"CLINICAL STUDY OF EFFECTS OF INJ. CAROVERINE AND GINKGO BILOBA EXTRACT IN COCHLEAR SYNAPTIC TINNITUS"

Dr. Mohammad Aftab*, Dr. Rajeet Kumar Nishad**, Dr. Prabhat Srivastava***, Dr. Ashutosh Rai****, Dr. Sachin Jain***** and Dr. Mangal Singhi******

BACKGROUND & OBJECTIVES:
Tinnitus, "ringing in the ear", is the most common problem encountered in everyday practice of otolaryngology. Considerable variations exist in Tinnitus prevalence with gender and age. It affects patient's life style, general health as well as emotional status. The most common variety of Tinnitus, Cochlear Synaptic Tinnitus is diagnosed with the help of various audiological tests. There is no standardised treatment till date. Yet Tinnitus Retraining Therapy, a medical therapy in form of psychotherapy or pharmacological therapy are commonly used. Ginkgo biloba extract in patients with tinnitus show significant improvements in symptoms and quality of life. Recently Caroverine, a spasmylytic drug, having glitamate antagonistic activity is used for tinnitus treatment. A randomised comparative study was designed to establish the effects of Caroverine and Ginkgo biloba extract in treatment of Cochlear Synaptic Tinnitus.

METHOD:
86 diagnosed patients of Cochlear Synaptic Tinnitus were treated with inj. Caroverine (group 1, n=22) and placebo (group 2, n=22). Ginkgo biloba extract (group 3, n=22) and placebo (group 4, n=22) and followed up at 1 month, 3 months, 6 months and improvements were evaluated in terms of Tinnitus Grading and Tinnitus Matching. Statistical analysis was done using statistical software SPSS. The baseline profile and any improvement after treatment between groups were compared using paired/ANOVA test.

RESULT:
In our study 54.4% (12 out of 22) patients responded immediately after infusion of Caroverine and remained effective at end of 1.5 and 6 months after drug infusion while 13.6% (3 out of 21) patients responded in placebo group and reverted back to pre-treatment level on subsequent follow ups. In Ginkgo biloba group 31.8% (7 out of 22) patients responded at one month follow-up, while none responded in placebo group. These responders showed further improvement in Tinnitus Matching and Tinnitus Grading at 3 months but a plateau occurred at followup at 6 month without further improvement. Two patients were cured in group 1 (Ginkgo biloba).

CONCLUSION:
Caroverine immediately improves tinnitus grading and matching and provides immediate relief in reducing the severity of tinnitus. Ginkgo biloba extract takes longer time to improve tinnitus but it provides greater relief on long term follow-up. It is finally suggested that inj. Caroverine should be given in severe cases of tinnitus to reduce its severity immediately and then patient should be put on Ginkgo biloba extract for a period of 3 months to provide sustained and long lasting relief.

KEYWORDS:
Cochlear Synaptic Tinnitus, Tinnitus Matching, Tinnitus Grading, Caroverine, Ginkgo Biloba.

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INTRODUCTION:

Tinnitus is defined as a sound perceived for more than five minutes at a time in the absence of any external acoustic or electrical stimulation of the ear and not occurring immediately after exposure to loud noise, phantom auditory perception or head noise.

Prevalence of Tinnitus has been estimated as high as 30% in an adult population. Population statistics suggested that females are more affected than males. Although considerable variation exists in Tinnitus laterality with age and gender, otoscopists suggested that the left ear has been affected more than the right ear. Tinnitus prevalence increases with increasing hearing loss with almost 75% of patients presenting with hearing loss having Tinnitus. It affects general status, lifestyle as well as emotional status of patients considerably.

Various conditions e.g. excessive noise, head trauma, hypoxia, aging or metabolic disorder lead to excess of toxic glutamate release which causes spontaneous depolarisation state perceived as Tinnitus.

Various classifications have been established for Tinnitus e.g. subjective vs objective, vibratory vs non-vibratory, conductive vs sensorineural or central Tinnitus. Cochlear Synthetic Tinnitus is synonymous with the signal transfer type of sensorineural Tinnitus and is the most common type of Tinnitus.

Tinnitus evaluation may include proper history with its onset, course, possible cause, characteristics, loudness and frequency with audiological tools as FTA, Tympanometry, SISI, ABR or BERA for its proper categorisation and various imaging modalities.

