Original Article

Effect of oral caroverine in the treatment of tinnitus: A quasi-experimental study

Anil K. Dash[1], Abinash Panda[2], Nilamadhaba Prusty[1], Manas R. Satpathy[1], Sasmita K. Bisoyi[3], Prasanjit A. Barik[1]

[1]Department of ENT, FMMCH, Balasore, Odisha, India, [2]Department of Pharmacology, JKMCH, Jajpur, Odisha, India, [3]Department of Community Medicine, MKCG Medical College, Berhampur, Odisha, India

Abstract

Objective: Caroverine is an antagonist of non-NMDA and NMDA glutamate receptors. Cochlear synaptic tinnitus arises from a synaptic disturbance of NMDA or non-NMDA receptors on the afferent dendrites of spiral ganglion neurons. This forms a basis for the use of caroverine in the treatment of tinnitus. Hence, the present study was carried out to find the effect of oral caroverine in the treatment of tinnitus. **Methodology:** This quasi-experimental study was carried out on sixty consecutive patients of tinnitus. Thirty patients were given the usual standard of care consisting of Tab. Cinnarizine 25mg twice daily along with fixed dose combination Cap. B-complex and Ginkgo biloba once daily for ninety days and thirty patients were given Cap. Caroverine 40mg, twice daily for ninety days. Outcome assessment was done using the tinnitus case history questionnaire, tinnitus handicap inventory score, and VAS. The data were analyzed using GraphPad Prism Trial Version. A P value ≤ 0.05 was taken as statistically significant. **Results:** There was a significant improvement in the tinnitus case history questionnaire score at 90 days in patients suffering from mild tinnitus when treated with caroverine. There was a larger decrease in the tinnitus handicap inventory score at 90 days of treatment in the caroverine-treated patients. The median VAS showed an improvement in the caroverine-treated group. The overall reduction in tinnitus in the caroverine-treated group was 53.3% with an odds ratio, 95% CI of 0.375 (0.12-1.08). **Conclusion:** Oral caroverine was found to be better than the usual standard of care in reducing mild cochlear synaptic tinnitus. It also improved sensory–neural hearing loss during the treatment period.

Keywords: Caroverine, tinnitus case history questionnaire, tinnitus handicap inventory score, tinnitus

Introduction

Tinnitus is the sensation of hearing a sound in the absence of an internal or external source and is a common problem encountered in primary care.[1] Subjective tinnitus is a common symptom with potentially negative impact on the quality of life.[2] It is also defined as a sound perceived for more than five minutes at a time in the absence of any external acoustical or electrical stimulation of the ear and not occurring immediately after exposure to loud noise, phantom auditory perception, or head noise.[3,4] The pooled prevalence of any tinnitus among adults is 14.4% (95% CI, 12.6%–16.5%) and ranged from 4.1% (95% CI, 3.7%–4.4%) to 37.2% (95% CI, 34.6%–39.9%).[5] Another study has reported the prevalence of tinnitus to be as high as 32% in the adult population, with approximately 13–17% of population reporting bothersome tinnitus.[6] The severity of tinnitus can range from trivial to completely disabling.[7] However, there is a lack of near perfect drug therapy for tinnitus. This may be due to limited understanding of the biological basis of tinnitus, the lack of an accepted tinnitus nosology, the heterogeneity of the tinnitus population, the wide range of medical conditions

Address for correspondence: Dr. Abinash Panda, Department of Pharmacology, Jajati Keshari Medical College and Hospital, Jajpur - 755 001, Odisha, India.
E-mail: abinashpanda3434@gmail.com

Received: 14-04-2024 **Revised:** 01-06-2024
Accepted: 03-06-2024 **Published:** 18-10-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_617_24

How to cite this article: Dash AK, Panda A, Prusty N, Satpathy MR, Bisoyi SK, Barik PA. Effect of oral caroverine in the treatment of tinnitus: A quasi-experimental study. J Family Med Prim Care 2024;13:4648-51.

that appear to cause tinnitus, and the huge cost associated with developing drugs to specifically treat tinnitus. Consequently, drugs developed for other medical conditions have generally been evaluated to determine whether they can relieve tinnitus and many such are used off-label in clinical practice to treat tinnitus.

Caroverine is used as a spasmolytic and acts as an antagonist of calcium, non-NMDA, and NMDA glutamate receptors.[8-13] It has been proposed that cochlear synaptic tinnitus arises from a synaptic disturbance of NMDA or non-NMDA receptors on the afferent dendrites of the spiral ganglion neurons. This forms a basis for the use of caroverine in the treatment of tinnitus. Caroverine has been used orally or intravenously or locally. Clinical trials have reported it to be safe, with no or mild adverse drug reactions and effective.[13] With this background, the present study was carried out to study the effect of oral caroverine in tinnitus as compared to the usual standard of care in the treatment of tinnitus.

