Research in Otolaryngology 2015, 4(2): 19-23
DOI: 10.5923/j.otolaryn.20150402.01

Management of the Cochlear Synaptic Tinnitus: A Comparative Study between Caroverine and Piracetam

Shruthi Byranahalli Channaraya Gowda, Karthik Shammanna, Hosaagrahara Subbegowda Satish, Borlingegowda Viswanatha*

Otorhinolaryngology department, Bangalore medical college & research Institute Bangalore, India

Abstract Background and Objective: Tinnitus is the subjective perception of sound by an individual, in the absence of external sounds. Tinnitus is not a disease in itself, but a symptom commonly associated with the auditory system. The pathophysiology being varied there is no uniform way of treating tinnitus. Various drugs have been used in its treatment with varying degree of success. This study was conducted to compare the efficiency of the two drugs, namely, Caroverine and Piracetam in the management of tinnitus in a selected group of patients with cochlear synaptic tinnitus. Methods: Patients were randomized into two study groups. The first study group comprised of 30 patients and were administered one dose of 160mg of Caroverine by slow intravenous infusion, followed with 40mg of oral Caroverine bid for 2 months. The second study group comprised of 30 patients and were administered Piracetam 800mg thrice daily for 2 months. All the patients were followed up for 3 months. In this study the THI (Tinnitus Handicap Inventory) scoring, pure tone audiometry, tinnitus frequency and intensity matching were done, pre and post treatment and the results were compared. Results: THI score showed significant improvement between pre and post treatment in the patients treated with Caroverine with p value <0.001 at the end of 2nd month and this improvement remained stable in the next 3 months of follow up. The significant improvement was observed in patients with moderate to severe THI score, no improvement was observed in patients with tinnitus of mild THI score. The patients treated with Piracetam, also showed improvement, but it was not statistically significant (with p value <0.100). Conclusions: By the observations made in this study, we conclude that caroverine is effective in the management of patients with cochlear synaptic tinnitus.

Keywords Tinnitus, Caroverine, Piracetam

1. Introduction

Tinnitus is defined as auditory perception of sound or noise in ear or head in the absence of external stimuli. The term Tinnitus stems from the Latin word 'tinnire', meaning to ring and was introduced by Pliny and Elder [1]. Tinnitus represents one of the most common and distressing otologic problems and it causes various somatic and psychological disorders that interfere with the quality of life [2]. A population based study of hearing loss in adults aged 48 to 92 years found that tinnitus had prevalence of 8.2% at baseline and an incidence of 5.7% during a 5-year follow-up [3].

The management of the tinnitus is a demanding need and it is one of the challenges faced by doctors in their daily practice. The history of attempts to treat and classify tinnitus dates back to ancient Egypt [4]. Diverse aetiology, associated co morbidities and failure of correct diagnosis has posed a challenge in the treatment of patients with tinnitus. Several modalities of treatment have been tried for the treatment of tinnitus, including various medications and surgery but with varying degrees of success [1].

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 like, 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 [5].

PIRACETAM is a cyclic derivative of GABA (Gamma Amino Butyric Acid). Piracetam has been found to be helpful in degenerative conditions affecting the auditory system which may lead to tinnitus, by increasing the blood

* Corresponding author:
drbviswanatha@yahoo.co.in (Borlingegowda Viswanatha)
Published online at http://journal.sapub.org/otolaryn

flow and oxygen consumption to parts of the brain and also to auditory system [6]. It also exerts cerebroprotective action because of its antithrombotic and rheological action.

Professor Klaus Ehrenberger conducted his study by topical administration of 1% caroverine drops into affected ear, in 77 patients with tinnitus. He registered a treatment success rate of 57%, by comparing the severity of tinnitus on scale of 0 to 10 [7].

A placebo controlled blind study was conducted by Denk DM et al., in total 60 patients with inner ear tinnitus of assumed cochlear-synaptic pathophysiology. In the caroverine group, 63.3% responded to therapy immediately after the single intravenous infusion of caroverine [8].

Another study conducted by Choung YH et al, to evaluate the effective use of Caroverine hydrochloride and memantine hydrochloride for tinnitus treatment and to determine their appropriate indication of glutamate antagonist therapy. Subjective tinnitus was improved in 55 (35.9%) of 153 patients who were treated with Caroverine hydrochloride and 11 (55.0%) of 20 patients with memantine hydrochloride [9].

