

A Clinical Study of Tinnitus

Abstract

Aim: This Article summarizes the Clinical Study of Tinnitus conducted in Government ENT Hospital, Koti and Hyderabad over a Period of two years.

Objective: To describe the results found in a group of people who have undergone treatment with various medical treatments using caroverine, Ginkgo Biloba, Multivitamin.

Method: Using Tchs Score 90 adult subjects with complaint of tinnitus and associated symptoms were analysed with Proper History, Clinical Examination and Pure Tone Audiometry and Tchs's to determine the Degree of Annoyance of the Tinnitus and to Assess Tinnitus Impact on the Quality of Life before and after Treatment.

Results: After the use of medicines there was a significant reduction in the degree of annoyance caused by Tinnitus, there was a significant reduction of tinnitus and there was significant improvement in hearing thresholds, consequently, on the Quality of Life of the respondents.

Conclusion: This Study allowed the Verification that the use of Caroverine, Ginkgo Biloba and Multivitamin for the Treatment of Tinnitus and their Effect.

Keywords: Tinnitus; Tchs; Hearing loss; Caroverine; Ginkgo biloba; Multiivitamin

Review Article

Volume 9 Issue 4 - 2017

Ravinder Raja and Sudarshan Reddy L*

Secretary AOI Hyderabad, India

*Corresponding author: Sudarshan Reddy L, Secretary AOI Hyderabad, Telangana State Branch, India, Tel: 8096817081; (R) 040-27768647; Email: drilsudarshanreddy9@gmail.com

Received: July 23, 2017 | Published: December 21, 2017

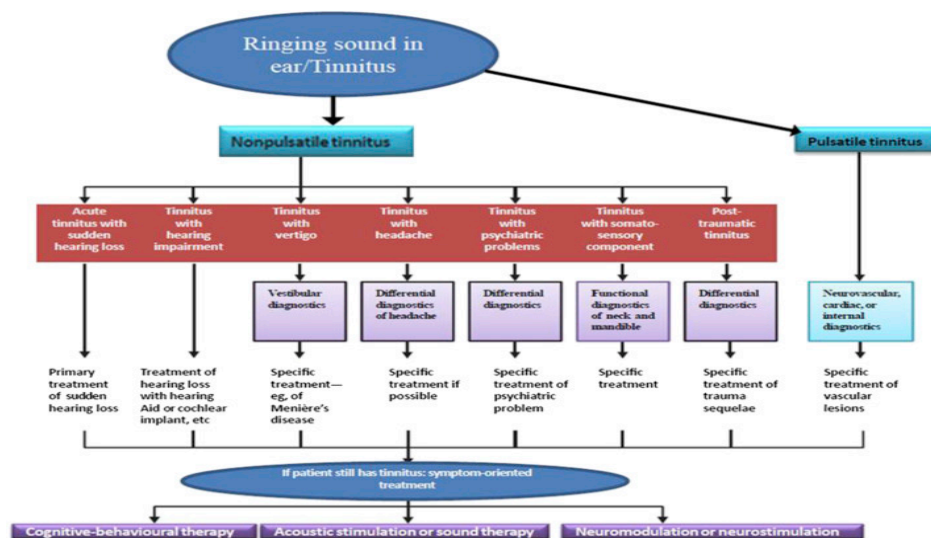
Introduction

Tinnitus can be defined as a Sound Sensation perceived in the ears or head that is not related to an external source of stimuli. The term tinnitus derives from the Latin word tinnier, Meaning to Ring. Tinnitus is classified in many cases into 2 categories. Tinnitus is either objective (Audible to anyone in addition to the affected individual) or subjective (Audible only to the affected individual).

Tinnitus is Described as a symptom that can accompany various pathologies or disorders of the External, middle or inner

ear, brainstem and cerebral cortex, among which are those that affect the ear directly or secondarily (Metabolic, Cardiovascular, Neurological, Psychiatric disorders, and Possibly drugs, Caffeine, Alcohol and Nicotine).

Tinnitus is also defined as the result of the dynamic Interaction of Several Centers of the Central Nervous System, including Auditory and Non-Auditory Pathways [1-3]. The interaction between these centers, especially between the limbic system and the Autonomic Nervous System, is responsible for triggering The Negative Emotional Associations and uncomfortable reactions reported by patients with Tinnitus.



Tinnitus is common and, according to Studies, affects about 15-20 % of world population. When manifested in an prominent way, it can significantly impair quality of life, affecting sleep, concentration, emotional balance and social activity, disabling the pursuit of normal activities.