Various treatment modalities have been described as Tinnitus Retraining Therapy, surgical therapy, instrumentation like Hearing Aids, noise generators or pharmacological therapy with Antidepressants, GABA Analogs, Ca2+-Channel Antagonists, Antiepileptics, Prostaglandin Analogs, or Inj Lidoaine.

Ginko biloba extracts were used for Tinnitus treatment and studies have shown better and faster improvement as compared to placebo.

Selective Glutamate Receptor Antagonist like Caroverine, a smooth muscle relaxant and a neuroprotective drug which blocks postsynaptic glutamate receptor, was given intravenously and reported to be effective in Tinnitus.

Restoration of hearing for the effective treatment of Tinnitus suggested that no treatment can yet be considered well established and no specific therapy is found to be satisfactory in all patients. Hence an intervention study was undertaken to establish efficacy of Caroverine and Ginko biloba in cochlear syneaptic tinnitus.

AIMS AND OBJECTIVE:

The present clinical study aims to evaluate the effects of inj Caroverine and Ginko biloba extract on sensorineural tinnitus in terms of improving tinnitus grading, tinnitus matching and quality of life of patient.

MATERIAL AND METHODS:

Study design: Randomised placebo controlled, double labelled, hospital based intervention prospective study.

Subjects:

100 patients who were having cochlear sensorineural tinnitus, attending outpatient department of Otorhinolaryngology were included in study.

Institutional Ethical Clearance was obtained before starting of study. Out of 100 only 86 were ready to participate in the study. Informed consent was taken from each patient for participation in study.

Patients were included irrespective of age, gender, occupation, social status and ethnicity. Patients with coexisting chronic illness, immediate post-operative, pregnancy, lactation women, Meniere's disease, masticatory movement problem influencing subjective tinnitus sensation or patients not willing to give written consent after receiving due instruction were excluded from study.

The cases were registered and given one number for each case. The age, sex, religion, socio-economic status, occupation and address of patients were recorded. The symptoms of the patients were recorded chronologically. The
CLINICAL STUDY OF EFFECTS OF INI. CAROVERINE AND GINKGO BILoba EXTRACT IN COCHLEAR SYNAPTIC TINNITUS

The history of present episode or previous such episodes were recorded. The past history of systemic disorders, oto-toxic drug use was recorded. These subjects were then given/explained a questionnaire adapted from University of Denver Tinnitus Centre. After the completion of the questionnaire the Pure Tone Audiometry (PTA) was done. Other audiological tests including Acoustic Reflex Test (ART), clenching reflex, Tympanometry, Short Increment Sensitivity Index (SISI), Alternate Binaural Loudness Balance (ABLb) and Tone Decay Test (TDT) were performed. Tinnitus frequency and loudness match using narrow band sound in the contralateral ear was performed in the same sitting. The masking of tinnitus was done in the diseased ear using narrow band noise.

Cochlear Synaptic Tinnitus was diagnosed based on finding from different audiological examinations, which localized pathology in Cochlea and excluded middle ear pathology. Tinnitus Grading was done on scale 0-10 in which “0” means no Tinnitus and “10” means disablilating tinnitus.

By using computer generated block randomization method participants were randomized into four groups:

**Group 1- Caroverine**: Patients were infused with a single dose of intravenously 160 mg/ 8ml of caroverine in 100 ml of physiological saline at the rate of 2 ml per minute.

**Group 2- Caroverine-Placebo**: patients were infused with a single dose of intravenously 8ml of caroverine placebo in 100 ml of physiological saline at the rate of 2 ml per minute.

**Group 3- Ginkgo Biloba**: patients were treated with 50 mg of Ginkgo biloba extract 12 hourly for a period of 3 months.

**Group 4- Ginkgo Biloba Placebo**: patients were treated with 50 mg of placebo 12 hourly for a period of 3 months.

Patients were treated accordingly, followed up and evaluated over a period of six months for improvement of clinical symptoms in term of tinnitus grading and quality of life.

**Statistical analysis:**

Statistical analysis was done using statistical software SPSS. The baseline profile and any improvement after treatment between groups were compared using paired/ANOVA test.

