# EVALUATION OF OTOPROTECTIVE EFFECT OF ANTIOXIDANT SUPPLEMENTATION WITH VITAMIN E ON SENSORINEURAL HEARING LOSS IN PATIENTS TREATED WITH CISPLATIN CONCURRENT CHEMORADIOTHERAPY FOR HEAD AND NECK SQUAMOUS CELL CARCINOMA

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**ABSTRACT**

**AIMS AND OBJECTIVES**

The objective of this study evaluation of otoprotective effect of antioxidant supplementation with Vitamin E on Sensorineural Hearing Loss (SNHL) in patients treated with cisplatin Concurrent Chemoradiotherapy (CRT) for Head and Neck Squamous Cell Carcinoma (HNSCC).

**METHODS**

The study comprised of audiological evaluation of 60 patients prior to and at the completion of treatment using pure tone audiometry.

**RESULTS**

At the end of 6 weeks, incidence of SNHL found to be 65.38% seen in patients who have not received Vitamin E supplement as compared to incidence of 10% seen in patients treated with CRT along with Vitamin E seen at higher frequencies and significant otoprotection offered by Vitamin E supplement was observed at 8kHz.

**DISCUSSION**

The possible mechanism for hearing loss are discussed and compared with the result of such studies in literature.

**CONCLUSION**

There is definitive benefit of oral Vitamin E supplement in preventing this hearing loss, more so at higher frequencies.

**KEYWORDS**

Ototoxicity, Head and Neck Squamous Cell Carcinoma, Vitamin E, Cisplatin, Sensorineural Hearing Loss, Pure Tone Audiometry.

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## INTRODUCTION

Cancers of the head and neck are the sixth most common type of cancer worldwide. There are approximately 5,60,000 new cases diagnosed and 300,000 deaths each year.[1] Incidence rates are more than twice as high in men than in women. Overall, 57.5% of global head and neck cancers occur in Asia, especially in India. Head and neck cancers in India accounted for 30% of all cancers and 60% to 80% of these patients present with advanced disease as compared to 40% in developed countries. Currently, the main treatment options for head and neck cancers are surgery, radiotherapy and chemotherapy.

The types of treatment used will depend on the site and disease stage as well as on the patient's overall health status. Surgical treatment is considered for early and locally advanced cancers, which is however associated with significant morbidity. Chemotherapy alone has been reserved for palliation of unresec table, recurrent, or metastatic disease.

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Concurrent CRT for organ preservation has been proved to be an effective alternative in achieving a high cure rate without morbidities associated with surgical resection. Cisplatin is an effective and widely used as chemotherapeutic agent and also as a radiosensitiser in radiotherapy.(2) Unfortunately, platinum agents have adverse effects such as nausea, vomiting, nephrotoxicity, neurotoxicity including ototoxicity and associated permanent hearing loss.(3) Platinum ototoxicity is typically manifested as bilateral high-frequency SNHL reported in 31% of patients.(4) Radiation to the ear enhances ototoxicity in patients treated with concurrent chemoradiation reported in 55% of patients.(5) Once clinically significant toxicity is observed on audiologic monitoring, available options include dose reductions or omissions, which will potentially reduce the cure. Further this hearing loss is permanent.(6) Therefore, prevention of this hearing loss would be valuable.

## MATERIALS AND METHODS

The present study was carried out in 60 patients in the age group of 18 to 75yrs. with 46 males and 14 females, presented to Department of Otorhinolaryngology and Head and Neck Surgery, Goa Medical College with diagnosis of advanced squamous cell carcinoma of the head and neck region proven by histopathology and were proposed to receive cisplatin concurrent CRT for the treatment of their cancer.

Patients receiving drugs known to cause ototoxicity other than cisplatin, patients with otitis media with effusion, tympanic membrane perforation, otosclerosis with conductive hearing loss and patients with concomitant neurological, psychological or medical disorders making them unsuitable for treatment or follow-up as per protocol were excluded from the study.

