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Original article

Efficacy and Safety for the Combination of Alpha Lipoic Acid, Gingko Biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E and Chromium Picolinate in the Patients of Sudden Sensorineural Hearing Loss and High Intensity Noise and Vibration Induced Hearing Loss: Post Marketing Surveillance Study

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Abstract

Introduction: Sudden sensorineural hearing loss (SSNHL) is defined as sensorineural hearing loss of 30 dB or more over 3 contiguous audiometric frequencies occurring over 72hrs. Conventionally the SSNHL is treated by corticosteroids but it is considered that, addition of antioxidants to the treatment can increase the percentage of patients with the complete recovery. So, this study was conducted to test the efficacy and safety for the combination of Alpha lipoic acid, Gingko biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E and Chromium Picolinate for the treatment of SSNHL and high Intensity noise and vibration induced hearing loss as a concomitant therapy in addition to the standard medical management. ***Methodology:*** Out of total 225 enrolled, 208 patients completed the study. Efficacy and safety evaluation was done on day 7 and 14 considering the baseline visit at day 0. Efficacy assessment was done by hearing Impairment questionnaire and hearing related quality of Life. ***Results:*** Mean score obtained from hearing impairment questionnaire at day 0 was 19.59 which was reduced to 12.56 at day 7 and was further reduced to 7.70 at day 14. On Visit 1 the mean hearing related quality of life score was 5.24 which was increased to 6.4 at day 7 and was found to be further increased to 7.41 at day 14. ***Conclusion:*** The investigational product was efficacious and safe for the treatment of SSNHL and high Intensity noise and vibration induced hearing loss when given as a concomitant therapy to the standard medical management.

Keywords: ***Sudden Sensorineural hearing loss, Alpha lipoic acid, Gingko biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E and Chromium Picolinate.***

Introduction

Hearing loss due to impaired function of auditory nerves, cochlea, or central auditory processing is characterized as sensorineural hearing loss (SSNHL). It is defined as sensorineural hearing loss of 30 dB or more over 3 contiguous audiometric frequencies occurring over 72 hrs. It is observed that sensorineural hearing loss is the most frequent complaint during otology and audiology practices [1]. Noise-induced hearing loss (NIHL) is the common audiological complaint characterized as sensorial deafness caused due to exposure of an individual to noise for a longer interval. Approximately 1.1 billion youngsters aged 12 to 35 years old suffers from NIHL. When an individual is exposed to traumatic noise it leads to damage to the cochlea and specifically destroys sensory cells. Researchers also observed that this traumatic noise also damages sensory epithelium and adjacent compartments [2]. SSNHL occurs in 5 to 20 adults per 1 lakh of the population. Individuals of all groups suffer from SSNHL but peak incidences were observed in the age group between 50 to 60 years [1]. Social changes day by day increase noise exposure. When an individual is exposed to sound with intensity above 85 dB may have the risk of NIHL. It varies from individual to individual depending upon the noise sensitivity. More intensity of noise is developed from

industrial sectors as well as from the recreational noises such as playing of personal music devices. Nowadays continuous usage of headphones by the younger population may increase the risk of NIHL [3]. Other prevailing factors are sedentary lifestyle with lack of exercise, alcoholism, diabetes, smoking and some non-modifiable causes including genetic heritage, race, and aging. These factors facilitate the NIHL disease progression [4].

Conventionally the SSNHL is treated with corticosteroids but addition of antioxidants to the treatment can increase the percentage of patients with the complete recovery [5]. So this study was conducted to test the efficacy and safety for the fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg per capsule for the treatment of SSNHL and NIHL in addition to the standard medical management in Indian patients.

