

## Original Research Article

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# Comparative study of the efficacy of oral caroverine versus oral *Ginkgo biloba* in the treatment of cochlear synaptic tinnitus

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## ABSTRACT

**Background:** Cochlear synaptic tinnitus (CST), also referred to as sensorineural type III tinnitus, is a type of transformation tinnitus, resulting due to aberrant signal transduction between Inner hair cells and afferent nerve fibres owing to excessive and pathologic glutamate release and subsequent spontaneous receptor depolarization (NMDA and AMPA receptors). Of the various pharmacologic agents used for treatment for CST, *Ginkgo biloba* and Caroverine have stood the test of time.

**Methods:** A total 48 selected patients of CST, otherwise free from any medical or surgical co-morbidity, were included in the study and divided randomly in two groups, one group receiving oral formulation of Caroverine and the other group receiving oral *Ginkgo biloba* in appropriate doses. Both the groups were followed up for 12 weeks. Treatment outcomes were measured in terms of improvement in subjective symptoms (tinnitus grading) and psycho-acoustic measure (tinnitus matching).

**Results:** Although oral caroverine yielded promising results in the initial month of treatment in terms of improved tinnitus matching, long term effect was found to be dissatisfying. Oral *Ginkgo biloba*, at the completion of 12 weeks of therapy was found to be more effective in terms of improvement of mean tinnitus grading and matching ( $p < 0.05$ ). Side effects of the test drugs were not noted in either group.

**Conclusions:** *Ginkgo biloba* is thus found to be more effective treatment modality for CST for long term basis and is also readily available in the market, cost effective and free of side effects as well.

**Keywords:** Cochlear synaptic tinnitus, Caroverine, *Ginkgo biloba*

## INTRODUCTION

Tinnitus may be defined variously, as an abnormal sound perceived in the ear for more than five minutes at a time in absence of any external acoustical or electrical stimulation of the ear and not occurring immediately after exposure to loud noise, phantom auditory perception or head noise.<sup>1-3</sup> The characteristic feature is that the origin of this abnormal sound is within the patient and it may vary in pitch and loudness, being more annoying in quiet

surroundings particularly at night when the masking effect of ambient noise from the surrounding environment is minimal. Being described variously by the patients like roaring, hissing, clicking or rustling noise, its prevalence has been estimated to be as high as 32% in the adult population, with approximately 13%-17% reporting bothersome tinnitus.<sup>4,5</sup> Prof. Klaus Ehrenberger, globally acclaimed otolaryngologist, said, "Study reveals that at least 10-15% Indians suffer from Tinnitus". However, the prevalence of 'clinical tinnitus' i.e. those

subjects who are bothered by tinnitus to the extent that they seek medical advice, has been estimated to be about 7.2 percent and related to urban population with good accessibility.<sup>6</sup> The severity of tinnitus can range from trivial to completely disabling. 93% of patients suffering from tinnitus reported that tinnitus affected their lifestyles. Some reported its presence made it more difficult for them to get to sleep, aggravated family problems, caused them to withdraw or avoid friends, or interfered with their work. 56% of patients stated that tinnitus had affected their general health and, finally, 70% attributed increased emotional difficulties to the presence of tinnitus, including such manifestations as despair, frustration, irritation, worry, insecurity and a decreased ability to relax or concentrate.<sup>7</sup> It was that found tinnitus prevalence as a positive function of age: 38% of patients <40 years of age and 62% of patients >40 years of age present with tinnitus.<sup>8</sup> Population statistics suggest that females are more affected than males: 46.9% males and 53.1% females.

Several variant classifications have been established for tinnitus. The diagnostic classifications may include those of perception (subjective versus objective, or vibratory versus nonvibratory) and location [tinnitus aurium (ear tinnitus) versus tinnitus cranii (head tinnitus)]. Subjective tinnitus can be subclassified into auditory tinnitus (permanent tinnitus inherent to the auditory system) and non-auditory tinnitus (perceived occasionally, being externally triggered and includes gaze-evoked tinnitus). Objective tinnitus can be either pulsatile tinnitus (related to blood flow) or clicking tinnitus (perceived in cases of jaw joint misalignment). Etiopathophysiologically tinnitus can be classified into vibratory tinnitus and non-vibratory tinnitus. While the former group includes pulsating clicking sounds having a mechanical basis and arising in or near the ear and can be heard by interested listeners (objective) and those heard only by the patient (subjective), the latter group is purely a subjective type of tinnitus, produced by biochemical changes in the nerve mechanism of hearing and caused by any conductive or sensorineural hearing defect.

