e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(1); 1118-1125

Original Research Article

Efficacy and Safety of Acamprosate as Add on to Tinnitus Retraining Therapy in Patients of Subjective Tinnitus

Sharmendra Singh[1], Jasleen Kaur[2], Dinesh K. Badyal[3], Ashish Varghese[4]

[1]Associate Professor, Department of Pharmacology, Government Institute of Medical Sciences, Greater Noida, U.P, India.

[2]Professor and Head, Pharmacology department, SKSS Dental College Sarabha Ludhiana, Punjab, India

[3]Professor, Department of Pharmacology, Christian Medical College Ludhiana, Punjab, India

[4]Professor & Head, Department of ENT, Christian Medical College Ludhiana, Punjab, India.

Received: 30-11-2022 / Revised: 30-12-2022 / Accepted: 20-01-2023

Corresponding author: Dr Sharmendra Singh

Conflict of interest: Nil

Abstract

Background and Aim: Tinnitus retraining therapy (TRT) is main treatment strategy in subjective tinnitus. Certain pharmacological agents also have role in treatment of tinnitus. This study designed to evaluate efficacy and safety of acamprosate as add on to TRT in subjective tinnitus of sensorineural origin.

Material and Methods: Study conducted in 60 patients visiting department of otolaryngology of CMC Ludhiana. Patients were divided in two groups (30 in each group). Group A(Control) patients received TRT treatment. Group B (Study) patients received TRT and tab acamprosate 333 mg TDS orally for 6 weeks. Patients assessed at baseline, 2, 4 and 6 weeks for tinnitus severity on VAS and THI scale. ADRs monitored at follow up visits. Results analyzed statistically by student t and ANOVA test.

Results: Baseline VAS score for Group A was 51.70±1.36 and Group B was 55.00±1.57(p=0.115). After 6-week treatment the VAS score were 32.00±1.48 and 16.67±1.10 respectively (p<0.001) for the two groups which were statistically significant. Baseline THI score for Group A was 23.93±2.31 and Group B was 24.40±2.83 (p=0.899). After 6 weeks treatment THI score were 14.40±1.86 and 7.27±1.05 respectively (p=0.002) for the two groups which were statistically significant. In group B 10% patients reported mild diarrhea, 6.70% nausea, 6.70% mild abdominal pain and 3.30% reported mild pruritus.

Conclusion: Acamprosate as add-on to TRT is more efficacious as compared to TRT alone in subjective tinnitus of sensorineural origin and has reported fewer adverse drug reactions for treatment of subjective tinnitus.

Keywords: Subjective Tinnitus, Tinnitus Retraining Therapy, Acamprosate.

Introduction

Tinnitus (which means to ring or to tinkle) refers to the sensation of any sound perceived in the head or in the ears without any evident external stimulus. [1] Tinnitus is not a single, well defined disease, but a symptom of many pathologies. Sometimes in one patient several pathological mechanisms may coexist. It varies in pitch and loudness.[2] There are two main types of tinnitus: a) subjective tinnitus, which is the perception of meaningless sounds without any physical sound being present and b) objective tinnitus, which is caused by sounds generated somewhere in the body.[3] Objective tinnitus accounts for 1% of all tinnitus patients. Subjective tinnitus is more common than objective tinnitus.

Otological disorders are the most common cause of subjective tinnitus.[4] Subjective tinnitus is subclassified into conductive, sensorineural and central.[5] Subjective tinnitus results from conductive and sensorineural deficits, which cause hearing loss.[6] The Tinnitus handicap inventory scale (THI) is a self-administered questionnaire to evaluate the impact of tinnitus on the quality of life.[7] Review of the literature for the treatment of tinnitus suggests that no treatment can be considered effective and no specific therapy is found to be satisfactory in patients. In patients with more persistent, troublesome tinnitus, the application of sound generators, formal psychotherapy and tinnitus retraining therapy (TRT) can be given.