Methodology

This quasi-experimental study was carried out in the Department of ENT, FMMCH, Balasore, during July 2020 to July 2023 on sixty consecutive patients with a confirmed diagnosis of tinnitus. Thirty patients were given the usual standard of care consisting of Tab. Cinnarizine 25mg twice daily along with fixed dose combination Cap. B-complex and Ginkgo biloba once daily for ninety days and thirty patients were given Cap. Caroverine 40mg, twice daily for ninety days. The drugs were provided to the patients during follow-up done every 7th day. To ensure adherence, the participants were instructed to send WhatsApp massage or give a missed call to the investigator after taking their daily medication. Outcome assessment was done by the investigators using the tinnitus case history questionnaire, tinnitus handicap inventory score, and visual analog score at onset (baseline) and on the 90th day. Adverse drug reactions were monitored during the study. All the demographic and clinical data of the study participants were recorded in a predesigned case record form. All consecutive and consenting patients with a confirmed diagnosis of tinnitus were included in the study as per the inclusion and exclusion criteria. Patients of tinnitus with conductive hearing loss in audiometry, perforated tympanus, tinnitus due to vascular causes, critically ill, and not giving consent were excluded. A P value ≤ 0.05 was taken as statistically significant. The data were analyzed using GraphPad Prism Trial Version. Ethical clearance was obtained from the Institutional Ethics Committee of FMMCH, Balasore (Approval No. 59/IEC/26-05-2022). Written informed consent was obtained from the participants before including them in the study.

Results

For the study, 128 patients with a diagnosis of tinnitus were screened. Based on the inclusion and exclusion criteria, 60 participants were finally included and received either the usual standard-of-care treatment as study arm A (n = 30) or caroverine as study arm B (n = 30) for the treatment of tinnitus. There was no drop-out and loss to follow-up during the study. The assessment of compliance was based on the difference between the numbers of tablets dispensed and returned, expressed as percentage of tablets due to be taken from the day of first to the day of last intake (90th day). The median compliance was 99.4% for the total treatment period in the study arm A and 98.8% in the study arm B.

In the present study, it was observed that most of the patients suffering from cochlear synaptic tinnitus were in fifth decade followed by fourth decade. There was a male predisposition. Left ear tinnitus was most common. The mean duration of tinnitus was comparable (10.46 ± 4.08 *vs* 10.67 ± 5.28 years) in both the study arms. In either arm, whistle type of tinnitus was most prevalent. The baseline characteristics of the subjects in the study arms are presented in Table 1. The tinnitus case history questionnaire score was assessed at the onset of treatment and at 90 days of treatment. In study arm A (usual standard of care), there was a no improvement in the score in mild, moderate, and severe cases of tinnitus during posttreatment assessment at 90 days of treatment, whereas in study arm B (caroverine treated), there was a significant improvement in the score of patients suffering from mild tinnitus. In this group, there was no improvement in patients suffering from moderate to severe tinnitus [Table 2]. The tinnitus-related discomfort was measured by the tinnitus handicap inventory score. There was a larger decrease (lower value) in the tinnitus handicap inventory score at 90 days of treatment in the caroverine-treated group [Table 3]. The median visual analogue scale score was same pretreatment and posttreatment in the study arm A, whereas there was an improvement in study arm B [Table 4]. The overall reduction in tinnitus in the caroverine-treated group was 53.3% with an odds ratio, 95% CI of 0.375 (0.12-1.08) [Table 5].

Discussion

Tinnitus is now a global burden. Increasing age, sensory–neural hearing loss, and male gender have been seen as the most relevant risk factors for the origin of tinnitus.[14] This corroborates the findings of the present study where it was observed that most of the patients suffering from cochlear synaptic tinnitus were in fifth decade and there was a male predisposition. The study observed that left ear tinnitus was most common; however, there was no similar published literature that indicated a predisposition of a particular ear for the occurrence of tinnitus. With an increase in professional and leisure noise along with demographic development, the prevalence of tinnitus is expected to rise.[14] In a study by Ledesma *et al.*,[15] they have reported the average age of patients with a diagnosis of tinnitus to be approximately 50 years. In addition, in contrast to the present study, other studies have found tinnitus to be more prevalent bilaterally.[16] This study observed that hearing loss was prevalent in about half of the patients in either group. Published literature has mentioned that the most widely reported risk factor for tinnitus is hearing