In a prospective randomized clinical study, conducted by Gutmann et al., the therapeutic efficacy of piracetam was compared with that of naftidrofuryl on 39 patients with tinnitus and sudden hearing loss. The improvement in tinnitus amounted 27dB (piracetam) and 19.9 dB (naftidrofuryl). Thus piracetam appeared of particular interest for the treatment of acute tinnitus [10].

A close association between tinnitus and co-morbid psychological disorders has been demonstrated and a high prevalence of anxiety and depression has been reported in tinnitus sufferers [11]. As tinnitus is one of the distressing symptoms having an adverse effect on the psychological behaviour of the patients, there is a need to find an effective modality in the management of tinnitus. Very few studies have been undertaken to evaluate the efficacy of these two pharmacological drugs, caroverine and piracetam, in the management of tinnitus. This study was undertaken to evaluate the efficacy of these two drugs in the management of cochlear synaptic tinnitus and to compare their efficacy, as these two drugs may be helpful to reduce the symptom in patients suffering from tinnitus.

2. Methodology

This study was conducted on the patients of age group between 20 to 60 years and of either sex presenting with tinnitus at Sri Venkateshwara ENT Institute and Bowring and Lady Curzon hospital attached to Bangalore Medical College and Research Institute, during the study period from November 2012 to October 2014.

In this study, 60 patients with cochlear synaptic tinnitus were selected and divided into two groups. One group containing 30 patients with tinnitus were treated with Caroverine and another group of 30 patients with tinnitus were treated with Piracetam.

2.1. Methods of Collection of Data

In this study patients were evaluated with detailed history, clinical examination, THI questionnaire score, pure tone audiometry and tinnitus frequency and intensity matching pre treatment and at 2nd and 5th month post treatment.

THI questionnaire: The Tinnitus Handicap Inventory Questionnaire was developed as a brief, easily administered way to evaluate the disabling consequences of tinnitus (THI; Newman et al., 1996). It has potential for use in an initial evaluation of handicap or later as well as a way to measure treatment outcome. The THI is a 25-item questionnaire with items that are grouped into three subscales: functional, emotional and catastrophic responses. The functional subscale items reflect the effect of tinnitus on mental, social, occupational and physical functioning. The emotional subscale items probe the individual's emotional reactions to the tinnitus and the catastrophic response items address whether tinnitus makes the respondent feel desperate, trapped, hopeless or out of control. Respondents were asked to answer the questions with 'Yes' (4 points), 'sometimes' (2 points) or 'No' (0 points). Tinnitus severity can be categorised based on the total THI score, into 'no handicap' (0–16), 'mild handicap' (18–36), 'moderate handicap' (38–56) and 'severe handicap' (58–100) [12]. Patients were considered as responders to treatment if there was improvement in THI score from severe to moderate, severe to mild scoring and moderate to mild scoring after treatment. Patients in whom there was no improvement in THI scoring post treatment were considered as non responders.

Psychoacoustic Analysis:

In our study, psycho acoustical measurement of tinnitus was included namely tinnitus frequency and intensity matching. It is one of the methods for 'authentication' of the presence of tinnitus [13]. These parameters were used pre treatment for assessing tinnitus and were compared with the post treatment parameter to evaluate the efficacy of the drug.

2.2. Inclusion Criteria

1) Age group –patients between 20 to 60 years.
2) Tinnitus for minimum of 6 weeks.
3) Tinnitus with sensorineural hearing loss and mixed hearing loss.
4) Noise induced hearing loss.
5) Patients willing to give informed consent.

2.3. Exclusion Criteria

1) Patients with pure conductive hearing loss.
2) Pulsatile tinnitus, vestibular schwannoma or cerebellopontine angle tumours.
3) Tinnitus due to systemic vascular or diabetic disease, hypertension and psychiatric disease.
4) Tinnitus occurring as adverse effect of medications.

2.4. Medication and Dosage

For Caroverine study group of patients, 1 dose of injection

of Caroverine was given as slow intravenous infusion followed by oral capsule 40mg bid for 2 months. One ampule containing 160mg of Caroverine was diluted in 100ml of saline and was infused slowly at the rate of 2-3ml/min. The vital parameters of the patients like pulse rate, blood pressure and respiratory rate were measured before starting the infusion. Under close observation the infusion was given slowly. During the infusion subjective assessment was done using the grading scale from 0 to 10. Improvement in the tinnitus severity on scale by 2 grades was considered significant.

Second study group of 30 patients were treated with 800mg of Piracetam, orally thrice daily for 2 months.

Statistical analysis was done using student paired and unpaired test, Chi square test and Mc Nemar test.