Zinc is commonly found in the cochlea and especially in the stria vascularis in the form of Copper/Zinc superoxide dismutase which is the first line of defense against the free radicle and oxidative damage. Copper/Zinc superoxide dismutase activity and stability is considered to be impaired at low levels of plasma Zinc or plasma Copper [6,7]. Ginkgo biloba has antioxidant and protective effects on nerve cells in the brain, auditory cortex, and subcortical field and it also contains monoamine oxygenase inhibitors including ginkgolide and bilobalide as well as myricetin and quercetin flavonoids because of which it can be used for the treatment of SSNHL and NIHL [8]. Alpha lipoic acid has antioxidant properties and it also strengthens and restores the intrinsic antioxidant systems and facilitates their development or cell accessibility [9]. Alpha-lipoic acid is one of the most important antioxidant that helps to protect mitochondrial function by preventing reactive oxygen species accumulation, oxidative stress and apoptotic cell death [10]. Vitamin E is an effective free radical scavenger and a potent fat-soluble antioxidant that protects the outer hair cells from oxidative stress and lipid peroxidation. Similar to Vitamin E, Vitamin C is also an important water soluble antioxidant and also have free radicle scavenging activity [11]. Vitamin B6 also has antioxidant properties which reduces the oxidative stress, it also has free radicle scavenging activity because of which it scavenges free radicles and inhibits the lipid peroxidation. Also vitamin B6 serves as an coenzyme in the glutathione antioxidant defense system and indirectly plays a role as an antioxidant [12]. Methylcobalamin (vitamin B12) scavenges reactive oxygen species mostly superoxide, it has important role in the preservation of Glutathione because of which it also has indirect role in the scavenging of reactive oxygen species, it also modulates the cytokine and growth factor production to offer protection from body's immune response induced oxidative stress, reduction of oxidative stress due to homocysteine and reduction of oxidative stress caused by advanced glycation end products [13]. Also, Chromium picolinate has antioxidant properties [14]. and because of which it can be used for the medical management of SSNHL. Magnesium has been shown to minimize noise-induced vasoconstriction, caused by the formation of free radicals. Few epidemiologic studies have shown that magnesium consumption protects against hearing loss. Antioxidants works in tandem with Magnesium intake to help reduce the hearing loss [15]. Ginkgo biloba extract which is derived from the ancient Chinese Ginkgo biloba tree contains flavones and terpenes. These phytoconstituents are known to prevent the development of free radicals and also has antioxidant activities [16].

Methodology

This study was conducted at 15 clinical trial sites from all over India. 225 patients were recruited for the study out of which 208 patients completed the study and 17 patients were lost to follow-up. This was a multicentric, non-randomized, open label, non-comparative, post marketing surveillance study which was conducted to test the efficacy and safety for the fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg per capsule on Indian patients of SSNHL and NIHL.

Inclusion and Exclusion Criteria

Patients with the confirmed clinical diagnosis of sudden sensorineural hearing loss and high intensity noise and vibration induced hearing loss were recruited in the study of any gender, ethnicity and comorbidity of age 18 to 75 years old who were willing to adhere to the study procedures as explained to the patient by the investigator and willing to sign the informed consent form.

Patients known to be hypersensitive to Alpha lipoic acid, Gingko biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E or Chromium Picolinate were excluded from the study. Also the patients suffering from the middle ear pathologies such as otitis media and the perforation of the tympanic membrane, patient suffering from any disease related to middle and external ear, patient planning to go for any surgery in the study duration, patients who cannot adhere to the study procedure (mentally Ill and patients with psychological problem) were excluded from the study. Also, patients with any known factor, condition or disease that, in the view of the investigator, might interfere with study compliance, conduct or interpretation were excluded from the study.

Investigational product

Investigational product used for the post marketing surveillance study was the fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg per capsule. The investigational product was dispensed at no cost by the investigator to the patient.

Study Procedure

Patients as per the inclusion and exclusion criteria were recruited for the study by the investigator. All the patients were well informed about risks and benefits of the investigational products and study procedures and only those patients were recruited for the study who were ready to stick to the study procedures. The study duration was of 14 days and considering the baseline visit as day 0, all the recruited patients were asked to visit the clinical trial site on day 7 and 14 for the efficacy and safety assessment. Day 0, 7 and 14 were considered as visit 1, 2 and 3 respectively. On baseline visit, 14 capsules of the investigational products were dispensed to the patient and were asked to take it in the dose of 1 capsule a day for the study duration of 14 days. Efficacy assessment was done by 2 parameters including hearing related quality of life and hearing impairment questionnaire. Whereas safety assessment was done by evaluation of reported adverse events. Brief information about the efficacy and safety assessment is provided in the efficacy and safety assessment section given below.