The TRT implements a habituation based protocol, which includes sound therapy and cognitive behavioural techniques (CBT). Cognitive counselling is aimed at identifying and dispelling patient's false beliefs, attitudes or fears related to tinnitus. TRT has become one of the main tinnitus treatment strategies in a number of audiology departments. Pharmacological treatment has a limited contribution to the treatment of patients with tinnitus. Therapy for tinnitus is focused on drugs that act directly on central nervous system (CNS) neurotransmitters, like glutamate, GABA, serotonin, acetylcholine and dopamine. Tricyclic antidepressants, GABA-ergic drugs like clonazepam and sulpiride, a dopamine (D2) antagonist have shown to decrease tinnitus complaints. [8-10].

Acamprosate, a drug used for treating alcohol dependence, was first reported as a potential treatment for tinnitus in 2005.[11] The drug acts by a dual mechanism of action, acting both as a glutamate antagonist and as a GABA agonist.[12] It blocks glutamate binding sites and prevents/attenuates the influx of calcium. A double-blind study reported relief of tinnitus in patients treated with acamprosate.

Moreover, acamprosate was found to be safe in this study. A clinical trial of acamprosate conducted on tinnitus patients showed 87% had some degree of relief and nearly 48% had a reduction of more than 50%.[11] Another study of acamprosate in sensorineural tinnitus patients have shown that acamprosate is an effective drug in treatment of sensorineural tinnitus. The results of this study have shown that there is a significant improvement in reducing the tinnitus score in 92.5% of the patients.[13] Few studies have been done comparing the efficacy of TRT and acamprosate in Indian patient population. So this study was designed to evaluate the efficacy and safety of acamprosate as add on therapy to TRT in patients who have subjective tinnitus.

Materials and Methods

Study design, Inclusion and exclusion criteria

The study was conducted in patients visiting the Out Patient Department of otorhinolaryngology, Christian Medical College and Hospital, Ludhiana. This was a

prospective, randomized, controlled study. The work was started after getting approval from the Institutional Ethics Committee of CMC and hospital Ludhiana Punjab. The study was conducted between January 2013 to January 2015. The inclusion criteria was that patients having Complaints of chronic tinnitus >3 months, unilateral or bilateral tinnitus and Age> 18 years of either sex. A total of 64 patients were taken. Two patients left in between, withdrawn their consent after day one without assigning any reason and two patient lost in follow up and could not complete even the first follow up. Hence we have taken only 60 patients for analysis. Exclusion criteria included epilepsy, pulsatile tinnitus, somatic tinnitus, pregnant and lactating women, middle ear pathology, hypersensitivity to the drug and patients with severe renal impairment.

Methodology

All patients first underwent a thorough clinical work up including a detailed history, general physical and systemic examination. Patients fulfilling the inclusion criteria were enrolled into the study after obtaining a written informed consent. In this study we have enrolled all the cases of subjective tinnitus of sensorineural origin. Sensorineural tinnitus is a subtype of subjective tinnitus. Patient's particular sheet was filled up. All the patient underwent a thorough clinical examination (Physical and otological examination) including history, vital signs and systemic examination. Detailed history of patient's presenting symptoms were taken including the duration, location, type, tone, severity, aggravating factors, noise exposure and any previous treatment taken for tinnitus. All patients enrolled were divided into two groups using computer generated random numbers. Relevant investigations were done in clinically suspicious patients in order to rule out other causes of tinnitus. All patients evaluated by pure tone audiometry for to diagnose sensorineural type hearing loss. Renal status of patients were evaluated by serum creatinine level for to rule out severe renal impairment patients. In physical examination, a comprehensive otological examination was done. The external auditory canal and tympanic membrane were inspected to see signs of cerumen impaction, perforation and infection. Auscultation over the neck, orbits, periauricular area and mastoid were performed. The preliminary assessment of the type and amount of hearing loss was done by tuning fork tests (TFT). The TFT include Rinne, Weber and Absolute Bone Conduction test. TFT were done by using a 512-Hz or 1024-Hz tuning fork. All patients in group A and B (n=30 in each) received treatment with TRT for 6 weeks. Group B patients, in addition received tab acamprosate 333 mg thrice a day, orally for 6 weeks.