3. Observations and Results

In our study, following results were observed. In Caroverine group, 18(60%) were female and 12(40%) were male. In Piracetam 15(50%) were female and 15(5%) were male [Table 1 & 2].

In our study, mean duration of tinnitus in study group of patients was between 7 and 12 months.

Table 1. Age and sex distribution in both the study groups

Age In Years	Caroverine		Piracetam	
	Female	Male	Female	Male
20-30	4	2	5	3
31-40	2	0	2	2
41-50	3	4	4	3
51-60	9	6	4	7
Total	18 (60%)	12 (40%)	15 (50%)	15 (50%)

Table 2. Distribution of various parameters of tinnitus in both the study group

Parameters Of Tinnitus	Caroverine	Piracetam
Onset	Insidious	Insidious
Laterality		
Bilateral	27(86.7%)	25(83.3%)
Right	1(10%)	2(10%)
Left	3(33.3%)	3(66.7%)
Hearing Level (Pure Tone Audiometry)		
Normal	13(43.3%)	17(56.7%)
Sensorineural	17(56.7%)	13(43.3%)
Conductive	0	0

3.1. Distribution of Tinnitus Intensity in both the Study Groups

In this study, 70% of the patients had tinnitus intensity matched between 51and 60 dB. In Caroverine group 11(36.7%) patients and in Piracetam group 10(33.3%) patients had tinnitus intensity between 51 to 60 dB [Figure 1].

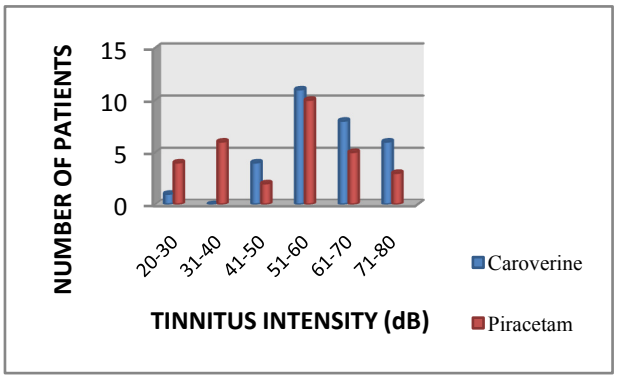

Figure 1. Showing the tinnitus intensity distribution in both the study group

3.2. Distribution of Tinnitus Frequency in both the Groups

In this study, 77% of the patients had the tinnitus with frequency matched between 6 to 8 kHz. In Caroverine group 22(73.3%) patients and in Piracetam group 11(46.7%) patients had tinnitus with frequency between 6-8 kHz [Figure 2].

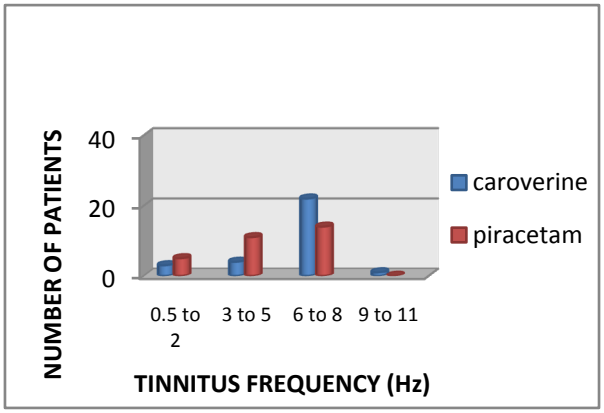

Figure 2. Distribution of tinnitus frequency in both the study groups

3.3. THI Questionnaire Score

In our study, patients were considered as responders when there was improvement in severity of tinnitus as assessed by THI score when compared with pre and post treatment scores and those patients who did not showed any improvement were considered as non responders.

In caroverine group, 28 patients responded to therapy, in piracetam group only 4 patients responded to therapy [Table 3, Figure 3].

Caroverine (FIGURE 3): Out of 30 patients, 28 patients with moderate and severe THI score responded to Caroverine treatment but patients with mild THI score did not show much improvement. However, none of the patients in our study group, showed complete abolition of tinnitus. THI score post treatment with Caroverine showed statistically significant reduction with p value <0.001

according to the Mc Nemar test [Figure 4].