**RESULTS:**

86 patients with Cochlear Synaptic Tinnitus were the subject of our study. 22 patients were in group 1 (caroverine), 21 patients in group 2 (caroverine placebo), 22 patients in group 3 (Ginkgo biloba) and 21 patients in group 4 (Ginkgo biloba placebo).

Most of the patients in our study were in fifth decade (40.59%) followed by fourth decade (22.09%).

In the present study 67.44% (n=58) of the patients were male and 32.56% (n=28) were female. So there was a male preponderance.

Left ear tinnitus was more common (53.4%) as compared to right ear tinnitus (36.04%) and only 10.4% were having bilateral tinnitus.

77.90% (67 out of 86 patients) patients had a Tinnitus Grading of 4-6 (moderate severity). (Table I) and Tinnitus Matching between 41-60 dB in 52.32% (45 out of 86 patients) (Table II).

<table>
<thead>
<tr>
<th>Tinnitus Grading</th>
<th>Group 1 (N = 22)</th>
<th>Group 2 (N = 21)</th>
<th>Group 3 (N = 22)</th>
<th>Group 4 (N = 21)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>0-3</td>
<td>1</td>
<td>4.55%</td>
<td>3</td>
<td>14.28%</td>
<td>2</td>
</tr>
<tr>
<td>4-6</td>
<td>17</td>
<td>77.27%</td>
<td>15</td>
<td>71.46%</td>
<td>18</td>
</tr>
<tr>
<td>7-10</td>
<td>4</td>
<td>18.18%</td>
<td>7</td>
<td>14.28%</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>100%</td>
<td>21</td>
<td>100%</td>
<td>22</td>
</tr>
</tbody>
</table>
### Table II: Pre-Treatment Tinnitus Matching

<table>
<thead>
<tr>
<th>Tinnitus matching</th>
<th>Group 1 (n = 18)</th>
<th>Group 2 (n = 20)</th>
<th>Group 3 (n = 18)</th>
<th>Group 4 (n = 21)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>0 - 20 dB</td>
<td>1</td>
<td>4.54%</td>
<td>7</td>
<td>9.26%</td>
<td>0</td>
</tr>
<tr>
<td>21 - 40 dB</td>
<td>8</td>
<td>45.45%</td>
<td>6</td>
<td>30.00%</td>
<td>12</td>
</tr>
<tr>
<td>41 - 60 dB</td>
<td>11</td>
<td>59.09%</td>
<td>12</td>
<td>60.00%</td>
<td>10</td>
</tr>
<tr>
<td>61 - 80 dB</td>
<td>3</td>
<td>14.29%</td>
<td>1</td>
<td>5.00%</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>100%</td>
<td>21</td>
<td>100%</td>
<td>22</td>
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</tbody>
</table>

### Table III: Post-Treatment Scoring

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T.G.</td>
<td>T.M.</td>
<td>T.G.</td>
<td>T.M.</td>
</tr>
<tr>
<td>Pre-treatment score</td>
<td>5.26</td>
<td>43.84</td>
<td>4.91</td>
<td>41.82</td>
</tr>
<tr>
<td>Immediate % improvement</td>
<td>3.57</td>
<td>32.12</td>
<td>2.92</td>
<td>33.32</td>
</tr>
<tr>
<td>At 1 month % improvement</td>
<td>3.57</td>
<td>32.12</td>
<td>2.92</td>
<td>33.32</td>
</tr>
<tr>
<td>At 3 month % improvement</td>
<td>3.57</td>
<td>32.12</td>
<td>2.92</td>
<td>33.32</td>
</tr>
<tr>
<td>At 6 month % improvement</td>
<td>3.57</td>
<td>32.12</td>
<td>2.92</td>
<td>33.32</td>
</tr>
</tbody>
</table>

* T.G.: Tinnitus Grading, T.M.: Tinnitus Matching

Group 1 was better than group 2 in improving Tinnitus Grading and difference was statistically significant (p < 0.05)
immediate after infusion, at 1 month, 3 month and 6 month post infusion. (Table IV and Graph)