Cochlear synaptic tinnitus, synonymous with signal transfer tinnitus, is a subjective sensorineural tinnitus type III, and is used to describe disorders arising during the signal transfer from the IHCs and the afferent nerve fibers. During normal mechano-electrical transduction of the amplified sound signal, there occurs release of naturally occurring excitatory neurotransmitter glutamate from the ending of inner hair cells, which subsequently act on post-synaptic membrane of the afferent dendrites via ionotropic (coupled directly to membrane ion channels) and metabotropic glutamate receptors (coupled to G-proteins and modulating the activity of intracellular second messengers, including calcium). While metabotropic receptors are insensitive to AMPA and NMDA, ionotropic receptors, based on their selective agonistic and antagonistic activity can be divided into NMDA, AMPA and kainite receptors. Even after

extensive research, pioneers of tinnitus research, it has not been possible to determine whether ionotropic, metabotropic or both quisqualate-sensitive receptors are involved in the genesis of inner ear tinnitus.<sup>9</sup>

The basic purpose of treating a patient with tinnitus is to alleviate him/her of symptoms and to improve the quality of life. The various pharmacological agents that have been tried for tinnitus include antidepressants, GABA analogues like benzodiazepine, gabapentin and baclofen, calcium channel antagonists, antiepileptics, prostaglandin analogues, lignocaine, *Ginkgo biloba* extracts and selective glutamate receptor antagonist (Caroverine). Recently, there has been an increased general interest in drug targeting glutamate receptors (Caroverine) and study by Prof Klaus Ehrenberger on Caroverine shows promising result in treatment of cochlear synaptic tinnitus. Caroverine exhibits competitive AMPA antagonism and at higher concentrations non-competitive NMDA antagonism, of the glycine modulatory site of the post-synaptically located ionotropic variety of glutamate receptors. *Ginkgo biloba*, a well-known herbal medicine, thought to be useful for memory, prevention and/or treatment of Alzheimer's dementia, intermittent claudication, erectile dysfunction, multiple sclerosis and tinnitus to name a few, exhibits the following actions: anti-inflammatory, antioxidant and free radical scavenging, cerebral glucose utilization, inhibition of platelet aggregation, neurotransmitter regulation and vasomotor activity. In addition, it increases disturbed microcirculatory blood flow by increasing the fluidity of blood. However, the relative importance of these actions in alleviating tinnitus is not properly understood. Our aim of study is to compare efficacy of oral Caroverine with oral ginkgo biloba in treatment of cochlear synaptic tinnitus.

## METHODS

The study is a hospital based, open level, randomized, prospective study of 1-year duration.

A total 48 selected cases of cochlear synaptic tinnitus attending the outpatient department of otorhinolaryngology and head and neck surgery MLN Medical College and Swaroop Rani Nehru Hospital Prayagraj Uttar Pradesh, from September 2014 to August 2015, were enrolled in the study after they were confirmed clinically and audio-logically to have tinnitus, either unilateral or bilateral, and a cochlear hearing deficit. Patients not willing to participate or not giving informed written consent and having any contraindication of test drugs were excluded from the study. Patients having suspected Mineire's disease, retro-cochlear hearing defect, any con-committent medical (including psychiatric illness) or surgical illness, or having tobacco, nicotine or any other substance abuse were excluded from the study. Also excluded were pregnant females and those women planning to conceive within the proposed study duration. The selected cases were registered and

given one number for each case. The age, sex, religion, socio-economic status, occupation and address of the patients were recorded. The symptoms of the patients were recorded chronologically. The history of present episode or any such previous episodes were recorded. The past history of systemic disorders and ototoxic drug use were also taken into account. The familial and personal history including the occupational status, drug abuse (including tobacco), use of headphones and life style were enquired into. Thorough clinical examination was carried out which included a general examination and complete otorhinolaryngological examination. Examination of ear with head mirror and otoscope was done, tuning fork tests performed, eustachian tube function checked by valsalva maneuver. Examination of facial nerve was also done. Oral cavity examination was done by using head mirror. The nasal cavities were examined by anterior and posterior rhinoscopy. Indirect laryngoscopy was performed to look for any laryngeal pathology. Each patient was handed over a questionnaire adopted from Colorado Tinnitus and Hearing Centre. After the completion of the questionnaire the patients were asked to rate their tinnitus on a scale of 1-10 akin to the VAS used for quantifying pain perception. Based on their rating, the patients were divided into three major subjective symptom categories (Tinnitus grading): baseline (1-3), moderate (4-6) and severe (7-10). Patients were then given appointment for pure tone audiometry. Pure tone sounds, ranging from 0 -16,000 Hz, were presented to the affected ear of the patients and they were asked to match their tinnitus to the nearest frequency (tinnitus matching), based on which the patients were divided into four categories. During the initial audiometry examination, other audiological tests including ART, clinching reflex, tympanometry, SISI, ABLB and TDT were also performed.