The use of Tinnitus Case History Questionnaire (Tchqs) is of great importance in the evaluation of individuals with Tinnitus because it helps confirm the presence of Tinnitus and Determine the Severity of Symptoms, the Greater the Impact of Tinnitus on the Patient's Quality of Life [4]. In addition to the assessment Protocols, Audiologic Diagnostics, I.E. The identification of some kind of hearing impairment and possible changes in efferent and afferent pathways is essential and the investigation of Tinnitus characteristics, i.e., measures of sensation, frequency and intensity are important, as well as laboratory and imaging tests, to rule out retrocochlear lesions.

Treatment

Tinnitus is complex and Multifactorial, and involves many Etiological Loci. Until now, there has been no specific therapy for all the different kinds of Tinnitus. Current schemes include the use of Hearing aids, Counselling, Supportive therapy including tinnitus retraining therapy, and different medications such as Vasodilators, Corticosteroids, Anticonvulsants, Spasmolytic drugs, Lidocaine, Benzodiazepines, and Gingko Biloba preparations and Caroverine.

This study attempts to compare the efficacy between Gingko Biloba and Caroverine in the management of idiopathic Tinnitus.

Materials and Methods

Source of data

The study was conducted on patients of age 18yrs and above of either sex who presented with Chronic. Tinnitus to Govt ENT Hospital from Oct 2011 to Sept 2013.

Method of collection of data

A) Detailed History taking and subjective assessment of the

Table 1: Age Distribution of Pts Studied.

Age in Years	Caroverine		Gingko Biloba		Multivitamins	
	Number	%	Number	%	Number	%
21-30	4	13.3	11	36.7	0	0.0
31-40	11	36.7	3	10	1	3.3
41-50	10	33.3	4	13.3	5	16.7
51-60	2	6.7	8	26.7	10	33.3
61-70	3	10	2	6.7	8	26.7
71-80	0	0.0	2	6.7	6	20
Total	30	100	30	100	30	100
Mean +/- Sd	62.03 +/- 8.96		56.83 +/- 13.37		60.90 +/- 10.52	

Samples are Age Matched with P= 0.168

Tchq Study is Age Matched. Age of the Pt in the Study Ranged from 21 to 80yrs.

Tinnitus using Tchqs

B) Clinical examination

C) Auditory assessment and imaging wherever appropriate

Patients were followed up for six months every 15 days routinely and every three months were assessed with Tchq and PTA both pre and post treatment to evaluate which drug is better.

Study Pattern

Patients were randomised into 2 study groups and 1 control group [5-7]. The first study group comprised of 30 patients were administered one dose of caroverine injection 10ml in 100ml normal saline, followed by Caroverine capsules /twice/daily for six months. The second study group comprised of 30 patients were administered Gingko Biloba 120mg twice daily for 6 months. The control group comprised of 30 PTS were administered multivitamins once daily for six months.

Inclusion Criteria	Exclusion Criteria
Min age 18yrs	Tinnitus due to Ototoxicity
Tinnitus early R late onset	Tinnitus due to systemic, Vascular or Diabetes, Anxiety and Depressions
Absence of Pshychiatric DS	Tinnitus due to external middle Ear causes
NIHL with Tinnitus	SP disorders like Oto, Mienerresds
Cochlear and retrocochlear pathology	Pulsatile tinnitus Cerebellopontine angle tumours

Observations and results

A comparative clinical study with 90 Pts Randomised into Three Groups, 30 in each was undertaken to study whether Caroverine or Gingko Biloba or Placebo is better in reducing Tinnitus (Table 1-7).

Table 2: Gender Distribution of Pts Studied.

Gender	Caroverine		Gingko Biloba		Multivitamins	
	Number	%	Number	%	Number	%
Male	14	46.7	16	53.3	18	60
Female	16	53.3	14	46.7	12	40
Total	30	100	30	100	30	100

Samples are Gender Matched with P= 0.585

Table 3: Comparison of Duration of Tinnitus in Months in Three Study Groups.

Duration	Caroverine		Gingko Biloba		Multivitamins	
	Number	%	Number	%	Number	%
</=6 Months	5	16.7	12	40	12	40
6-9	8	26.7	2	6.7	5	16.7
9-12	14	46.7	11	36.7	5	16.7
>12 Month	3	10	5	16.7	8	26.7
Total	30	100	30	100	30	100
Mean +/- Sd	10.46+/- 4.08		10.67 +/- 5.28		10.80 +/-5.85	

Duration is Statistically Similar in three Groups with P = 0.968.

Mean Duration of Tinnitus in the Study Group was Between 9 To 12 Months.