Table 1: Baseline characteristics of study participants

Baseline characteristic	Study arm A-usual standard of care (*n*=30)	Study arm B-caroverine 40 mg twice daily treated (*n*=30)	*P*
Age (in yrs)	62.03±8.96	56.83±13.37	0.642
Gender			
Male	14 (46.7%)	16 (53.3%)	0.654
Female	16 (53.3%)	14 (46.7%)	
Duration of tinnitus (in months)	10.46±4.08	10.67±5.28	
Site of tinnitus			
Left ear	7 (23.1%)	8 (26.4%)	0.053
Right ear	6 (19.8%)	6 (19.8%)	
Bilateral	0	0	
Mode of onset			
Sudden	0	0	0.047
Insidious	19 (60%)	14	
Progressive	0	0	
Continuous	19 (60%)	14	
Intermittent	0	0	
TIH Classification			
No handicap	8 (26.6%)	7 (23.3%)	0.012
Mild handicap	7 (23.3%)	11 (36.6%)	
Moderate handicap	10 (33.3%)	7 (23.3%)	
Severe handicap	5 (16.6%)	3 (10%)	
Catastrophic handicap	0%	2 (6.7%)	
Hearing loss			
Present	15 (50%)	14 (47.5%)	0.18
Absent	15 (50%)	16 (52.5%)	
Tinnitus type			
Whistle	25 (83.3%)	23 (76.6%)	0.027
Wheeze	5 (16.6%)	7 (23.3%)	

Table 2: Comparison of tinnitus severity using tinnitus case history questionnaire score pre and posttreatment (at 90 days)

Tinnitus case history questionnaire score	Pretest *n* (%)	Posttest *n* (%)	% change	*P*
Study Arm A (Usual standard of care)				
Mild	2 (6.7)	21 (70)	-63.3	<0.001
Moderate	22 (53.3)	9 (30)	-43.3	
Severe	6 (20)	0 (0)	-20	
Study Arm B (Caroverine 40 mg twice daily)				
Mild	9 (30)	13 (43.3)	+13.3	0.001
Moderate	16 (53.3)	14 (46.7)	-6.7	
Severe	5 (16.7)	3 (10)	-6.7	

Table 3: Comparison of tinnitus handicap inventory score pre and posttreatment (at 90 days)

Tinnitus handicap inventory score	Pretest Mean±SD	Posttest Mean±SD	*P*
Study Arm A (Usual standard of care)	35±18	31±17	0.051
Study Arm B (Caroverine 40 mg twice daily)	32±14	25±10	0.042

loss. Environmental influences that damage the auditory system and lead to hearing loss, such as the exposure to loud noise and ototoxic medications, can also trigger tinnitus.[17] When comparing the results of pre and posttreatment, there was a significant improvement in the tinnitus handicap inventory score in the caroverine-treated group. A study was performed by Smith *et al.*[18] to examine whether a single infusion of caroverine, a quinoxaline derivative, can be used successfully in the treatment of inner ear tinnitus. Microionophoretical experiments in Guinea pigs by different researchers 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 noncompetitive n-Methyl-d-Aspartame (NMDA) antagonist.[19-21] According to the working hypothesis on the pathophysiology of inner ear tinnitus (Cochlear-Synaptic) proposed by Atik *et al.*,[22] these forms of tinnitus occur when the physiological activity of the NMDA and AMPA receptors at the subsynaptic membranes of inner hair cells afferent is disturbed. However, the present study observed an overall better improvement of tinnitus with the use of caroverine in the oral route as compared to the usual standard of care.

Conclusion

The treatment with caroverine reduced the mild cochlear synaptic tinnitus better than the usual standard of care treatment. It also improved sensory-neural hearing loss during the treatment. However, further studies are essential to find out the efficacy of caroverine in long-term use, i.e. when it is continued for as long as tinnitus persists.

Table 4: Comparison of visual analog score pre and posttreatment (at 90 days)

Visual Analogue Scale score	Pretest Median (IQR)	Posttest Median (IQR)	*P*
Study Arm A (Usual standard of care)	6 (3)	6 (5)	0.685
Study Arm B (Caroverine 40 mg twice daily)	3 (1)	5 (4)	0.854

Table 5: Tinnitus improvement (overall reduction) at 90 days of treatment

Treatment group	Tinnitus reduction *n* (%)	OR, 95% CI	*P*
Study Arm A (Usual standard of care, *n*=30)	9 (30)	0.375 (0.12-1.08)	0.0698
Study Arm B (Caroverine 40 mg twice daily, *n*=30)	16 (53.3)		

Acknowledgements

The authors acknowledge the support by Entod Pharmaceuticals Ltd. (India) for providing Cap. Caroverine 20 mg for use in this study.

Financial support and sponsorship

Entod Pharmaceuticals Ltd. (India) supported this study by providing Cap. Caroverine 20 mg for use in this study. Other drugs were provided as free supply in the hospital under the Niramaya Scheme of Government of Odisha.