### Table IV: Comparison of Tinnitus Grading (Mean ± SD) between Caroverine (group 1) and Caroverine Placebo (group 2)

<table>
<thead>
<tr>
<th>Tinnitus grading</th>
<th>Pre-TT</th>
<th>Immediate</th>
<th>1 month</th>
<th>3 month</th>
<th>6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Group 1</td>
<td>5.26 ± 1.21</td>
<td>3.57 ± 1.5</td>
<td>3.57 ± 1.5</td>
<td>3.84 ± 1.5</td>
<td>3.96 ± 1.6</td>
</tr>
<tr>
<td>Group 2</td>
<td>4.91 ± 1.31</td>
<td>4.69 ± 1.29</td>
<td>4.91 ± 1.31</td>
<td>4.91 ± 1.31</td>
<td>4.91 ± 1.31</td>
</tr>
<tr>
<td>p value</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

**GRAPH**
Comparison of Tinnitus Grading (mean) between Caroverine (group1) and Caroverine Placebo (group2)
Group 3 was better than group 4 in improving Tinnitus Grading and it was statistically significant (p<0.05) at 1 month, 3 month and 6 month. (Table V and Graph II)

Table V: Comparison of Tinnitus Grading (Mean±SD) between Ginkgo Biloba (group 3) and Ginkgo Biloba Placebo (group 4)

<table>
<thead>
<tr>
<th>Tinnitus grading</th>
<th>Pre-TT</th>
<th>1 month</th>
<th>3 month</th>
<th>6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
</tr>
<tr>
<td>Group 3</td>
<td>4.79±1.21</td>
<td>4.08±1.44</td>
<td>3.90±1.44</td>
<td>3.90±1.44</td>
</tr>
<tr>
<td>Group 4</td>
<td>5.01±1.44</td>
<td>5.01±1.44</td>
<td>5.01±1.44</td>
<td>5.01±1.44</td>
</tr>
<tr>
<td>p value</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
<td>p&gt;0.05</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>

GRAPH II Comparison of Tinnitus Grading (Mean) between Ginkgo Biloba (group 3) and Ginkgo Biloba Placebo (group 4)

Group 1 was better than group 3 in improving Tinnitus Grading but it was statistically not significant (p>0.05) at 1 month and 3 month. At 6 month group 3 was found to be better than group 1 but difference was statistically not significant (p>0.05). (Table VI and Graph III)

Table VI: Comparison of Tinnitus Grading (Mean±SD) between Caroverine (group 1) and Ginkgo Biloba (group 3)

<table>
<thead>
<tr>
<th>Tinnitus grading</th>
<th>Pre-TT</th>
<th>1 month</th>
<th>3 month</th>
<th>6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
</tr>
<tr>
<td>Group 1</td>
<td>5.26±1.21</td>
<td>3.87±1.5</td>
<td>3.84±1.5</td>
<td>3.95±1.6</td>
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<tr>
<td>Group 3</td>
<td>4.79±1.11</td>
<td>5.08±1.24</td>
<td>5.02±1.44</td>
<td>5.01±1.44</td>
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<tr>
<td>p value</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
<td>p&gt;0.05</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>

GRAPH III Comparison of Tinnitus Grading (Mean) between Caroverine (group 1) and Ginkgo Biloba (group 3)

Group 1 was better than group 2 in improving Tinnitus Matching and it was statistically significant (p<0.05) at immediate after infusion, at 1 month, 3 month and 6 month. (Table VII and Graph IV)
Table VII: Comparison of Tinnitus Grading (Mean±SD) between Caroverine (group 1) and Caroverine Placebo (group 2)

<table>
<thead>
<tr>
<th>Tinnitus grading</th>
<th>Pre-TT Mean ±SD</th>
<th>Immediate Mean ±SD</th>
<th>1 month Mean ±SD</th>
<th>3 month Mean ±SD</th>
<th>6 month Mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>43.84±14</td>
<td>29.23±14</td>
<td>29.23±14</td>
<td>31.34±13.39</td>
<td>32.69±16.32</td>
</tr>
<tr>
<td>Group 2</td>
<td>42.82±13</td>
<td>41.7±13.36</td>
<td>42.8±13</td>
<td>42.8±13</td>
<td>42.8±13</td>
</tr>
<tr>
<td>p value</td>
<td>p&lt;0.05</td>
<td>p&gt;0.05</td>
<td>p&lt;0.05</td>
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<td>p&gt;0.05</td>
</tr>
</tbody>
</table>

GRAPH IV: Comparison of Tinnitus Matching (Mean) between Caroverine (group 1) and Caroverine Placebo (group 2).

