

Effect of Gingko Biloba Versus Caroverine in the Treatment of Tinnitus-A One Year Randomized Control Study

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Abstract— Introduction: Chronic tinnitus is a prevalent condition that causes distress to at least 10-15% of the adult population which directly affects the quality of life and is commonly associated with anxiety and depression. *Gingko biloba*, a well-known herbal medicine exhibits anti-inflammatory, antioxidant, neurotransmitter regulation and vasomotor activity, increases disturbed microcirculatory blood flow. Caroverine is a glutamate receptor antagonist and also reduces the excitability of the nerve cell function. It is postulated that caroverine blocks both NMDA and AMPA induced firing. **Objective:** To study the effect of oral caroverine versus oral *gingko biloba* in the treatment of tinnitus patients. **Method:** A total 80 selected patients of tinnitus, without any medical or surgical co-morbidity, were included in the study and divided randomly in two groups, one group receiving 120mg of *Gingko biloba* and the other group receiving 60mg Caroverine. Both the groups were followed up for 3 months. Treatment outcomes were measured in terms of improvement in subjective symptoms (tinnitus functional index) and objective measure (tinnitus pitch matching and loudness). **Result:** Both groups showed improvement in tinnitus function index scores, tinnitus pitch matching and loudness at the end of 3 months. **Conclusion:** Both *Gingko biloba* and Caroverine are found to be an effective treatment for tinnitus and is also readily available in the market, cost effective and free of side effects as well.

Keywords— Caroverine; *Gingko biloba*; Tinnitus.

I. INTRODUCTION

Tinnitus is the perception of sound in the absence of any external acoustical or electrical stimulation of the ear.[1] Tinnitus lasting longer than 3 months is considered as chronic tinnitus. Tinnitus frequently presents as ringing, although the disorder can also sound like buzzing, hissing, whistling, roaring, or other combinations of these sounds.[2] The traditional view that tinnitus is a degenerative disorder of the cochlea caused by damaged hair cells has led to a philosophy that nothing much can be done to alter it, and patients can only be helped to cope with the situation or learn to live with it. Although our knowledge of auditory processing by no means finished, enough is known to explain the basic mechanisms for the emergence and persistence of tinnitus, and to describe quite accurately the mechanism of distress caused by tinnitus.

Chronic tinnitus is a condition that causes distress to 10-15% of the adult population which affects the quality of life and is commonly associated with anxiety and depression.

Approximately 25% of tinnitus sufferers claim that it disrupts their daily activities, One percent to three percent of people

claim that it seriously reduces their quality of life.[2] Tinnitus being a common illness, does not have a standardized and effective treatment plan. Tinnitus can be mild or severely incapacitating in its severity.

One of the age-old herbal remedies that is most frequently prescribed is *gingko biloba*. *Gingko biloba*, a herbal medicine, exhibits anti-inflammatory, anti-oxidant, free radical scavenging, cerebral glucose consumption, platelet aggregation inhibition, neurotransmitter modulation, and vasomotor

activity. Enhances microcirculatory flow, which in turn increases blood fluidity.[3]

Taking into consideration the multiple advantageous properties, it is put to use in the treatment of neurologic, psychiatric, functional, and physiologic symptoms such as issues with memory, attention and concentration, psychomotor function, mood is supported by the plant's putative neuroprotective and cognitive enhancing properties. Common indications include Alzheimer's disease and age-related dementia, cerebrovascular disease, multi-infarct dementia, cerebral atherosclerosis, cerebral insufficiency, inflammation, intermittent claudication, and glutamate toxicity.

The most common excitatory neurotransmitters are glutamate while the primary inhibitory neurotransmitter is GABA. Both classes of ionotropic glutamate receptor subtype NMDA and AMPA are present in afferent nerve fibres of inner hair cells. Increase in the release of glutamate has been suggested to be involved in the generation and maintenance of tinnitus by causing excitotoxicity and thus over expression of NMDA receptors.

Taking into account this biochemical theory of tinnitus, caroverine, a quinoxaline derivative and a relatively new drug, was considered for this study for its properties.

Caroverine inhibits the activation of both NMDA and AMPA receptors. It functions as a competitive AMPA receptor antagonist, a non-competitive NMDA receptor antagonist, and an N-type calcium channel blocker.[4]

Various other drugs like pentoxifylline, Korean red ginseng, etc., are also being researched to alleviate tinnitus as the complete cure for tinnitus is yet to be achieved.