Conflicts of interest

There are no conflicts of interest.

References

1. Dalrymple SN, Lewis SH, Philman S. Tinnitus: Diagnosis and management. Am Fam Physician 2021;103:663-71.
2. Stohler NA, Reinau D, Jick SS, Bodmer D, Meier CR. A study on the epidemiology of tinnitus in the United Kingdom. Clin Epidemiol 2019;11:855-71.
3. Jastreboff PJ. Phantom auditory perception (tinnitus): Mechanisms of generation and perception. Neurosci Res 1990;8:221-54.
4. Fowler EP. Subjective head noises. (Tinnitus aurium.). Genesis and differential diagnostic significance. A few facts and several speculations. Laryngoscope 1965;75:1610-8.
5. Jarach CM, Lugo A, Scala M, van den Brandt PA, Cederroth CR, Odone A, *et al.* Global prevalence and incidence of tinnitus: A systematic review and meta-analysis. JAMA Neurol 2022;79:888-900.
6. Cooper JC Jr. Health and nutrition examination survey of 1971-75: Part II. Tinnitus, subjective hearing loss, and well-being. J Am Acad Audiol 1994;5:37-43.
7. Coles RR. Epidemiology of tinnitus: (1) prevalence. J Laryngol Otol Suppl 1984;9:7-15.
8. Kudo Y, Shibata S. Effects of caroverine and diltiazem on synaptic responses, L-glutamate-induced depolarization and potassium efflux in the frog spinal cord. Br J Pharmacol 1984;83:813-20.
9. Koppi S, Eberhardt G, Haller R, König P. Calcium-channel-blocking agent in the treatment of acute alcohol withdrawal--caroverine versus meprobamate in a randomized double-blind study. Neuropsychobiology 1987;17:49-52.
10. Saletu B, Grünberger J, Anderer P, Linzmayer L, König P. Acute central effects of the calcium channel blocker and antiglutamatergic drug caroverine. Double-blind, placebo-controlled, EEG mapping and psychometric studies after intravenous and oral administration. Arzneimittelforschung 1995;45:217-29.
11. Ehrenberger K, Felix D. Receptor pharmacological models for inner ear therapies with emphasis on glutamate receptors: A survey. Acta Otolaryngol 1995;115:236-40.
12. Ehrenberger K, Felix D. Caroverine depresses the activity of cochlear glutamate receptors in guinea pigs: *In vivo* model for drug-induced neuroprotection? Neuropharmacology 1992;31:1259-63.
13. Chen Z, Duan M, Lee H, Ruan R, Ulfendahl M. Pharmacokinetics of caroverine in the inner ear and its effects on cochlear function after systemic and local administrations in Guinea pigs. Audiol Neurootol 2003;8:49-56.
14. Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA. Ringing ears: The neuroscience of tinnitus. J Neurosci 2010;30:14972-9.
15. Ledesma ALL, Leite Rodrigues D, Monteiro de Castro Silva I, Oliveira CA, Bahmad F Jr. The effect of caffeine on tinnitus: Randomized triple-blind placebo-controlled clinical trial. PLoS One 2021;16:e0256275. doi: 10.1371/journal.pone.0256275.
16. Wu V, Cooke B, Eitutis S, Simpson MTW, Beyea JA. Approach to tinnitus management. Can Fam Physician 2018;64:491-5.
17. Biswas R, Genitsaridi E, Trpchevska N, Lugo A, Schlee W, Cederroth CR, *et al.* Low evidence for tinnitus risk factors: A systematic review and meta-analysis. J Assoc Res Otolaryngol 2023;24:81-94.
18. Smith PF, Zheng Y, Darlington CL. Ginkgo biloba extracts for tinnitus: More hype than hope? J Ethnopharmacol 2005;100:95-9.
19. Morgenstern C, Biermann E. The efficacy of Ginkgo special extract EGb 761 in patients with tinnitus. Int J Clin Pharmacol Ther 2002;40:188-97.
20. Meyer B. Etude multicentrique randomisée à double insu face au placebo du traitement des acouphénes par l'extrait de Ginkgo biloba [Multicenter randomized double-blind drug vs. placebo study of the treatment of tinnitus with Ginkgo biloba extract]. Presse Med 1986;15:1562-4.
21. Eggermont JJ, Roberts LE. The neuroscience of tinnitus. Trends Neurosci 2004;27:676-82.
22. Atik A. Pathophysiology and treatment of tinnitus: An elusive disease. Indian J Otolaryngol Head Neck Surg 2014;66(Suppl 1):1-5. doi: 10.1007/s12070-011-0374-8.