Group 3 was better than group 4 in improving Tinnitus Matching and it was statistically significant (p<0.05) at 1 month, 3 month and 6 month. (Table VII and Graph IV)

Table VIII: Comparison of Tinnitus Grading (Mean±SD) between Ginkgo biloba (group 3) and Ginkgo biloba Placebo (group 4)

<table>
<thead>
<tr>
<th>Tinnitus grading</th>
<th>Pre-TT Mean ±SD</th>
<th>1 month Mean ±SD</th>
<th>3 month Mean ±SD</th>
<th>6 month Mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 3</td>
<td>42.06±11.69</td>
<td>35.2±12.7</td>
<td>34.09±14.27</td>
<td>34.09±14.27</td>
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<tr>
<td>Group 4</td>
<td>45.9±12.5</td>
<td>45.9±12.5</td>
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<td>45.9±12.5</td>
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<tr>
<td>p value</td>
<td>p&gt;0.05</td>
<td>p&gt;0.05</td>
<td>p&gt;0.05</td>
<td>p&gt;0.05</td>
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</tbody>
</table>

GRAPH V: Comparison of Tinnitus Matching (Mean) between Ginkgo biloba (group 3) and Ginkgo biloba Placebo (group 4).
Group 3 was better than group 3 in improving Tinnitus Grading but it was statistically not significant (p>0.05) at 1 month, 3 month and 6 month. (Table IX and Graph VI)

<table>
<thead>
<tr>
<th>Tinnitus grading</th>
<th>Pre-TT</th>
<th>1 month</th>
<th>3 month</th>
<th>6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ±SD</td>
<td>41.84±14</td>
<td>29.23±14</td>
<td>31.34±15.39</td>
<td>32.69±16.32</td>
</tr>
<tr>
<td>Group 1</td>
<td>42.08±11.60</td>
<td>35.2±12.72</td>
<td>34.09±14.27</td>
<td>34.09±14.27</td>
</tr>
<tr>
<td>p value</td>
<td>p&gt;0.05</td>
<td>p&gt;0.05</td>
<td>p&gt;0.05</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>

**Graph VI** Comparison of Tinnitus Matching (Mean) between Caroverine (group 1) and Ginkgo biloba (group 3)

**Discussion:**

Tinnitus, “ringing in the ears,” is one of the most common problems encountered in every day 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 & tinnitus maskers are the wearable behind-the-ear or in-the-ear devices, used for presentation of sound in a controlled manner 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 modulation of avoidance behavior motivated by tinnitus. Antidepressant like selective serotonin reuptake inhibitor (SSRI) may also find an application for the treatment of tinnitus in elderly, in whom a down-regulation in serotonergic transmission, as part of aging process, has been suspected.

GABA anologue like Alprazolam (benzodiazepine) has been reported to be beneficial for the treatment of tinnitus following a randomized controlled trial. Car++ channel antagonists like Flunarizine is primarily used for the treatment of migraine, but it has been demonstrated to reduce tinnitus in subset of patients with dizziness. Lidocaine is one of the most intriguing drug used in controlling tinnitus and probably the most effective one.

Many trials have been reported on the effectiveness of Ginkgo biloba in tinnitus. The results suggest that the Ginkgo biloba treated group experienced greater and faster improvement in symptoms.

Caroverine, a quinoline derived from bucareline, the basic structure of papaverine, originally developed as a spasmolytic drug which may, however, exert central effects due to an unspecified calcium channel blocking action and glutamate antagonism. Experiments in guinea-pigs have shown that caroverine acted as a potent competitive alpha-amino
3. Hydroxyl-5-methyl-4-isoxazole-proprionic acid (AMPA) receptor antagonist, in higher dosages, is a non-competitive N-Methyl d-aspartate (NMDA) antagonist. Glutamate is a principal excitatory neurotransmitter in brain. In physiological conditions, glutamate releases from pre-synaptic vesicles of inner hair cell in response to appropriate stimuli and acts on post-synaptic NMDA and AMPA receptors resulting in corresponding depolarization and impulse is conducted through the postsynaptic NMDA and AMPA receptors in the inner hair cell membrane, excess amount of glutamate leaks through the vesicles and acts on post-synaptic NMDA and AMPA receptors in the inner hair cell membrane. Due to its glutamate antagonist activity on NMDA- and AMPA receptors, Caroverine reverses the spontaneous depolarization state and receptor starts responding as per the acoustic stimulus.