By using computer generated block randomization method, patients were divided into two groups, patients treated with oral Caroverine 60 mg/day in three divided doses were Group A where as Group B consisted of patients treated with oral *Ginkgo biloba* 120 mg/day in two to three divided doses.

They were then systematically followed up and evaluated monthly over a period of 3 months for improvement of clinical symptoms in terms of tinnitus grading and

tinnitus matching. Result was statically analysed by spss version percentage, mean, standard deviation.

## RESULTS

Out of the 48 patients (males 31 and females 17) participating in the study, 41.67% (n=20) belonged to their third decade of life followed by 18.75% (n=9) who belonged to fifth decade. Male patients predominated in the study with a male to female ratio of 1.82:1.

Affection of bilateral ears was most common (35.42%) followed closely by that of right ear (33.33%) and left ear (31.25%).

Most of the patients (77.08%, n=37) had a pre-treatment tinnitus grading of 4-6 i.e. moderate tinnitus followed by 14.58% (n=7) who had a severe tinnitus (grade 7-10) (Table 1). Remaining 4 patients (4.35%) had a baseline tinnitus.

Before initiation of treatment, 50% patients (n=24) experienced a tinnitus that matched with a pure tone sound of 41-60 dB, 41.67% (n=20) had a tinnitus match of 21-40 dB. Only one patient had a tinnitus that matched with 0-20 dB and 3 patients (6.25%) had a tinnitus matching of 61-80 Db (Table 2). After initiation of therapy with the respective drugs, tinnitus grading and matching were observed and compared with the pre-treatment values at the completion of each month of treatment (Table 3 and 4).

It has been found that in patients treated with *Ginkgo biloba*, the percentage of patients with baseline tinnitus grading and tinnitus matching progressively increases with continuation of therapy as percentage of patients from higher grading and matching categories decreases with time, thereby implying a positive response to the drug. On the contrary, in Caroverine treated patients, an initial rise in percentage of patients in baseline category of tinnitus grading and matching at the end of 1<sup>st</sup> month of treatment was subsequently followed by a decrease in percentage in subsequent months, implying that the effect of the drug, which showed much promise initially, gradually waned off. Clinical response to treatment is considered positive when there is a fall in tinnitus grading by 2 points on a 1-10 point scale.

**Table 1: Pre-treatment tinnitus grading.**

Tinnitus grading	Group A (n=23)		Group B (n=25)		Total	
	No. of patients		No. of patients		No.	%
<b>1-3</b>	1	4.35	3	12	4	8.34
<b>4-6</b>	17	73.91	20	80	37	77.08
<b>7-10</b>	5	21.74	2	8	7	14.58
<b>Total</b>	23	100	25	100	48	100

1-3: mild (baseline) tinnitus; 4-6: moderate tinnitus; 7-10: severe tinnitus.

**Table 2: Pre-treatment tinnitus matching.**

Tinnitus matching	Group A (n=23)		Group B (n=25)		Total	
	No. of patients	%	No. of patients	%	No.	%
0-20 dB	1	4.35	0	0	1	2.08
21-40 dB	7	30.43	13	52	20	41.67
41-60 dB	12	52.17	12	48	24	50
61-80 dB	3	13.05	0	0	3	6.25
Total	23	100	25	100	48	100

**Table 3: Pre and post-treatment tinnitus grading after each month of treatment.**

Tinnitus grading	Treatment status	1-3 months		4-6 months		7-10 months	
		No.	%	No.	%	No.	%
Group A (n=23)	Pre-treatment	1	4.35	17	73.91	5	21.74
	Post treatment (1 <sup>st</sup> month)	12	52.17	11	47.83	0	0
	Post treatment (2 <sup>nd</sup> month)	11	47.83	12	52.17	0	0
	Post treatment (3 <sup>rd</sup> month)	10	43.48	13	56.52	0	0
Group B (n=25)	Pre treatment	3	12	20	80	2	8
	Post treatment (1 <sup>st</sup> month)	7	28	17	68	1	4
	Post treatment (2 <sup>nd</sup> month)	11	44.0	13	52.0	1	4.0
	Post treatment (3 <sup>rd</sup> month)	12	48.0	12	48.0	1	4.0