Efficacy assessment

For this study the efficacy assessment was done by 2 parameters including hearing Impairment Questionnaire and hearing related quality of life. For efficacy assessment via hearing impairment questionnaire, patients were asked to answer 10 questions including, 1) How much difficulty do you face while hearing in crowded places?, 2) How much difficulty do you face while hearing in quiet places in one to one conversation? 3) How much difficulty do you face while hearing the sounds of the doorbell or the mobile phone ringing?, 4) How much difficulty do you face while hearing the sound of the car honking?, 5) How much difficulty do you face while hearing the sound of people whispering?, 6) How much difficulty do you face while hearing the sound of a person in a telephonic conversation?, 7) How much difficulty do you face while hearing the announcements made at the airport or at the Railway station or at any other public places?, 8) Are there symptoms of dizziness or tinnitus in the ears when it is quiet?, 9) Do you often ask people to repeat what they say? and 10) Do you play the TV or the radio louder than your friends or relatives?. All the patients were asked to answer the above-mentioned questions in 4 options for which the score was ranging from 0 to 4 where 0 means no difficulty at all to 4 means cant hear at all. Accordingly sum of the score from all 10 questions were referred as hearing impairment questionnaire score. For the second parameter of efficacy assessment, hearing related quality of life, the patients were asked to rate the hearing related quality of life on a 10 point scale ranging from 1 to 10 where 1 means very poor to 10 means very good.

Safety assessment

Safety assessment was performed by recording the reported adverse event thorough investigation. Causality assessment for the reported adverse events was done to investigate the correlation of adverse event and investigational product.

Regulatory Matters

The investigational product was approved for manufacturing and marketing in India. The informed consent form was read and signed freely by all the patients recruited in this study.

Concomitant therapy

For the study duration of 14 days, all the investigators were asked to provide standard medical management to the patient for SSNHL or high intensity noise and vibration induced hearing loss but during the treatment no concomitant therapy was allowed to be taken by the patient containing Alpha lipoic acid, Gingko biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E and Chromium Picolinate or any other therapy containing the antioxidants.

Results

Total 225 patients were enrolled in this study at 15 clinical trial sites in India out of which 208 patients completed the study. Demographic details for the patients completed the study were as mentioned below in Table 1.

Table 1: Demographic details of the patients recruited in the study

Mean age of subjects	46.5
No. of Males in the study	157
No. of Females in the study	51

Efficacy Assessment

On Visit 1, the mean score obtained from hearing impairment questionnaire was 19.59 which was found to be reduced to 12.56 at visit 2 and was further reduced to 7.70 at visit 3. Graphical presentation of the percentage reduction in the mean score obtained from hearing impairment questionnaire is provided below in figure 1.

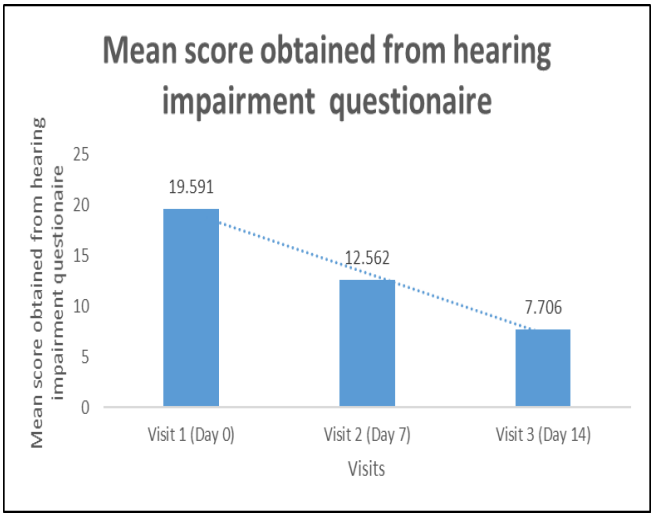

Fig. 1: Mean score obtained from hearing impairment questionnaire at visit 1, 2 and 3

The percentage reduction in mean score obtained from hearing impairment questionnaire at visit 2 and 3 was 35.87 % and 60.66 % respectively as compared to baseline which is graphically presented below in figure 2.