Table 3. Table showing responders and non responders in both the study groups

	Caroverine (%)	Piracetam (%)
Responders	28(93.3%)	4(13.3%)
Non Responders	2(6.7%)	26(86.7%)
Total	30	30

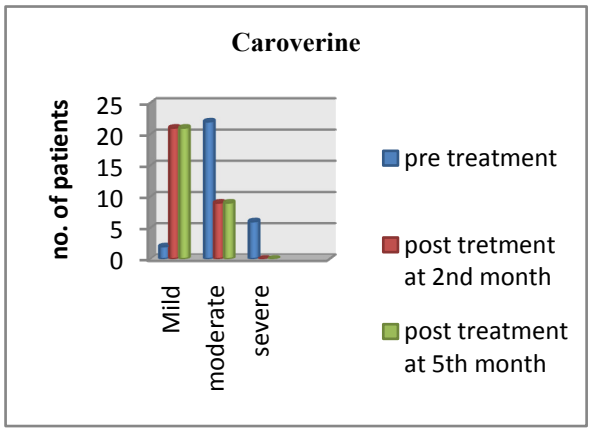

Figure 3. Comparison of THI score pre and post treatment in Caroverine group

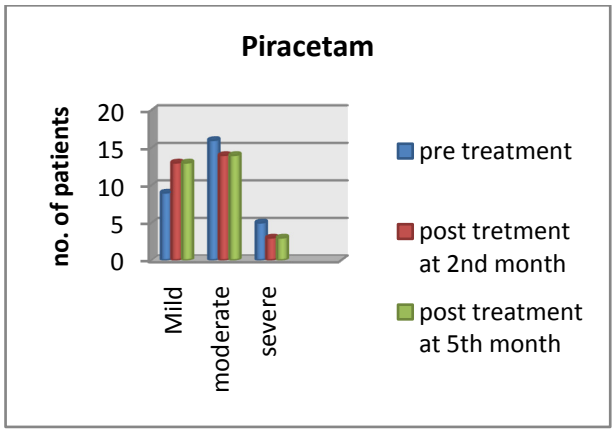

Figure 4. Comparison of THI score pre and post treatment in piracetam group

Piracetam (FIGURE 4): Out of 30 patients only 4(13.3%) patients had improvement in their THI score, post treatment. THI score post treatment with Piracetam, showed improvement but not statistically significant (with p value 0.100) according to the Mc Nemar test.

However, there was no change in THI score in both the study groups, in the subsequent three months of follow up period. There was no worsening of the tinnitus in both the groups during the study period.

In both, Caroverine and Piracetam group, tinnitus frequency and intensity matching showed significant improvement after treatment at the end of 2nd month and also at the end of 5th month with p value < 0.001.

3.4. Dosage

In our study, patients in Caroverine study group, were given one injection of Caroverine by slow infusion over one hour, under observation. In the 30 patients, intensity of tinnitus reduced with the infusion of 100mg of Caroverine in 10 i.e., 33.3% of the patients. Out of the 30 patients, only 4(13.3%) patients with severe tinnitus required 140mg of Caroverine.

Table 4. Dosage of the caroverine for reduction of the tinnitus intensity during caroverine infusion

Dosage of caroverine infusion(mg)	NO. of patients (%)
50	7(23.3%)
80	6(20.0%)
100	10(33.3%)
120	3(10.0%)
140	4(13.3%)

3.5. Side Effects

In our study, out of the 30 patients, Caroverine infusion had to be stopped in 4(13.3%) patients. Three of the four patients had giddiness and hypertension after starting the infusion, but the symptom subsided in the same day. Other patient had subjective feeling of increase in intensity of tinnitus, but after one day the intensity had reduced. In all these four patients it was observed that, these adverse effects occurred due to the fast infusion of the injection. In all other patients, infusion was given under observation and slowly at controlled rate of 2-3 ml/hr and no adverse effects were observed [Table 4].

In our study, in Piracetam group, no adverse effects occurred during the treatment and even during the follow up period of three months.

4. Discussion

Tinnitus is the symptom which may be subjective, heard only by the patient or objective, heard by both patient and the examiner. The tinnitus is one of the distressing symptoms which may adversely affect the psychological and social life of the suffering patient. The efficacy of Caroverine in the management of tinnitus was observed in studies conducted by Professor Klaus Ehrenberger (2005) [6] and Denk et al (1997) [7] upto 57% and 63.3% respectively. A study conducted by Gutmann (1995) [9], showed piracetam as effective in the management of patient and was well tolerated by all patients. In these studies, no significant adverse effects were observed after treatment. This made us to undertake the study of evaluating the efficacy of the Caroverine and Piracetam in the management of cochlear synaptic tinnitus and to compare their efficacy.

In our study, evaluation of the patients were done both by subjective, THI questionnaire scoring and objective assessment using tinnitus frequency and intensity matching pre and post treatment at 2nd and 5th month.