All the patients were follow up at 2, 4 and 6 weeks of the study. Assessment of the severity of tinnitus was done by VAS and THI scale at baseline and on each follow up visit. Patient were explained and trained to mark the these two scales a)Visual Analogue Scale (VAS) before starting the therapy. Patients marked the scale at the onset of study and at each follow up according to the severity of tinnitus. b) Tinnitus Handicap Inventory Scale (THI) is a measuring scale for the severity of tinnitus.

It is a questionnaire which consist of 25 questions. For every question the answers are 'yes' or 'sometimes' or 'no'. For scoring of THI scale, 4 marks is given for 'yes ', 2 for 'sometimes' and 0 for 'no'. In THI scale the minimum score is 0 and maximum score is 100. The total obtained score were calculated. In THI scale, higher score indicate the greater disability caused by the tinnitus. During the entire study period, the patients were monitored for any adverse drug reaction, both according to the adverse drug reaction checklist and by voluntary reporting.

Primary outcome measures were to evaluate the effectiveness of acamprosate in subjective tinnitus using visual analogue scale (VAS) and tinnitus handicap inventory (THI) Scale scores. Secondary outcome measures were to evaluate the adverse drug reactions associated with the use of acamprosate. The collected data were analyzed statistically by using student t test and analysis of variance (ANOVA) and p< 0.05 considered to be statistically significant.

Results

A total of 64 patients were taken. Two patients left in between, withdrawn their consent after day one without assigning any reason and two patient lost in follow up and could not complete even the first follow up. Hence we have taken only 60 patients for analysis. The values are expressed as mean ± SE (Standard Error). *p* value < 0.05 is taken to be statistically significant. The mean age of patients in both the groups was comparable (53.00±2.78 years in group A and 48.03±2.20 years in group B). In group A there were 16 males and 14 females whereas group B had 20 males and 10 females.

There were no significant difference in the demographic profile in both the groups as shown in table-1, (*p* value> 0.05). The baseline clinical characteristics of the patients in both the groups are given in table 2. The baseline clinical characteristics included body weight(kg), blood pressure (SBP and DBP in mm Hg), tinnitus duration (Months), VAS score and THI score. The baseline clinical characteristics of the patients in both the groups was comparable as shown in table 2.

Effect on primary outcome measure: Efficacy was measured by using visual analogue scale (VAS) and tinnitus handicap inventory (THI) scale. These scales were measured at the baseline and at 2, 4, and 6 weeks.

VAS score in group A and B

The mean VAS scores (mm) in both the groups are depicted in table 3. The mean Baseline VAS score (mm) for group A was 51.70±1.36 and for group B was 55.00±1.57 (*p*- value=0.115). The mean VAS score (mm) at 2 week for group A was 45.00±1.26 and for group B was 41.83±1.48 (*p*-value=0.111). The mean VAS score (mm) at 4 week for group A was 38.27±1.38 and for group B was 28.83± 1.26 (*p*-value<0.001). The mean VAS score (mm) at 6 week for group A was 32.00±1.48 and for group B was 16.67±1.10 (p-value<0.001).

In group A, the mean VAS score (mm) reduced significantly to 32.00±1.48 at the end of 6 weeks (*p*-value<0.001). In group A, statistically significant reduction in VAS score were noted at all follow-up visits as shown in table 3.

The mean VAS score (mm) at baseline in group B was 55.00±1.57 which reduced significantly to 16.67±1.10 at the end of 6 weeks (*P*-value<0.001). In group B, statistically significant reduction in VAS scores were noted at all follow-up visits as shown in table 3.

The VAS score decreased significantly to 28.83±1.26 at 4 weeks and 16.67±1.10 at 6 weeks in group B which was statistically significant as compared to group A. (*p*-value<0.001).