Table 4: Comparison of Site of Tinnitus in Three Study Groups.

Site of Tinnitus	Caroverine		Gingko Biloba		Multivitamins	
	Number	%	Number	%	Number	%
Left	7	23.1	8	26.4	7	23.1
Right	6	19.8	6	19.8	11	36.3
Bilateral	17	56.6	16	52.8	12	39.6

Tinnitus was Present in both Ears in Most Cases.

Table 5: Comparison of Mode of Onset and Progression of Decreased Hearing.

Decreased Hearing	Caroverine		Gingko Biloba		Multivitamins	
	Number	%	Number	%	Number	%
Mode of Onset						
Sudden	-	-	-	-	-	-
Insidious	19	60	14	46.7	14	46.7
Progression						
Continous	19	60	14	46.7	14	46.7
Intermittent	-	-	-	-	-	-

All Patients with Hearing Loss had Insidious Onset and Continous Progression of Hearing Loss.

Table 6: Comparison of Tinnitus Severity using Tinnitus Case History Questionnaire (Tchq) Score Pre and Post Treatment.

Tchq Score	Pre Treatment	Post Treatment	% Change in Tinnitus Severity	Mc Nemar Test
Caroverine	Number / (%)	Number / (%)		
Mild	9 / (30%)	13 / (43.3%)	+13.3	0.100
Moderate	16 / (53.3%)	14 / (46.7%)	-6.7	
Severe	5 / (16.7%)	3 / (10%)	-6.7	
Gingko Biloba				
Mild	2 / (6.7%)	21 / (70%)	+63.3	<0.001
Moderate	22 / (53.3%)	9 / (30%)	-43.3	
Severe	6 / (20%)	0 / (0)	-20.0	
Multivitamins				
Mild	11 / (36.7%)	12 / (40%)	+3.3	0.317
Moderate	16 / (53.3%)	15 / (50%)	-3.3	
Severe	3 / (10%)	3 / (10%)	0.0	
P Value	0.077	0.129		

Tchq Score Showed Significant Change between Pre and Post Treatment in Those Patients who treated with Gingko Biloba.

Tchq Score Post Treatment with Caroverine Showed Reduction but not Statistically Significant with P Value. 0.100

Tchq Score Post Treatment with Gingko Biloba showed Statistically Significant Reduction with P Value <0.001

Table 7: Comparison of Improvement in Hearing in Pure Tone Audiometry Pre and Post Treatment.

Pure Tone Audiometry	Caroverine	Gingko Biloba	Multivitamins
Right Ear			
Pre Treatment	40.69 +/- 15.37	32.39 +/- 15.01	34.33 +/- 14.61
Post Treatment	40.42 +/- 15.25	31.06 +/- 14.42	34.21 +/- 14.57
Difference	0.273	1.329	0.120
P Value	0.095	0.007	0.458
Left Ear			
Pre Treatment	36.82 +/- 13.10	31.69 +/- 13.30	32.73 +/- 13.99
Post Treatment	36.59 +/- 12.94	30.78 +/- 13.54	32.19 +/- 14.10
Difference	0.230	0.915	0.533
P Value	0.176	0.007	0.10

Pure Tone Audiometry showed Statistically Significant Improvement in Hearing in Those Treated with Gingko Biloba with P Value of 0.007

Discussion

Tinnitus is a common complaint among patients coming for auditory problems. Several theories about the etiology of Tinnitus were proposed and treatment modalities in the form of medications and surgery were developed with varying degree of success [8]. In Tchqs study we have compared the efficacy between Caroverine and Gingko Biloba in the management of tinnitus in a selected placebo controlled group of patient. Patients were randomised into two study group and one control group. The

first study group of 30 patients and were administered caroverine injection followed by capsules for six months. The second study group comprised of thirty patients and was administered using gingko biloba twice dilly for 6 months [9]. The controlled grouped comprised of thirty patients and were given multivitamins daily once. Thus 90 pt with chronic tinnitus were evaluated and studied using Tchqs score. All three groups were matched by the distribution of age gender sex and duration of tinnitus. In our study maximum patients were seen in the age group of 52-60 yrs.

Tchqs study was performed to examine whether a single infusion of caroverine, a quinoxaline derivative, can be used successfully in the treatment of inner Ear Tinnitus [10-12]. Microionophoretical experiments in Guinea Pigs have shown that Caroverine acted as a potent Competitive alpha- amino-3-Hydroxy-5 Methyl-4 - Isoxazone- Propionic Acid (AMPA) Receptor Antagonist and, in higher dosages, a Non Competitive n-Methyl-d-Aspartate (NMDA) antagonist [13-15]. According to our working hypothesis of the pathophysiology of inner ear tinnitus (Cochlear-Synaptic), these forms of tinnitus occur when the physiological activity of the NMDA and AMPA receptors at the sub synaptic membranes of inner hair cells afferents is disturbed.