In our study, it was observed that, in Caroverine group, out of 30 patients, 28(93.3%) patients responded to Caroverine treatment. The THI score showed significant reduction

between pre and post treatment in Caroverine study group (with p value < 0.001). After treatment with Caroverine, significant improvement was observed in patients with moderate and severe THI score, no improvement was observed in patients with mild THI score. However, there was no complete abolition of tinnitus. In Piracetam group, out of 30 patients, only 4 (13.3%) patients responded to the treatment. The improvement in THI score post treatment with Piracetam was not significant.

In both, Caroverine and Piracetam group, tinnitus frequency and intensity matching showed significant improvement after treatment at the end of 2nd month and also at the end of 5th month with p value < 0.001.

In both the study groups, no crucial side effects was observed during or after treatment and improvement in tinnitus was stable in next 3 months of follow up period.

5. Conclusions

From our study, it was observed that, Caroverine given as a controlled infusion under direct observation is one of the effective modality in the management of tinnitus. Piracetam also showed improvement in tinnitus frequency and intensity matching after treatment but there was discrepancy as the patients did not show improvement in subjective assessment done by THI questionnaire. Thus, study has to be done on large population and comparison of the other pharmacological agent efficacy, in suppressing tinnitus with Caroverine and Piracetam has to done, as these pharmacological agents can be an effective modality in suppressing tinnitus. By the observations made in this study, we conclude that Caroverine is effective in the management of patients with cochlear synaptic tinnitus.

REFERENCES

[1] Borka Ceranic and Linda M Luxon: Tinnitus and other dysacusis: Scott Brown's Otorhinolaryngology and Head and Neck surgery. 7thEd. Great Britain: Hodder Arnold Ltd; 2008 vol 3.p.3594-3619.

[2] Yetiser S, Tosun F, Satar B, Arslanhan M, Akcam T, Ozkaptan Y. The role of zinc in management of tinnitus. Auris Nasus Larynx. 2002;29:329–333.

[3] Nondahl DM, Cruickshanks KJ, Wiley TL, Klein R, Klein BE, Tweed TS. Prevalence and 5 Year incidence of tinnitus among older adults: the epidemiology of hearing loss study. J Am Acad Audiol.2002; 13:323–331.

[4] Stephens SDG. Historical aspects of tinnitus. In: Hazell JWP, editor. Tinnitus. New York: Churchill Livingstone; 1987. p. 1–19.

[5] Brix R, Denk DM, Ehrenberger K. Neurophysiological control in therapy of tinnitus with cochlear disorders. In: Reich GE, Vernon JA (Eds). Proceedings of the V International Tinnitus Seminar 1995. Portland, OR: Scandinavian American Tinnitus Association, 1995: 101-105.

[6] Jordaan, B; Oliver, DW; Dormehl, IC; Hugo. Cerebral blood flow effects of Piracetam, pentifylline, and nicotinic acid in the baboon model compared with the known effect of acetazolamide. 1996, Arzneimittel-Forschung 46(9): 844–847.

[7] Ehrenberger K, Topical administration of Caroverine in somatic tinnitus treatment: proof of Concept studying tinnitus J.2005; 11:34-37.

[8] Denk DM, Heinzl H, Franz P, Ehrenberger K. Caroverine in tinnitus treatment. A placebo-controlled blind study. Acta Otolaryngologica. 1997; 117: 825-830.

[9] Choung YH, Park HJ, Song JW, Ryu SJ, Moon SK, Park K. Treatment Effects of Glutamate Antagonist for Tinnitus. Department of Otolaryngology, Ajou University School of Medicine, Suwon, Korea. Korean J Otolaryngol-Head Neck Surg. 2003 Nov; 46(11):935-939

[10] Guttmann R, Mees K. Klinik und Poliklinik fur Hals, Nasen und Ohrenkranke, Ludwig. Piracetam infusions in acute tinnitus and sudden deafness. Fortschr Med 1995 Jun 30; 113(18):288-290.s

[11] Eva-Signe Falkenberg and Ona Bø Wie. Anxiety and Depression in Tinnitus Patients: 5-Year Follow-Up Assessment after Completion of Habituation Therapy International Journal of Otolaryngology, Volume 2012 (2012).

[12] Newman, C.W et al: The Tinnitus Handicap Inventory (THI): A quick and reliable method for measuring tinnitus outcomes. Journal of the American Academy of Audiology 9, 2012, 153-160.

[13] Tyler RS. The Psychoacoustical measurement of tinnitus. In: Tyler R (ed.). Tinnitus handbook. San Diego: Singular, 2000: 149-179.