In our present study, 86 patients suffering from cochlear synaptic tinnitus were registered. Most of the patients were in fifth decade of life (40.69%) followed by fourth decade of life (22.09%) and age range of patients was from 13 years to 60 years. The relatively lower percentage of elderly people in this study i.e. 20.93% in sixth decade of life as compared to 40.69% of fifth decade in life was not due to lower prevalence of tinnitus in elderly, but due to lower turnover of elderly patients to healthcare facilities to seek help due to underlying socioeconomic conditions in this part of world. Our data correlated well with the study of Coles et al (1990) who found that prevalence of tinnitus was a positive function of age. 38% of patients were less than 40 years of age and 62% of patients were more than 40 years of age.

In present study male to female ratio was 2.97:1 showing male preponderance. This difference might be because in Indian population males are more exposed to sound pollution in their work place or other factors which may cause tinnitus. Second most of the females in India are house wives and are dependent on their father, husband or children. They look after, like elderly and hence they are also often neglected. So, very few female patients reported to health-care facilities for tinnitus. However, our data does not correlate with population statistics of Cooper Jr (1994) that suggest females (57.5%) are more affected than males (42.5%).

In the study conducted by Prof. Klaus Ehrenberg to evaluate the efficacy of single dose infusion of Caroverine in the caroverine group, 63.3% responded to therapy immediately after the infusion and the value sustained at 3, 6 and 9 months. In the placebo group, none of the patients treated showed significant response according to the defined success criteria. We conducted our study in 86 patients and also compared it with other treatment modalities i.e. Ginkgo biloba. Patients were randomly assigned to receive either single dose infusion of Caroverine or single infusion of placebo or tab Ginkgo Biloba or Ginkgo biloba placebo.

In our study, 54.4% (12 out of 22) patients responded immediately after infusion of Caroverine and 13.6% (3 out of 21) patients responded in placebo group. However all 3 responders of placebo group reverted back to their pre-treatment level at one month follow-up. All the patients who initially responded to Caroverine infusion, remained responder at 1 month followup in Caroverine group. At three month followup two patients who initially responded to Caroverine reverted back to pre-treatment level, so the number of responders at three month follow-up were 19 (i.e. 45.4%). At 6 month followup, one more patient reverted back to pre-treatment level and so, number of responders drop down to 18 (40.9%). One of patient in our study complained of nausea following Caroverine infusion which was amenable to intravenous on demecol. No specific side effect was reported in Ehrenberg study. However, none of the patients in Caroverine study became symptom free completely.

From our study we found that single dose infusion of Caroverine is effective in reducing the severity of cochlear synaptic tinnitus but, it cannot abolish the tinnitus, and its effect wears off with time in 25% of responders.

Thus from our study on Caroverine it can be concluded that it may be of great use in patients who are in acute distress, to provide immediate relief. Compared to Prof. Ehrenberg's study we also found statistically significant improvement in subjective symptom (Tinnitus Grading) and psycho-acoustic measure (Tinnitus Matching) in the experimental group.

In our study 43 patients of cochlear synaptic tinnitus were randomized and treated either with 2x60mg of oral Ginkgo biloba or with placebo and patients were followed up at 1 month, 3 month and 6 month time interval for observation of improvement in Tinnitus Matching and Tinnitus Grading. In Ginkgo biloba group 31.8% (7 out of 22) patients responded
at one month followup, and none responded in placebo group. At subsequent followups responders showed further improvement in Tinnitus Matching and Tinnitus Grading at 3 months. However, plateau occurred at subsequent followups at 6 months with no further improvement. No side effects were noted during the 6 months of followup. Two of the patients in Ginkgo biloba group were cured after three months of treatment. Compared to study on Ginkgo biloba by Meyer, B. 1986)32, we also found statistically significant improvement (p=0.05) in subjective symptom (Tinnitus Grading) and psychoacoustic measure (Tinnitus Matching) in the experimental group. From our study on Ginkgo biloba we found that Ginkgo biloba is effective in treating cochlear synaptic tinnitus and response increases with continuation of therapy and its effectiveness persist even after the cessation of treatment. Ginkgo biloba can also abolish the tinnitus (Table 3).