All patients underwent diagnostic audiological assessment involving a case history, physical examination, otoscopy and baseline audiological evaluation with Pure Tone Audiometry (PTA). PTA was performed for both air conduction and bone conduction using Arphi Diagnostic Audiometer 2001 model for 250Hz to 4kHz. Because bone conduction hearing testing is limited to 4000Hz, measurements at 8000Hz was performed using air conduction testing alone. Sensorineural hearing at high frequencies (8000Hz) tested by air conduction is unaffected by and independent of middle ear effusion.

Patients were randomly divided into two groups with group 1 assigned to receive cisplatin concurrent CRT without Vitamin E and group 2 assigned to receive cisplatin CRT along with Vitamin E supplementation as shown in Table 1.

| Groups | Treatment Received | Number of Patients | Percentage |
|---|---|---|---|
| Group 1 | Chemoradiation only | 26 | 43.33 |
| Group 2 | Chemoradiation+Vitamin E | 34 | 56.66 |

***Table 1: Number of Patients in Each Study Group***

All the patients were treated with cobalt-60 teletherapy unit with radiation dose of 60Gy in 30 fractions for the period of 6 weeks. Cisplatin was administered weekly interval to all 60 patients at the dose 50mg/sqm BSA starting from day 1.

Patients were required to be admitted overnight to allow for sufficient hydration. Cisplatin was administrated as IV infusion in 500ml of 0.9% saline at a rate of 1mg cisplatin per minute. In conjunction, all the patients were given Ondansetron 8mg IV, Pantoprazole 40mg IV and 500ml of 0.9% saline over one hour. In addition, patients in group 2 received 400mg of Vitamin E capsules once daily from day 1 till the completion of treatment.

PTA was repeated for all frequencies at completion of treatment. To ensure consistency, all PTA were performed by same Audiologist. Ototoxicity was measured using intrasubject audiogram comparisons. Each patient served as his/her control with the pretreatment audiogram serving as the baseline. Hearing threshold change was determined relative to each patient's baseline.

**RESULTS**

The mean pure tone thresholds of the patients of treatment group 1 (who received only CRT) of both ears is shown in Table 2.

| Frequency (Hz) | Mean Pretreatment PT Threshold (dbHL) | Mean Post Treatment PT Threshold (dbHL) | Mean Threshold Shift from Baseline (dbHL) |
|---|---|---|---|
| 250 | 11.15 | 11.15 | 0 |
| 500 | 10.76 | 10.76 | 0 |
| 1000 | 10.96 | 14.03 | 3.07 |
| 2000 | 11.4 | 21.4 | 10 |
| 4000 | 12.5 | 34.23 | 21.73 |
| 8000 | 13.26 | 51.53 | 38.26 |

***Table 2: Comparison of Mean dBHL Values of 26 Patients of Treatment Group 1 (who Received only CRT Without Vitamin E) at Baseline and Post CRT at Different Frequencies in PTA.***

The mean pure tone thresholds of the patients of treatment group 2 (who received CRT along with Vitamin E) of both ears is shown in Table 3.

| Frequency in Hz | Mean Pretreatment PT Threshold (dbHL) | Mean Post Treatment PT Threshold (dbHL) | Mean Threshold Shift from Baseline (dbHL) |
|---|---|---|---|
| 250 | 11.32 | 11.62 | 0.29 |
| 500 | 11.18 | 11.62 | 0.44 |
| 1000 | 11.32 | 12.94 | 1.61 |
| 2000 | 11.62 | 15.59 | 3.97 |
| 4000 | 13.24 | 31.47 | 18.23 |
| 8000 | 14.26 | 38.09 | 23.82 |

***Table 3: Comparison of Mean dBHL Values of 34 Participants of Group 2 (who Received CRT Along With Vitamin E) at Baseline and post-CRT at Different Frequencies in PTA.***

In study group 1 (who received only CRT without Vitamin E), there was a statistically significant ($P < 0.05$) increase in the mean threshold values from baseline to post CRT values seen at frequencies 1000Hz, 2000Hz, 4000Hz and 8000Hz with mean hearing loss of 3dB, 10dB, 21dB and 38dB respectively.

