Protective Role of Calcium Channel Blocker Flunarizine on Cisplatin Induced Ototoxicity: A Clinical Study

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ABSTRACT

Introduction: Cisplatin is a well known platinum-based anticancer agent used for the treatment of various malignant tumours. A frequent side effect of cisplatin therapy is hearing loss. flunarizine is a calcium channel blocker frequently used in prophylaxis of migraine.

Material and methods: In this study we evaluated the effectiveness of flunarazine in prevention of cisplatin induced ototoxicity. The study included 40 cancer patients to be started on cisplatin. Out of 40 patients, 20 patients received flunarizine 10 mg daily and the rest 20 received placebo(control group).Serial pure tone audiograms were evaluated at 0,3 and 6 weeks.

Results: In our study, flunarizine treated patients were protected mainly at speech frequencies of 1 and 2 kHz. At 3 weeks the maximum average hearing loss in study group was 39 dB against 57 dB in the control group.

Conclusions: The patients who received concomittant flunarizine with cisplatin showed better average pure tone score over speech frequencies than control group. There were no significant side effects reported with flunarizine.

Keywords: platinum, calcium channel blocker, migraine, pure tone audiograms.

INTRODUCTION

Cisplatin is a widely used chemotherapeutic agent to treat solid tumours such as metastatic testicular and ovarian carcinoma. Cisplatin is highly emetic drug with various side effects like nephrotoxicity, ototoxicity, hyperuricaemia. Nearly all the patients treated with cisplatin have reported some degree of sensorineural hearing loss.[1] High frequency sounds in the range of (4000-8000kHz)[2] are commonly affected. Even low doses of cisplatin (10mg/kg) can be detrimental to hair cells and stria vascularis[3] of cochlea. Flunarizine is calcium channel blocker used in migraine prophylaxis and various cerebrovascular disorders. Various antioxidant agents have been tried to decrease cisplatin induced ototoxicity like intratympanic corticosteroids[4], N acetylcysteine, neurotrophins. The invasive approach to deliver the agent into inner ear and inconsistent response made their use troublesome. The purpose of this study was to evaluate the preventive effect of oral flunarizine on cisplatin induced hearing loss.

MATERIAL AND METHODS

The study included 40 cancer patients who were to receive cisplatin as a chemotherapeutic agent at G.G.S medical college, faridkot department of E.N.T from January 2014 to September 2015. Sample size was based on the inclusion exclusion criteria. Study was approved by the institutional ethical committee and was done after taking informed consent from the subjects.

The inclusion criteria were

- Cancer patients in the age group 15 to 60 who were planned for cisplatin therapy(50-100mg/m^2).
- Patients with pretreatment normal hearing sensitivity.

The exclusion criteria were

- Patients with previous irradiation to head and neck region.

Patients were distributed into 2 equal groups of 20 each with age and dose standardization. Oral flunarizine 10 mg was started to study group at start of cisplatin therapy. Patients in the control group received oral placebo. Serial pure tone audiometries were recorded at 0,3 and 6 weeks.

STATISTICAL ANALYSIS

Results obtained were tabulated and statistically analyzed using descriptive statistics.

RESULTS

40 cancer patients who were to receive cisplatin infusions in the dose range 50-100mg/m^2 were included in the study. Out of 40 patients, oral flunarizine tablets were given to 20 patients in the study group while control group of 20 patients received oral placebo for six weeks.

Table -1 shows that out of 40 patients 28 were male and 12 were female. Age group 51-60 had maximum number of patients.

Out of 40 patients,31 had bilateral hearing loss (table-2).

All the patients in the control group showed loss at 8kHz at 6 week follow up (table-3).

At 3 and 6 weeks maximum patients had hearing loss in the range of 21-40 dB in both groups (table-4).

DISSCUSION

Cisplatin is one of the most widely used chemotherapeutic agent in treatment of human tumors. The risk of ototoxicity and nephrotoxicity commonly hampers the use of higher doses to maximize its antineoplastic effects. Cisplatin-induced ototoxicity lesions usually appear in early stages (from hours to days after exposure)[5], leading to symmetri-

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Age group	Male	Female
15-20	2	1
21-30	4	2
31-40	8	2
41-50	5	3
51-60	9	4

Table-1: Distribution of patients according to age and gender

Total	Right	Left	Bilateral
40	4	5	31

Table-2: Distribution of patients according to site

Frequency	Follow up	Study group	Control group
500 Hz	3 weeks	0	0
	6 weeks	0	0
1 kHz	3 weeks	0	2
	6 weeks	0	12
2 kHz	3 weeks	2	5
	6 weeks	4	12
4 kHz	3 weeks	8	10
	6 weeks	12	16
6 kHz	3 weeks	13	18
	6 weeks	18	19
8 kHz	3 weeks	11	15
	6 weeks	17	20

Table-3: Distribution of patients according to affected frequency of hearing loss

Degree of hearing loss	Study group	Control group
0-20 dB		
3 weeks	9	3
6 weeks	11	0
21-40 dB		
3 weeks	11	11
6 weeks	7	12
41-60 dB		
3 weeks	0	6
6 weeks	2	8
61-80 dB		
3 weeks	0	0
6 weeks	0	0
81-100 dB		
3 weeks	0	0
6 weeks	0	0
100-120 dB		
3 weeks	0	0
6 weeks	0	0

Table-4: Distribution of patients according to degree of hearing loss

cal[6], progressive, irreversible, cumulative and dose-dependent bilateral sensorineural hearing loss. Wang et al. showed that giving a dose of 10 mg/kg cisplatin induces apoptosis of cochlear cells, especially in inner and outer hair cells, and stria vascularis.[3] Nearly all patients treated with cisplatin have some degree of sensorineural hearing loss. Ototoxicity and nephrotoxicity are major dose limiting side effects of cisplatin, requiring discontinuation and subsequent replacement by other chemotherapeutic agent. Ototoxicity caused by cisplatin has effects on a number of inner ear structures, including the stria vascularis, supporting cells, spiral ganglion cells, and outer hair cells (OHCs).[9] Symptoms of ototoxicity include subjective hearing loss, ear pain, or tinnitus.[10] Ideal otoprotectant to be used along with cisplatin should be easy to administer and should not interfere with antitumoral effect of cisplatin. Cisplatin increased cell death via increase in lipid peroxidation and altered mitochondrial permeability transition[11], which was inhibited by a calcium-channel blocker, flunarizine. Flunarizine is an antagonist of T-type specific calcium channels has been widely used to treat vertigo, migraine, epilepsy and tinnitus. The protective mechanism of flunarizine on cisplatin-induced cytotoxicity is associated with direct inhibition of lipid peroxidation and mitochondrial permeability transition.[12] In our study, flunarizine treated patients were protected mainly at speech frequencies of 1 and 2 kHz(Table 3). At 3 weeks the maximum average hearing loss in study group was 39 dB against 57 dB in the control group (Table 4). At 6 weeks only 2 patients in the study group had hearing loss above 40 dB while it was 4 times in the control group (Table 4).

CONCLUSION

Cisplatin is widely used anticancer agent which causes irreversible hearing loss. Various treatment modalities have been tried concomitantly to prevent cisplatin ototoxicity like intratympanic steroids, ginkgo biloba, various antioxidants like vitamin E, lipoic acid. Oral flunarizine is a novel approach to decrease the irreversible assault of cisplatin and its metabolites on auditory cells. Flunarizine is well tolerated and has minimal side effects with oral mode of administration thus making flunarizine ideal otoprotective agent to be coadministered with cisplatin infusions.

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