Thus Ginkgo biloba seems to be a better drug for control of cochlear synaptic tinnitus. However a further study is needed with a repeat dose of inj. Caroverine in non-responder.

CONCLUSION:

Following conclusions were drawn from the present study:

Most of the patients suffering from cochlear synaptic tinnitus were in fifth decade (40.69%) followed by fourth decade (22.09%) while male to female ratio was 1:0.48.

A single dose infusion of Caroverine immediately improves tinnitus grading and matching and provides immediate relief in reducing the severity of tinnitus in 54.54% of cases.

One third of initial responders in Caroverine group reverted back to pre treatment level however rest two third of responders had sustained effect after six months of follow-up.

Ginkgo biloba is also effective in improving Tinnitus Grading and Tinnitus Matching in 31.8% of cases. There is further improvement of tinnitus grading and matching on continuation of treatment but, plateau occurred after cessation of treatment. Improvement was sustained in Ginkgo biloba group even after 3 month of cessation of treatment i.e. at 6 month follow-up. Two of the patients in Ginkgo biloba group were cured after three months of treatment.

Ginkgo biloba takes longer time to improve tinnitus but it provides greater relief on longer term follow-up.

Due to its sustained effectiveness and without side effect, Ginkgo biloba seems to be a better drug for control of cochlear synaptic tinnitus.

It is finally suggested that inj. Caroverine 160 mg/ 8ml in 100 ml of physiological saline as intravenous infusion should be given in severe cases of tinnitus to reduce its severity immediately and then patient should be put on tab. Ginkgo biloba 60mg twice a day for a period of 3 months to provide sustained and longest relief.

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"CLINICAL STUDY OF EFFECTS OF INJ. CAROVERINE AND GINKGO BILOBA EXTRACT IN COCHLEAR SYNAPTIC TINNITUS"

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BACKGROUND & OBJECTIVES:
Tinnitus, "ringing in the ear", is the most common problem encountered in every day of otolaryngology practices. Considerable variations of Tinnitus prevalence with gender and age. It affects patient's life-style, general health as well as emotional status. The most common variety of Tinnitus, Cochlear Synaptic Tinnitus is diagnosed with the help of various audiological tests. There is no standardised treatment till date yet Tinnitus Retraining Therapy, medical therapy in form of psychotherapy or pharmacological therapy are commonly used one. Ginkgo biloba extract suggest greater and faster relief as compared to placebo. Recently Caroverine, a spasmytic drug, having glialamine antagonist activity is used for Tinnitus treatment. A randomised comparative study was designed to establish effects of Caroverine and Ginkgo biloba extract in treatment of Cochlear Synaptic Tinnitus.

METHOD:
86 diagnosed patients of Cochlear Synaptic Tinnitus were treated with In Caroverine (group 1, n=22) and placebo (group 2, n=21). Ginkgo biloba extract (group 3, n=22) and placebo (group 4, n=21) and followed up at 1 month, 3 months and 6 months and improvements were evaluated in terms of Tinnitus Grading and Tinnitus Matching. Statistical analysis was done using statistical software SPSS. The baseline profile and any improvement after treatment between groups were compared using paired/ANOVA test.

RESULT:
In our study 54.4% (12 out of 22) patients responded immediately after infusion of Caroverine and remained effective at end of 1, 3 and 6 months after drug infusion while 13.6% (3 out of 21) patients responded in placebo group and reverted back to pre treatment level on subsequent follow ups. In Ginkgo biloba group 31.8% (7 out of 22) patients responded at one month followup, while none responded in placebo group. These responders showed further improvement in Tinnitus Matching and Tinnitus Grading at 3 months but a plateau occurred at follow up at 6 month without further improvement. Two patients were cured in group 3 (Ginkgo biloba).

CONCLUSION:
Caroverine immediately improves tinnitus grading and matching and provides immediate relief in reducing the severity of tinnitus. Ginkgo biloba extract takes longer time to improve tinnitus but it provides greater relief on long term follow-up. It is finally suggested that inj. Caroverine should be given in severe cases of tinnitus to reduce its severity immediately and then patient should be put on Ginkgo biloba extract for a period of 3 months to provide sustained and long lasting relief.

KEY WORDS:
Cochlear Synaptic Tinnitus, Tinnitus Matching, Tinnitus Grading, Caroverine, Ginkgo biloba.

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