In study group 2 (who received CRT along with Vitamin E), there was a statistically significant ($P < 0.05$) increase in the mean threshold values from baseline to post CRT values seen at frequencies 1000Hz, 2000Hz, 4000Hz and 8000Hz with mean hearing loss of 2dB, 4dB, 18dB and 24dB respectively.

**DISCUSSION**

As combined modality therapy becomes the standard of care in the treatment of many head and neck cancers, there are

increasing concerns of ototoxicity as cisplatin and radiation are known to cause hearing loss independently.

Clinically, cisplatin ototoxicity has been described as a bilateral, cumulative, dose-related and usually permanent SNHL that starts at ultra-high frequencies and with increasing dose or prolonged treatment, progressively extends to frequencies involved in speech perception.[7] This ultra-high to low frequency gradient seems biologically explained by the finding that outer hair cells near the base of the cochlea are reported to be affected first by cisplatin, progressing to apical cells with increasing dose.[8] In addition, the drug interferes with the morphology and function of the stria vascularis with special affinity to the marginal cells in the basal turn of the cochlea.[9]

Adverse effects of radiotherapy involving the ear are chronic external otitis, stenosis of the external ear canal, atrophy or ulceration of the skin, otitis media due to dysfunction of the Eustachian tube and in the long-term osteoradionecrosis of the temporal bone and mastoiditis. Radiation-induced SNHL has been observed to an incidence of 49% directly post-treatment and to an incidence of 46% at 4-5 years after therapy of patients treated with RT fields exposing the inner ear.[10] Radiation-induced vascular insufficiency has been regarded as the etiology of SNHL, while in animal models the exposure of inner ears to radiation resulted in destruction of outer hair cells and inner hair cells, atrophy of the stria vascularis and a reduced number of afferent nerve endings.[11]

In present study, the incidence of SNHL seen at higher frequencies in patients treated with CRT along with Vitamin E (Group 2) found to be 10% as compared to the incidence of 65.38% seen in patients who have not received Vitamin E supplement (Group 2). On statistical analysis, significant otoprotection ($p < 0.05$) offered by Vitamin E supplement was observed at 8kHz. In a study conducted by Paksoy et al. on Wistar rats found significant otoprotection of Vitamin E on cisplatin induced ototoxicity and suggested that Vitamin E appears to have an easier, safer, usable protective effect against cisplatin ototoxicity.[12]

In a study conducted by Fetoni et al. on Hartley albino guinea pigs, found beneficial effects of alpha-tocopherol and tiopronin on cisplatin-induced ototoxicity.[13]

In a study conducted by Tokgöz et al. observed Vitamins B, E and C and L-carnitine appear to reduce cisplatin induced ototoxicity in rats.[14]

In a study conducted by Weijl et al., 27 patients of carcinoma undergoing cisplatin-based combination chemotherapy, 13 were randomized to receive a beverage supplemented with Vitamin C, Vitamin E and selenium, while the remaining 14 cancer patients received a beverage without Vitamins E and C and selenium. They have found no statistical significance in between the study groups.[15]

## CONCLUSION

There is definitive risk of developing significant hearing loss at high frequencies with the incidence of 65.38% in patients with HNSCC undergoing treatment with Cisplatin concurrent CRT. There is definitive benefit of oral Vitamin E supplement in preventing this hearing loss more so at higher frequencies, which is around 8 kHz. Therefore, it is recommended that oral Vitamin E, which is inexpensive and readily available should be used in patients with HNSCC undergoing treatment with cisplatin concurrent CRT so as to protect the hearing loss.

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