**Table 4: Pre and post treatment tinnitus matching after each month of therapy.**

Group	Treatment status	0-20 dB		21-40 dB		41-60 dB		61-80 dB	
		No.	%	No.	%	No.	%	No.	%
Group A (n=23)	Pre treatment	1	4.35	7	30.43	12	52.17	3	13.05
	Post treatment (1 <sup>st</sup> month)	10	43.48	8	34.78	4	17.39	1	4.35
	Post treatment (2 <sup>nd</sup> month)	9	39.13	8	34.78	5	21.74	1	4.35
	Post treatment (3 <sup>rd</sup> month)	9	39.13	7	30.43	6	26.09	1	4.35
Group B (n=25)	Pre treatment	0	0	13	52.0	12	48.0	0	0
	Post treatment (1 <sup>st</sup> month)	2	8.0	17	68.0	6	24.0	0	0
	Post treatment (2 <sup>nd</sup> month)	8	32.0	12	48.0	5	20.0	0	0
	Post treatment (3 <sup>rd</sup> month)	9	36.0	11	44.0	5	20.0	0	0

**Table 5: Pre and post treatment scoring.**

Treatment	Group A (n=23)		Group B (n=25)	
	Mean tinnitus grading	Mean tinnitus matching	Mean tinnitus grading	Mean tinnitus matching
	N (%)	N (%)	N (%)	N (%)
Pre treatment	5.08	46.30	4.48	39.4
At 1 <sup>st</sup> month post treatment (percentage improvement)	3.73 (26.57)	34.34 (25.83)	3.60 (19.64)	36.0 (8.64)
At 2 <sup>nd</sup> months post treatment (percentage improvement)	4.0 (21.26)	34.35 (25.80)	3.24 (27.68)	31.2 (20.81)
At 3 <sup>rd</sup> months post treatment (percentage improvement)	4.04 (20.47)	35.22 (23.93)	3.20 (28.57)	30.6 (22.34)

Out of the 23 patients treated with oral Caroverine, only 11 (47.83%) showed response at 1st month of treatment. 1 patient reverted back to his pretreatment grade at completion of 2nd month and further 1 patient reverted back after 3 months of treatment. Clinical response in terms of reduced subjective score was rather promising with oral *Ginkgo biloba* as the percentage of responders increased from 32% at the end of 1st month of treatment to 48% at the end of 3<sup>rd</sup> month (Table 5). However, no

patients in either groups reported complete abolition of tinnitus in the three month of treatment period.

The mean values of tinnitus grading and tinnitus matching of both the study groups were calculated at completion of each month of treatment and compared with the pre-treatment mean in a bid to find the percentage improvement in reducing the pretreatment mean tinnitus grading and matching. It was found that



while oral *Gingko biloba* is effective in reducing the mean tinnitus grading and matching at each month of therapy, oral Caroverine initially reduces the means but the percentage improvement slowly wanes off over time. Both the study groups are compared on the basis of reduction of mean value of tinnitus grading and matching.

It is found that, *Gingko biloba* is statistically significant over Caroverine in reducing the mean tinnitus grading ( $p=0.0415$ ) and mean tinnitus matching ( $p=0.0379$ ), but only at the end of 3<sup>rd</sup> month of treatment (Table 6 and 7). Although it reduces the mean values at the end of 1st and 2nd month of therapy, but it was statistically not significant ( $p>0.05$ ).

**Table 6: Comparison of mean tinnitus grading over time.**

Groups	1 month	2 months	3 months
	Mean±SD	Mean±SD	Mean±SD
Group A (n=23)	3.73±1.45	4.0±1.41	4.04±1.36
Group B (n=25)	3.6±1.47	3.24±1.37	3.2±1.41
P value	0.7352	0.0646	0.0415

**Table 7: Comparison of mean tinnitus matching over time.**

Groups	1 month	2 months	3 months
	Mean±SD	Mean±SD	Mean±SD
Group A (n=23)	34.34±16.19	34.35±16.67	35.22±16.34
Group B (n=25)	36±14.83	31.2±13.17	26.4±11.95
P value	0.7125	0.4694	0.0379

## DISCUSSION

Tinnitus, “ringing in the ears,” is one of the most common problems encountered in everyday otolaryngology practice. In spite of a long history of tinnitus research and a rapid increase in the understanding of the auditory system, tinnitus remains a mystery. A relatively recent shift towards recognizing that tinnitus is a phantom auditory perception and importance of various structures and systems in the brain have yielded substantial progress in the understanding and treatment of tinnitus. Many treatments have been proposed during last 30 years and the effectiveness of these treatments has increased considerably during this time. Surgical treatment of tinnitus provided little evidence of effectiveness. Tinnitus retraining therapy has become one of the main tinnitus treatment strategies in a number of audiology departments. Noise generator and tinnitus maskers are the wearable behind-the ear or in-the-ear devices, used for presentation of sound in a controlled manner in order to reduce or eliminate the perception of tinnitus. Psychotherapy includes cognitive re-structuring, that is dislocation of negative emotions from the perception of tinnitus and the modification of avoidance behavior motivated by tinnitus. Pharmacotherapy has, however, remained the mainstay of treatment in controlling tinnitus.