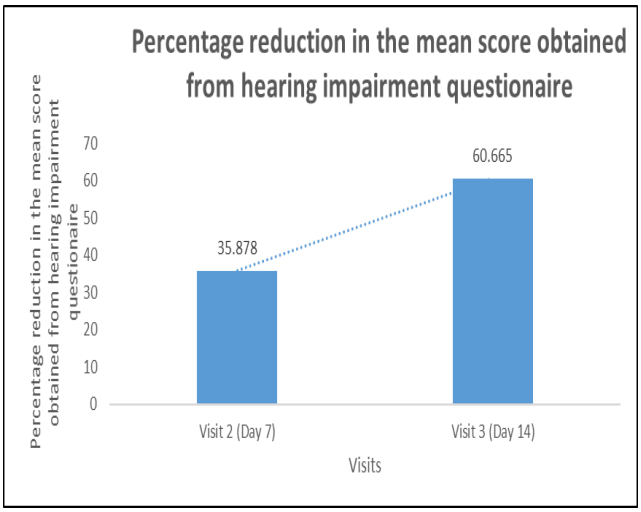

Fig. 2: Percentage reduction in the mean core obtained from hearing impairment questionnaire at visit 2 and 3 as compared to baseline

The second parameter for efficacy assessment was hearing related quality of life score. On Visit 1 the mean hearing related quality of life score was 5.240 which further increased to 6.403 on Visit 2 (day 7) and was found to be further increased to 7.408 at visit 3 (day 14). Data regarding the increase in the mean hearing related quality of life is graphically presented below in figure 3.

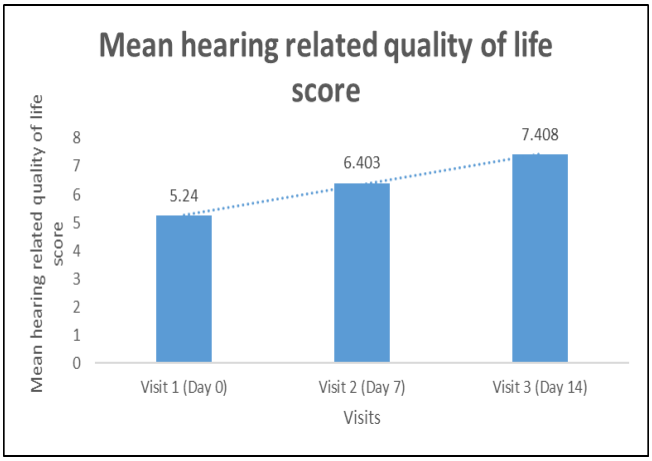

Fig. 3: Mean Hearing related Quality of Life score at visit 1, 2 and 3

Safety Assessment

In the study duration, 5 episodes of adverse drug reactions were reported which is presented in the tabular format below in the table 2.

Table 2: List of adverse drug reactions reported during the post marketing surveillance study

Adverse Drug Reactions	Number of episodes
Skin rashes	2
Nausea	1
Diarrhea	2

All the reported adverse drug reactions were of non-serious nature and mild in intensity.

Discussion

SSNHL is normally treated with corticosteroids but it is considered that, addition of antioxidants to the treatment can increase the percentage of patients with the complete recovery [17]. So this study was conducted to test the efficacy and safety for the fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg per capsule for the treatment of SSNHL and high intensity noise and vibration induced hearing loss in addition to the standard medical management in Indian patients. The efficacy assessment was made by hearing impairment questionnaire and hearing related quality of life. Mean score obtained from hearing impairment questionnaire was found to be reduced from 19.59 at baseline visit to 12.56 at visit 2 i.e. reduction of 35.87 % and further reduced to 7.70 at visit 3 i.e. reduction of 60.66 % as compared to baseline. The second parameter used for efficacy assessment was hearing related quality of life score. On Visit 1 the mean hearing related quality of life score was 5.24 which was increased to 6.4 on visit 2 (day 7) and was found to be further increased to 7.41 at visit 3 (day 14). So overall improvement was observed in both the efficacy parameters in most of the patients recruited in this study. Below we have discussed some of the studies which supports the study that we have conducted.

