiological assessment conventionally limited to frequencies of 8 kHz and below, unfortunately, does not permit the earliest detection of ototoxic changes which tend to manifest in the outer hair cells (OHCs) of the basal cochlear turn. Another important limitation of OAE testing mentioned in literature is that the results are significantly affected by middle ear pathology such as otitis media. That is, OAEs are difficult to record reliably, if detected at all, in the presence of otitis media.[7,8] Our study was in accordance with one in which conventional pure-tone audiometry (0.5 to 8 kHz) and evoked distortion product otoacoustic emissions (DPOAEs) were conducted for 32 patients age 8 months to 20 years who were treated with cisplatin and/or carboplatin chemotherapy. The study found EHF audiometry provided the earliest indication of ototoxicity in their series.[9] Another study found that both EHF-PTA and DPOAE showed the same sensitivity in detecting ototoxicity, the incidence rate of cisplatin-induced ototoxicity was 40% with EHF-PTA or DP-OAE.[10] On the contrary one study found that DPOAE could be recorded in a greater number of patients than could EHF thresholds and that they were equally sensitive in detecting ototoxic change in those patients who could be tested using both measures.[11] In our study the probable reason for the development of significant ototoxic changes in patients with head and neck malignancy could only be explained on the basis of concurrent cranial irradiation along with chemotherapy. There were 24 patients of head and neck malignancy of which 22 (91.6%) received cranial irradiation. Ototoxicity occurred in 18 (60%) patients out of 24 including 2 of those patients who did not received cranial irradiation, therefore 16 (59.2%) patients were those who received both chemotherapy and radiotherapy and developed ototoxic changes. 2 patients were those who developed ototoxic changes without receiving radiation. 6 head and neck patients did not have any ototoxic changes. In our study majority of the patients receiving cranial irradiation also developed ototoxic changes which could be due to radiation induced cochlear damage. This finding is consistent with several studies reflecting cranial irradiation as a risk factor for the development of ototoxicity and have observed that concurrent or prior cranial irradiation increased susceptibility to the ototoxic potential of cisplatin.[12-15] No correlating study could be found between the development of ototoxicity and site of malignancy. A single chemotherapeutic agent like cisplatin can be administered in a wide variety of cancers in different regimens so correlating the site of malignancy with ototoxicity is not feasible. This could be because the ototoxic damage is largely dependent on the chemotherapeutic agent characteristics, its cumulative dosage, schedule and cranial irradiation. In our study the development of ototoxicity increased with increasing number of cycle and increasing dosage/cycle which was in accordance with another study finding which suggested that the audiological changes are typically bilateral, irreversible and progressive; they begin in high frequencies with subsequent extension for medium and low frequencies as the number of cycles increases.[16]

CONCLUSION

Significance of early detection of ototoxicity lies in identifying cisplatin induced hearing loss in already debilitated patients and thus trying to improve the quality of life and preventing the disability caused by the treatment. Comparison between the two tests is not feasible as HFA being a subjective test can be less reliable as compared to DPOAE which is an objective test but again has its limitation in patients with middle ear diseases. We concluded that both the tests are equivalent and complementary in detection of cisplatin induced ototoxicity.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 18-05-2017; **Accepted:** 23-06-2017; **Published:** 06-07-2017