In total, 90n Pt with inner Ear Tinnitus of assumed Cochlear-Synaptic Pathophysiology Were included in the study, 30 patients were treated with Caroverine, 30 patients with Ginkgo Biloba and 30 Patients with Multivitamins. For a response to have an occurred, tinnitus had to show a reduction in both subjective rating and psychoacoustic measurement (Tinnitus Matching).

In the caroverine group 63.3% responded to therapy immediately after the infusion. In Ginkgo Biloba group 60% responded and in the placebo group none of the PT showed a significant response according to the defined success criteria.

The results confirmed are working hypothesis on the genesis of cochlear synaptic tinnitus. In one study, conducted in 1997, caroverine reduced timnnitus symptoms for most pts, 63% of pt responded immediately with significant in sound level. There were no significant side effects and mild side effects were transitory typically disappearing less than 24 hrs.

The highly purified and concentrated mono extract EGB 761 obtained from dried leaves of Ginkgo Biloba tree [16,17]. It is a SPL extract manufactured according to a patent standardised pharmaceutical process. The combined effects of its components a.o.ginkgo flavon glycoside and terpene lactones (Gingkolites, Bilobolide) results in a multifactor pharmacological action profile comprising of positive Effect on rheological parameters and the energy metabolism of the nerve cells protecting them from d sequels of hypoxia and ischemia, and radical -scavanging properties.

Several reviews addressing the efficacy of Ginkgo Biloba have been published in recent years. Smith et al. [10] uncritically lumped together studies of Ginkgo Biloba preparations irrespective of their quality and dosage. They may have relied on publication in a peer -reviewed journal as proof of quality rather going into the detection of flaws in the different publications. In a metaanalysis of trials of Ginkgo Biloba in the treatment of tinnitus, Rejali et al. [9] also pooled studies using variuos Ginkgo products of different and partly unknown quality. Their conclusion was that Ginko Biloba does not benefit patient with tinnitus. Similarly, filton and steward included pre clinical trials with three different products in their cochrane review. On the contrary, holstein, who only included studies with a Ginko Biloba extract egb761 in his review, found evidence of efficacy for tchqs standardised extract from randomised, placebo-control trials,supported by findings from reference -controlled and uncontrolled trials in a more true -to - life setting. In all identify and retrieve studies using

the standardised Ginkgo Biloba extract, EGB & Tchqs specific preparation was found to placebo in the treatment of tinnitus.

Conclusion

1. No treatment for tinnitus has been well established and no specific therapy is found to be satisfactory in all patients.
2. Tinnitus is a symptom of different pathology, different to measure and has different underlying mechanism. Possible mechanism are:
 - i. Abnormal afferent excitation at cochlear level due to:
 - a. Mechanical Tinnitus based on spontaneous otoacoustic emissions,
 - b. Glutamate Neurotoxicity,
 - c. Enhance sensitivity of NMDA and NON -NMDA receptors,
 - d. Normal Ion channels conductance - Ca channel dysfunction.
3. Efferent dysfunction/reduction of Gaba effects.
4. Alteration of spontaneous activity and tonotopic reorganisation.
5. Many treatment modalities have been tried with varying degrees of success such as Antidepressants, Tricyclic anti depressants (SSRI), Gaba analogues (Benzodiazepene, Gabapentine, Balofen), Glutamate receptor antagonists (Caroverine), ca channel antagonists (Nimodipine, Flnzazine), Antiepileptics (Carbamazepine, Sodium valporate, Lamotrigiene), prostaglandin analogues, Misoprostol, Lignocaine, Ginkgo Biloba.
6. Surgical procedure for the treatment such as auditory nerve section, cochlear distruction has been tried. There is little evidence of effectiveness and may even make tinnitus worse.
7. Caroverine is one of the latest drugs which are tried in the treatment of tinnitus. Caroverine, glutamate antagonistic activity was used for cochlear synaptic tinnitus. Caroverine is drug used as a spasmolytic and otoneuroprotective (inner ear protective) agent in some countries. It acts as an n type Calcium channel blocker, competative AMPA receptor antagonist and non competative NMDA receptor antagonist. It also has antioxidant effects.
8. Ginkgo Biloba: Its main constituents are Gingkolides and Bilobalides, both Terpenoids and a range of flavonoids. Ginkgo Biloba has been shown to have anti ischaemic, anti edema, antihypoxic, radical scavanging and metabolic actions. In addition it increases disturbed microcirculatory blood flow through increasing the fluidity of blood.
9. Our study was done to ascertain the effectiveness of caroverine and Ginkgo Biloba in the treatment of tinnitus in a placebo controlled group of patients.
10. We followed up patients for 6 months and they were assessed with Tchqs and Pta both pre and post treatment.