II. METHODS

The study is a hospital based, open level, randomized, prospective study of 1-year duration. The present study was carried out at Department of Otorhinolaryngology and Head and Neck Surgery in a tertiary care centre from January 2021-December 2021 to study the effect of ginkgo biloba versus caroverine in the treatment of tinnitus. A total of 80 patients were chosen randomly for the study after they were confirmed clinically and audiological to have tinnitus, either unilateral or bilateral. Patients not willing to participate or not giving informed written consent and having any contraindication of test drugs, any blood disorders, recent vascular injury, major surgical illness and undergone or undergoing surgery, having excessive tobacco, nicotine or any other substance abuse were excluded from the study. After taking informed consent from the patient, their details and a thorough clinical history will be obtained for duration and nature of tinnitus, duration and nature of any previous treatment. All patients will be clinically examined including general physical examination, careful examination of the ear, nose and throat and routine blood investigations will be done. All patients had to undergo pure tone audiometry ranging from 0-16000Hz and tinnitus pitch matching and loudness was done. On pure tone audiometry, the frequency at which the tinnitus was perceived by the patient was matched by providing tones at similar frequency to obtain the value of pitch matching, to objectively measure severity of tinnitus in the patient. All patients were asked to fill a questionnaire - Tinnitus functional index before, during and after the course of treatment being day 1, day 45 and day 90 respectively. A total of 80 patients of tinnitus will be considered for the trial and will be randomly divided into 2 equal groups. One group will be given 120mg ginkgo biloba divided in 3 doses for treatment of tinnitus whereas the other group will be given 60mg caroverine divided into 3 doses daily for a period of 3 months. Patients will be asked to follow up monthly for a period of 3 months and severity of tinnitus will be assessed. Result was statically analyzed by spss version percentage, mean, standard deviation.

III. RESULT

Group A consisted of 16 females and 24 males (range: 18 – 75 years) and their mean age was 43.3 ± 13.7 years. There were 11 females and 29 males in group-B, and their mean age ranged from min to max at 43.9 ± 13.74 years.

Age wise distribution of tinnitus patients in this study between the age group 18-75. In group A ,13 patients (32.5%) belonged to the age group 35-44 years and in group B,13 patients (32.5%) belonged to the age group 25–44 years, comprising the majority respectively.

Group A had 20 patients (50%) with only left ear being affected, group B had 16 patients (40%) with right ear affected. Tinnitus of the left ear was most common in this study.

In group A the mean score of Pure tone audiometry - pitch matching(kHz) were 3.53,2.81,2.43 on day 0,45 and 90 respectively and in group B 3.26,2.7,2.31on day 0,45 and 90 respectively and mean score of pure tone audiometry - loudness (dB)were 45.25,40.25,35.25 on day 0,45 and 90 respectively

and in group B 43.75,37.88,33.25 on day 0,45 and 90 respectively.

TABLE 1: Pitch matching mean scores

Day	PURE TONE AUDIOMETRY - PITCH MATCHING (kHz)			
	CAROVERINE		GINGKO BILOBA	
	Mean	S.D	Mean	S.D
0	3.53	1.25	3.26	1.15
45	2.81	1.03	2.70	1.09
90	2.43	1.02	2.31	0.95

TABLE 2: Loudness mean scores

Day	PURE TONE AUDIOMETRY - LOUDNESS (dB)			
	CAROVERINE		GINGKO BILOBA	
	Mean	S.D	Mean	S.D
0	45.25	8.24	43.75	6.58
45	40.25	7.68	37.88	6.19
90	35.25	6.79	33.25	5.94

TABLE 3: Mean TFI scores between the groups

Day	TINNITUS FUNCTIONAL INDEX SCORE			
	CAROVERINE		GINGKO BILOBA	
	Mean	S.D	Mean	S.D
0	109.00	34.34	97.43	28.31
45	79.48	25.24	71.55	19.79
90	61.05	22.63	53.93	16.91

TABLE 4: Mean TFI sub scores between the groups

Subscale	MEAN TFI SUBSCORES					
	CAROVERINE			GINGKO BILOBA		
	DAY 0	DAY 45	DAY 90	DAY 0	DAY 45	DAY 90
INTRUSIVE	16.05	12.23	10.25	14.00	11.45	9.30
CONTROL	13.13	11.20	9.13	12.38	11.50	9.10
COGNITIVE	14.85	11.18	10.25	14.00	10.88	9.95
SLEEP	13.80	10.10	8.08	12.35	9.20	6.90
AUDITORY	10.25	7.15	5.38	8.80	6.03	4.20
RELAXATION	13.48	9.73	7.78	12.40	8.85	6.88
QUALITY OF LIFE	11.28	7.55	5.75	9.68	5.83	4.10
EMOTIONAL	14.48	8.78	4.68	14.20	8.40	4.33

In group A the mean TFI score were 109,79.48,61.05 on day 0,45 and 90 respectively and in group B 97.43,71.55,53.93 on day 0,45 and 90 respectively. The tinnitus functional index was further divided into subscales i.e., intrusive (unpleasantness, intrusiveness, persistence), sense of control (reduced sense of control), cognitive (cognitive interference), sleep (sleep disturbance), auditory (auditory difficulties attributed to tinnitus), relaxation (interference with relaxation), quality of life (quality of life reduced), emotional (emotional distress) and sub scores were calculated accordingly to show the improvement in each subcategory.