In the present study, out of the 48 selected patients suffering from CST, most were in third decade of life (41.67%) followed by fifth decade of life (18.75%). Our data does not correlate with study 8 who found tinnitus to be a positive function of age: 38% of patients were less than 40 years and the remaining 62% more than 40 years of age. In our study, 64.59% of patients were less than 40

years of age whilst 35.41% were above 40 years. The relatively lower percentage of elderly people in this study i.e. 18.75% in the fifth decade and even lower 16.66% in sixth decade of life as compared to 41.67% in third decade of life is not due to the lower prevalence of tinnitus in elderly, but due to lower turnover of elderly patients to health-care facilities to seek medical care due to the prevailing underlying socioeconomic conditions in the developing nations. In our study, tinnitus is found to be higher in males with a male to female ratio of 1.82:1. This is in sharp contrast to population statistics which states females have a higher preponderance (53.1% versus 46.9%).<sup>4</sup>

In the landmark study conducted 10 to evaluate the efficacy of single dose infusion of Caroverine in patients suffering from cochlear synaptic tinnitus, 63.3% responded to therapy immediately after the infusion and the value sustained at 1, 3 and 6 months. In the placebo group, none of the patients showed a significant response according to the defined success criteria of the study.

A study was conducted 11 to evaluate the efficacy and safety of single infusion of Caroverine in cochlear synaptic tinnitus. 60% patients receiving Caroverine showed response immediately after infusion while 34.5% patients receiving placebo responded as well.

In the present study, 23 patients were given oral Caroverine for 12 weeks. At the end of 1st month of treatment, 11 patients out of 23 (47.83%) showed response to therapy according to our working hypothesis. Even with the continuation of treatment, the number of responders gradually decreased over time. Though Caroverine was found to be effective in reducing the

mean tinnitus grading and mean tinnitus matching from the pre-treatment value but the effects were not sustained at the 2<sup>nd</sup> and 3<sup>rd</sup> month of treatment.

No side effect of caroverine was noted in any of the patients in our study. No specific side effect of infusion Caroverine either was mentioned in Prof. Klaus Ehrenberger's study as well.

In our study, 25 patients were given oral *Ginkgo biloba* for 12 weeks. At the end of 1st month of therapy, 8 out of 25 (32%) patients showed response. However, unlike Caroverine, with the continuation of therapy, further response was obtained and at the completion of 12 weeks, 48% patients showed response to therapy. *Ginkgo biloba* also showed improvement in reducing the mean tinnitus grading and matching over pre-treatment values and unlike caroverine, the effects were sustained over time with continuation of therapy. No adverse drug reactions were observed during the course of treatment. The result the present study is in accordance with the result of landmark studies conducted which shows statistically significant improvement in subjective symptoms and psycho-acoustic measure of tinnitus.<sup>12-14</sup> In a systematic review of the efficacy of standard *Ginkgo biloba* extracts in patients of tinnitus, in which a randomized, placebo-controlled clinical trials of Ginkgo biloba extract preparations were searched for and reviewed systematically.<sup>15</sup> There is evidence of efficacy for the standardized extract, in the treatment of tinnitus from three trials in patients in whom tinnitus was the primary complaint. Supportive evidence comes from a further five trials in patients with age-associated cognitive impairment or dementia in whom tinnitus was present as a concomitant symptom.

## CONCLUSION

Tinnitus is a common problem encountered in day to day ENT practice and is often bothering as it causes sleepless nights, constant anxiety, crazy mood swings, helpless depression and energy sapping exhaustion. Of the various available pharmacological treatment modalities, *Ginkgo biloba* in a dose of 120 mg/day in two to three divided doses appears to be quite effective when given for three months as it is shown to improve subjective symptom score and psychoacoustic measure. Moreover, it is cheap, easily available in the market and is devoid of significant adverse reactions. The novel drug targeting glutamate receptors, Caroverine is not as effective as ginkgo in terms of improved subjective sensation and psychoacoustic measure. Further double-blind placebo-controlled studies of long duration are required to establish the long-term efficacy of *Ginkgo biloba* in treatment of CST.

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