Chao-Hui Yang et al conducted a study to investigate the efficacy of Zinc when given as a concomitant therapy to corticosteroid treatment for the treatment of idiopathic sudden sensorineural hearing loss. The study was conducted on 66 patients out of which, 33 were randomized to corticosteroid treatment (control group) and 33 were randomized to oral Zinc gluconate plus corticosteroid treatment (Zinc group). Efficacy assessment was done by analyzing percentage of recovery and hearing gain. A significantly larger hearing gain, an increased percentage of recovery and an increased rate of successful recovery were observed in the Zinc group compared with the control group ($P < 0.05$). There was a significant correlation between serum Zinc level changes and post-treatment hearing thresholds by correlation analysis ($P < 0.05$), as well as between changes of serum zinc levels and percentage of recovery in the Zinc group ($P < 0.05$). So, it was concluded that, Zinc supplementation may enhance the hearing recovery of SSNHL patients [18].

Miyako Hatano et al conducted a study to evaluate the efficacy of vitamin E and C for the treatment of idiopathic sudden sensorineural hearing loss. In the retrospective study, 87 patients were recruited. All the patients were treated with steroids and/or alprostadil and out of all the patients, a group of patients were additionally given combination of Vitamin C (1200 mg/day) and Vitamin E (tocopherol nicotinate, 600 mg/day). The hearing gain after therapy was 29.4 dB and the improvement rate was 63.3% in the group of patients who received vitamin C and E as compared to 18.5 dB and 44.0% who were only treated with steroids and/or alprostadil. So, it was concluded that the administration of the combination of vitamin E and C to patients with idiopathic sudden sensorineural hearing loss was found to be efficacious when given as a parallel therapy with steroids and/or alprostadil as compared to only treatment with steroids and/or alprostadil [11].

David Ulanovski et al conducted a randomized, prospective, placebo-controlled, double-blind clinical trial on 28 patients with idiopathic sudden sensorineural hearing loss. Patients were either randomized to the combination of steroid and Magnesium which was referred as study group or the steroid and placebo which was referred as control group. Compared to control group the study group had a significantly higher proportion of patients with improved hearing (> 10 dB hearing level) across all frequencies tested, and a significantly greater mean improvement in all frequencies. As per the clinical trial data analysis, the patients treated with Magnesium as compared to not treated with the Magnesium had experienced greater hearing improvement and at a larger magnitude. Also the Magnesium was found to be safe for enhancing the improvement in hearing, specially the patients in the low tone range with SSNHL [19].

Mohamed et al conducted a clinical trial to analyze the role of vitamin-B12 and folate blood concentrations in children suffering from moderate, severe and severe-to-profound SSNHL. The study was conducted on total 95 pediatric patients out of which 30 were of severe to profound SSNHL who were scheduled for cochlear implantation, 25 were hearing aid users for moderate and severe SNHL and remaining 40 healthy volunteers considered as the control group. In all the patients serum folate and vitamin B12 levels were analyzed and it was found that in the patients of SSNHL, the serum folate and vitamin B12 levels were at a lower side as compared to healthy volunteers [20].

As per the best knowledge of the author, there was no study conducted for the fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg per capsule to test the efficacy and safety on Indian population for SSNHL or high intensity noise and vibration induced hearing loss so this was the first study conducted on Indian patients for the above mentioned combination.

Conclusion

The fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg per capsule was found efficacious as well as safe for the treatment of SSNHL and high intensity noise and vibration induced hearing loss when given as a concomitant therapy to the standard medical management.

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Disclosure

Authors are employees of Centaur Pharmaceuticals Pvt. Ltd. This study was conducted as post marketing surveillance for Otocap Capsules (fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg per capsule) which is a product of Centaur Pharmaceuticals Pvt. Ltd.

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