IV. DISCUSSION

Tinnitus is the perception of sound in the absence of an external acoustic stimulus or electrical stimulation of the ear.[1] Tinnitus is a common and occasionally debilitating medical condition. The severity of tinnitus can range from trivial to completely disabling. Tinnitus being a common illness, does not have a standardized and effective treatment plan.

Group A consisted of 16 females and 24 males (range: 18 – 75 years) and their mean age was 43.3 ± 13.7 years. There were 11 females and 29 males in group B, and their mean age ranged

from min to max at 43.9 ± 13.74 years. Out of total 80 cases, showed statistical gender preponderance among males between both the groups. Likewise, In the study conducted by Nishad et al,^[8] among 86 patients suffering from tinnitus, most of the patients were between 50-60 years (40.69%) followed by 40-50 years (22.09%) with the male to female ratio 2.07:1 showing male preponderance.

In our study, improvement in symptoms of tinnitus was objectively measured with pure tone audiometry pitch matching(kHz) and loudness(dB) on day 0,45 and 90. On day 0, the mean value of loudness in patients on ginkgo biloba was 43.75 ± 6.58 dB, which improved on day 45 to 37.88 ± 6.19 dB and on day 90 to 33.25 ± 5.94 dB showing significant improvement in the loudness in the ginkgo biloba group with a p value <0.0001 . Similarly in a study conducted by Morgenstern and Biermann [6] with 99 patients, 50 of them received ginkgo biloba and 49 placebo over 12 weeks. Over the period of 12 weeks the loudness improved from a mean value of 42.2 dB to 39 dB in the ginkgo biloba group and 44.3 dB to 45.1 dB in the placebo group with a p value of 0.015. In a study conducted by Sachin Jain et al,^[5] of 48 patients, before initiation of treatment, 24 (50%) patients experienced tinnitus that matched with a pure tone sound of 41-60 dB, 20 (41.67%) had a tinnitus match of 21-40 dB. Only one patient had a tinnitus that matched with 0-20 dB and 3 (6.25%) had a tinnitus matching of 61-80 dB. After 3 months of treatment, in caroverine group 6(26.09%) patients experienced tinnitus that matched with a pure tone sound of 41-60 dB, 7(30.43%) had a tinnitus match of 21-40 dB. 9(39.13%) patients had a tinnitus that matched with 0-20 dB and 1(4.35%) had a tinnitus matching of 61-80 dB whereas in ginkgo biloba group, 5(20%) patients experienced tinnitus that matched with a pure tone sound of 41-60 dB, 11 (44 %) had a tinnitus match of 21-40 dB. 9(36%) patients had a tinnitus that matched with 0-20 dB and 0 had a tinnitus matching of 61-80 dB. In a study conducted by Peter Franz [7] ,of 60 patients, 30 received caroverine and 30 placebo, whose mean value of tinnitus matching was 60dB and 45dB respectively before treatment, which changed to 50dB and 50dB after treatment.

In our study, for subjective assessment of tinnitus, tinnitus functional index questionnaire was used, which contained a total of 25 questions with 8 subscales and adding to a total score of 250. This questionnaire has not been used in any similar studies. The questionnaire was filled on day 0,45 and 90. In the caroverine group, the mean TFI scores on day 0,45 and 90 were 109.00 ± 34.34 , 79.48 ± 25.24 and 61.05 ± 22.63 respectively, showing an improvement over 3 months with a significant p value <0.0001 . In the ginkgo biloba group, the mean TFI scores

on day 0,45 and 90 were 97.43 ± 28.31 , 71.55 ± 19.79 and 53.93 ± 16.91 respectively, showing an improvement over 3 months with a significant p value <0.0001 . The subscales of the questionnaire comprise of intrusive, control, cognitive, sleep, auditory, relaxation, quality of life, emotional. The mean scores showed improvement across all subscales between both groups. In a study conducted by Sachin Jain et al,^[5] of 48 patients, before initiation of treatment mean tinnitus grading scores were 5.08 in caroverine group and 4.48 in ginkgo biloba group whereas after 3 months the mean tinnitus grading scores reduced to 4.04 and 3.20 respectively.

V. CONCLUSION

The result of this study implies that the drugs ginkgo biloba and caroverine given orally helped alleviate tinnitus. Improvement was seen in pitch matching and loudness on pure tone audiogram at the end of the study period of 3 months. Improvement was seen in tinnitus functional index scores at the end of 3 months. Improvement was across all subscales of TFI at the end of 3 months.

Hence, from the observations in this study, we can conclude that ginkgo biloba and caroverine are both effective in alleviating tinnitus and can be administered as an effective mode of treatment as it is readily available in the market, cost effective and free of side effects as well.

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