11. In our study we concluded that use of Caroverine helps in reducing Cochlear Synaptic Tinnitus and also improves sensorineural hearing loss in patients with tinnitus and the treatment should continue as long as tinnitus persists. Ginkgo Biloba was also found to be effective in reducing tinnitus.
12. In the Caroverine group 63.3 % responded to therapy immediately after infusion. Out of responded case in the follow up 25% had a recurrence and rest had better response as capsules were continued two tabs twice daily
13. In the Ginkgo Biloba group 50% responded after a three months treatment, so in long term Ginkgo Biloba had better response over caroverine
14. In the Placebo Group 40% responded according to the defined success criteria
15. According to the study I have conducted Ginkgo Biloba is a better drug when compared with Caroverine in the long term treatment where as Caroverine has a better response immediately after administration.

Caroverine has approximately same response in other studies but Ginkgo Biloba has Variable Responses in different studies saying it is more useful in Tinnitus associated with Cerebral Insufficiency.

Acknowledgment

None.

Conflict of Interest

None.

References

1. Ahmad N, Siedman M (2004) Tinnitus in Older Adult: Epidemiology, Pathophysiology and Treatment Options. *Drugs Aging* 21(5): 297-305.
2. Ann Belen, E Igoyen, Bertheld Langguth (2000) Pharmacological Approaches to Tinnitus Treatment. *Textbook of Tinnitus*, pp. 625-631.
3. Scott Browns *Otorhinolaryngology and Head and Neck Surgery* (7th edn), pp. 3594-3619.
4. Byung Han, Ho Won Lee, Tae Yu Kim, Jun Seong Lim Kyoungsik Shin *Md Tinnitus: Characteristics, Causes, Mechanisms, and Treatments*.
5. Denk DM, Heinzl H, Franzp, Ehrenberger K (2003) Caroverine in Tinnitus Treatment. A Placebo Controlled Blind Study.
6. Drew S, Davies E (2002) Effectiveness of Ginkgo Biloba in Treating Tinnitus. Double Blind Placebo Controlled Trial.
7. Holgers Km, Axelsson A, Pringle I (1994) Ginkgo Biloba Extract for the Treatment of Tinnitus. *Audiology* 33(2): 85-92.
8. Drew S, Davies E (2001) Effectiveness of Ginkgo Biloba Treating Tinnitus: Double Blind, Placebo Controlled Trial. *BMJ* 322(7278): 1-6.
9. Rejali D, Sivakumar A, Balaji N (2004) Ginkgo Biloba Does Not Benefit Patients With Tinnitus: A Randomized Placebo-Controlled Double-Blind Trial And Meta-Analysis Of Randomized Trials. *Clin Otolaryngol Allied Sci* 29(3): 226-231.
10. Smith PF, Zheng Y, Darlington CL (2005) Ginkgo Biloba Extracts for Tinnitus: More Hype than Hope? *J Ethnopharmacol* 100(1-2): 95-99.
11. Hilton MP, Zimmermann EF, Hunt WT (2004) Ginkgo Biloba for Tinnitus. *Cochrane Database Syst Rev* 3: Cd003852.
12. Holstein N (2000) Ginkgo Biloba Special Extract Egb 761 in the Treatment of Tinnitus. An Overview of the Results of Clinical Trials. *Fortschr Med Orig* 118(4): 157-164.
13. Morgenstern C, Biermann E (2002) The Efficacy of Ginkgo Special Extract Egb 761 in Patients with Tinnitus. *Int J Clin Pharmacol Ther* 40(5): 188-197.
14. Meyer B (1986) Multicenter randomized double-blind drug vs. placebo study of the treatment of tinnitus with Ginkgo biloba extract. *Presse Med* 15(31): 1562-1564.
15. Eggermont J, Roberts Le (2004) The Neuroscience Of Tinnitus. *Trends Neurosci* 27(11): 676-682.
16. Ehrenberger K (2002) Clinical Experience with Caroverine in Inner Ear Diseases. *Adv Otorhinolaryngol* 59: 156-162.
17. Domeisen H, Hotz MA, Häusler R (1998) Caroverine in Tinnitus Treatment. *Acta Otolaryngol* 118(4): 606-608.