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Comparison of the efficacy between Ginkgo Biloba and Caroverine in the management of Idiopathic Tinnitus.

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Aim: This Study of Tinnitus management conducted to compare the efficacy of two drugs namely caroverine and gingko Biloba in Mahavir institute of medical sciences, Vikarabad over one year. **Objective:** To describe the results found in a group of people who have undergone treatment with carvoverine, gingko Biloba,placebo. **Method:** Using Tchqs Score 90 adult subjects with the complaint of tinnitus and associated symptoms were analyzed with Proper History, Clinical Examination and Pure Tone Audiometry and Thcq'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:** There was a significant reduction in the degree of annoyance caused by Tinnitus, there was a significant reduction of tinnitus and there was a significant improvement in hearing thresholds, consequently, on the Quality of Life of the respondents after using the caroverine, gingko Biloba. **Conclusion:** This study allowed the Verification that the use of Caroverine, gingko bilobaand placebo for the Treatment of Tinnitus and their Effect.

Keywords: Tinnitus,Tchqs, Hearing loss, Carvoverine, Gingko biloba, Placebo

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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 centres, 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 5-20 % of the world population. When manifested prominently, 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. 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, Counseling, Supportive therapy including tinnitus retraining therapy, and different medications such as Vasodilators, Corticosteroids, Anticonvulsants, Spasmolytic drugs, Lidocaine, Benzodiazepines, and Gingko Biloba preparations and Caroverine.

CAROVERINE [1-(diethylaminoethyl) -3 – (p-methoxybenzyl) – 1, 2 – hydroquinoxaline-2-one] is a quinoxaline derivative developed in the 1960s. Caroverine, an N-Methyl-D-aspartate (NMDA) and α-amino-3-hydroxy- 5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist together with the antioxidant activity. Glutamate is the main excitatory and main neurotransmitter of the cochlear afferents [1].being released on to the inner hair cell (IHC) synaptic region. In some pathological condition, excessive noise exposure leads to excessive glutamate release and excitotoxic intracellular calcium overload, which could be a basis for tinnitus. It has been reported that glutamate receptors, e.g. NMDA (N-Methyl-D-aspartate), can be selectively blocked by their antagonist (e.g. caroverine), abolishing tinnitus in a significant number of patients [4].

Gingko 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.

Von Boetticher reviewed 8 clinical studies, all of which used EGb 761, and came to the same conclusion: Ginkgo biloba is effective in reducing tinnitus sound levels for most people who use it. [7].

This study attempts to compare the efficacy between Ginkgo 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 Mahavir Institute of Medical Sciences, Vikarabadfor one year.

Method of collection of data

01. A) Detailed History taking and subjective assessment of the Tinnitus using Tchqs
02. B) Clinical examination
03. 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 randomized into 2 study groups and 1 control group [4-6]. The first study groups comprised of 30 patients were administered one dose of carvoverine injection 10ml in 100ml normal saline, followed by Carvoverine capsules /twice/daily for six months. The second study groups comprised of 30 patients were administered Gingko Biloba 120mg twice dailyfor six months. The control groups comprised of 30 patients were administered placebos once daily for six months.

Inclusion Criteria

1)Minimal age 18years,

2) Tinnitus early or late-onset,

3) Absence of Psychiatric diseases,

4) NIHL with Tinnitus Cochlear and retro cochlear pathology

Exclusion Criteria

1) Tinnitus due to Ototoxicity,

2) Tinnitus due to systemic,

3) Vascular or Diabetes, Anxiety and Depressions,

4) Tinnitus due to external, middle Ear causes.

5) Pulsatile tinnitus Cerebellopontine angle tumours.

Observations and results

A comparative clinical study with 90 PatientsRandomised 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 1: Age distribution of patients

Age in years	Caroverine		Gingko biloba		Placebo	
	Number	%	number	%	Number	%
21-30	2	6.7	11	36.7	00	0.0
31-40	11	36.7	3	10	1	3.3
41-50	10	33	4	13.3	5	16.7
51-60	4	13.4	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	

Table 2: Gender distribution of patients

Gender	Caroverine		Gingko biloba		Placebo	
	Number	%	Number	%	Number	%
Male	12	40	16	53.3	18	60
Female	18	60	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		Placebo	
	Number	%	Number	%	Number	%
	3	10	12	40	10	33
6-9	9	29.7	2	6.7	5	16.7
9-12	15	49.5	11	36.7	7	23.6
>12 months	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 the site of tinnitus in three study groups

Site of tinnitus	Caroverine		Gingko biloba		Placebo	
	Number	%	Number	%	Number	%
Left	7	23.1	8	26.4	8	26.4
Right	7	23.1	7	23.1	10	33.3
Bilateral	16	52.8	15	49.5	12	39.6

Tinnitus was present in both in most cases

Table 5: Comparison of the mode of onset and progression of decreased hearing

Decreased hearing	Caroverine		Gingko biloba		Placebo	
	Number	%	Number	%	Number	%
Mode of onset						
Sudden						
Insidious	19	60	14	46.7	14	46.7
Progression						
Continuous	19	60	14	46.7	14	46.7
Intermittent						

All patients with hearing loss had insidious onset and continuous 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/(00)	-20.0	
Multivitamin				
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		

Thcq scores showed significant change between pre and post-treatment in those patients who treated with Gingkobiloba,

Tchq score post-treatment Caroverine showed reduction but not statistically significant p-value 0.100

Tchq score post-treatment with Gingko biloba showed statistically reduction with a value less than 0.001

Table 7:Comparison of improvement in hearing in pure tone audiometry pre and post-treatment

Pure tone audiometry	Caroverine	Gingko biloba	Placebo
Right ear			
Pre treatment	40.69+/-15.37	32.39+/-85.01	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 n those treated with gingko bilobawith a p-value of 0.007.

Discussion

Tinnitus is a common complaint among patients coming for auditory problems. Several theories about the aetiology of Tinnitus were proposed and treatment modalities in the form of medications and surgery were developed with varying degree of success [7]. 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 carovrine injection followed by capsules for six months. The second study group comprised thirty patients and was administered using gingko biloba twice daily for 6 months [8]. The controlled group comprised thirty patients and were given multivitamins daily once. Thus 90 patients 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.

Infusion of caroverine, a quinoxaline derivative, can be used successfully in the treatment of inner Ear Tinnitus [9-11]. 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-Aspartame (NMDA) antagonist [12,14].

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 subsynaptic membranes of inner hair cells afferents is disturbed. In total, 90n Pt with inner Ear Tinnitus of assumed Cochlear- Synaptic Pathophysiology Was included in the study, 30 patients were treated with Caroverine, 30 patients with Gingko Biloba and 30 Patients with Multivitamins.

For a response to having 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 Patients showed a significant response according to the defined success criteria. The results confirmed our working hypothesis on the genesis of cochlear synaptic tinnitus. In one study, conducted in 1997, caroverine reduced tinnitus symptoms for most pts, 63% of pt responded immediately with a significant 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 special extract manufactured according to a patent standardized pharmaceutical process.

The combined effects of its components a.o.gingkoflavon glycoside and terpene lactones (Gingkolites, Bilobolide) results in a multifactor pharmacological action profile comprising of positive Effect on rheological parameters andthe energy metabolism of the nerve cells protecting them from d sequels of hypoxia and ischemia, and radical - scavenging properties. Several reviews addressing the efficacy of Gingko Biloba have been published in recent years. [9].Uncritically lumped together studies of Ginko Biloba preparations irrespective of their quality and dosage.

They may have relied on the publication in a peer-reviewed journal as proof of quality rather than going into the detection of flaws in the different publications. In a meta-analysis of trials of Ginkgo Biloba in the treatment of tinnitus, [9]. also pooled studies using various Ginkgo products of different and partly unknown quality. They concluded 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 tchqsstandardized extract from randomized, placebo-control trials,supported by findings from reference - controlled and uncontrolled trials in a morestandardized Ginkgo Biloba extract, EGB &Tchqs specific preparation was found to placebo in the treatment of tinnitus.

RecommendationL: As most tinnitus cannot be cured, helping patients cope with the symptoms through conservative measures and reassurance can have the best results.

All the patients with tinnitus should be referred to an audiologist to undergo an audiologic evaluation to help determine the auditory function and the presence of any hearing loss.Red flags for referral to another specialist include pulsatile or unilateral tinnitus, and abnormal findings on otoscopy.Further double-blind placebo-controlled studies of long duration are required to establish the long term efficacy of Ginko Biloba and carvoreinein treatment of tinnitus.

Conclusion

01. No treatment for tinnitus has been well established and no specific therapy is found to be satisfactory in all patients.
02. Tinnitus is a symptom of different pathology, different to measure and has a different underlying mechanism. Possible mechanisms are: i.eabnormal afferent excitation at a cochlear level due to:
    - Mechanical Tinnitus based on spontaneous otoacoustic emissions,
    - Glutamate Neurotoxicity,
    - Enhance sensitivity of NMDA and NON -NMDA receptors,
    - Normal Ion channels conductance – Ca channel dysfunction.
03. Efferent dysfunction/reduction of Gaba effects.
04. Alteration of spontaneous activity and tonotopic reorganization.
05. Many treatment modalities have been tried with varying degrees of success such as Antidepressants, Tricyclic anti-depressants (SSRI), Gaba analogues (Benzodiazepine, Gabapentine, Baclofen), Glutamate receptor antagonists (Caroverine), ca channel antagonists (Nimodipine, Flnrazine), Antiepileptics (Carbamazepine, Sodium valproate, Lamotrigine), prostaglandin analogues, Misoprostol, Lignocaine, Ginkgo Biloba.
06. Surgical procedure for the treatment such as auditory nerve section, cochlear destruction has been tried. There is little evidence of effectiveness and may even make tinnitus worse.
07. 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 a drug used as a spasmolytic and otoneuroprotective (inner ear protective) agent in some countries. It acts as an n-type Calcium channel blocker, competitive AMPA receptor antagonist and noncompetitive NMDA receptor antagonist. It also has antioxidant effects.

01. 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-oedema, antihypoxic, radical scavenging and metabolic actions. In addition, it increases disturbed microcirculatory blood flow by increasing the fluidity of blood.
02. Our study was done to ascertain the effectiveness of caroverine and Gingko Biloba in the treatment of tinnitus in a Placebo-controlled group of patients.
03. We followed up patients for 6 months and they were assessed with Tchqs and Pta both pre and post-treatment.
04. In our study we concluded that the 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.
05. 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 the rest had a better response as capsules were continued two tabs twice daily
06. In the Ginkgo Biloba group 50% responded after a three months treatment, so in long term Gingko Biloba had a better response over caroverine.
07. In the Placebo Group 40% responded according to the defined success criteria.
08. According to the study I have conducted Ginkgo Biloba is a better drug when compared with Caroverine in the long term treatment whereas Caroverine has a better response immediately after administration. Caroverine has approximately the 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.

What does this study add to present knowledge?

A new thing in the study is that we have found that the carnosine can give immediate relief from tinnitus as well as improvement in sensorineural hearing, whereas ginkoBiloba gives good results from tinnitus in longterm. Ginko biloba is cost-effective in the treatment of tinnitus.

Author contribution

Both the authors have equally participated in the journal work, contributed to the literature review and interpretation, and to preparing the manuscript for submission.

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