THI score in group A and B

The mean THI scores in both the groups are depicted in table 4. The mean baseline THI scores for group A was 23.93±2.31 and for group B was 24.40±2.83 (*p*-value=0.899). The mean THI score at 2 week for group A was 20.67±2.21 and for group B was 18.87±2.34 (*p*- value=0.579). The mean THI score at 4 weeks for group A was 17.60±2.17 and for group B was 12.47±1.50 (*p*-value=0.057). The mean THI score at 6 week for group A was 14.40±1.86 and for group B

was 7.27±1.05 (*p*-value=0.002). In group A, the mean THI score reduced significantly to 14.40±1.86 at the end of 6 weeks (*p*-value<0.001). In group A, statistically significant reduction in THI scores was noted at all follow up visits (*p*-value<0.001) as shown in table 4. In group B, the mean THI score reduced significantly to 7.27±1.05 at the end of 6 weeks (*p*-value<0.001). In group B, statistically significant reduction in THI score was noted at all follow up visits (*p*-value<0.001) as shown in table 4. The mean THI scores decreased more at each follow up in group B as compared to group A. There was a statistically significant difference between the two groups at the end of 6 weeks (*p*-value=0.002) but there were no statistically significant difference in between the groups at 2 weeks (*p* value=0.579) and 4 weeks (*p* value=0.057) visits**.**

Effect on the secondary outcome measures

Adverse drug reaction monitoring was done at all follow up visits through adverse drug reaction checklist and through spontaneous reporting. There was no serious adverse drug reaction noted in the study group (B). In study group B, three, out of thirty patients (10%) reported mild diarrhoea, two patients(6.70%) reported nausea, two patients(6.70%) reported mild abdominal pain and one patient(3.30%) patients reported pruritus. Diarrhea was the commonest adverse drug reaction observed in the study group patients (Group B) as shown in Table 5.

Table 1: Demographic profile of patients in both the groups at baseline

Characteristics	Group A (n=30)	Group B (n=30)	P value
Age(years)	53.00±2.78	48.03± 2.20	0.167
Sex (M:F)	16:14	20:10	0.292

Values represent mean±SE (Standard error)
p value<0.05 is considered to be statistically significant.
M-Male, F-Female

Table 2: Clinical profile of patients in both the groups at baseline

Characteristics	Group A (n=30)	Group B (n=30)	P value
Weight (kilogram)	64.83 ±1.96	63.00±1.93	0.509
Blood pressure(BP) (mm Hg)			
Systolic BP	124.13±1.15	124.87± 0.89	0.617
Diastolic BP	80.40± 0.79	79.80± 0.62	0.556
Tinnitus duration(month)	14.27± 2.75	26.23± 5.36	0.052
VAS score(Baseline)	51.70± 1.36	55.00±1.57	0.115
THI score(Baseline)	23.93± 2.31	24.40±2.83	0.899

Values represent mean±SE (Standard error)
P value<0.05 is considered to be statistically significant.

Table 3: VAS score (Mean±SE) at different time intervals in both groups

Weeks	0	2	4	6
Group A (n=30)	51.70±1.36	45.00±1.26.*	38.27±1.38*	32.00±1.48*
Group B (n=30)	55.00 ±1.57	41.83 ±1.48*	28.83 ±1.26*#	16.67 ±1.10*#

Values represents mean±SE (Standard error)
*p<0.05 as compared to baseline,
# p<0.05 as compared to group A

Table 4: THI Score (Mean±SE) at different time intervals in both groups

Weeks	0	2	4	6
Group A (n=30)	23.93±2.31	20.67±2.21.*	17.60±2.17*	14.40±1.86*
Group B (n=30)	24.40±2.83	18.87±2.34*	12.47±1.50*	7.27±1.05*#

Values represents mean±SE (Standard error)

*p<0.05 as compared to baseline

#p<0.05 as compared to Group A

Table 5: Adverse drug reactions in Group B patients.

S.no.	Adverse drug reaction	Percentage of patients (n = 30)
1.	Diarrhea	10%
2.	Nausea	6.70%
3.	Mild Abdominal pain	6.70%
4.	Pruritus	3.30%

Discussion

The baseline demographic and clinical profile were comparable in the two groups. In this study we have enrolled all the cases of subjective tinnitus of sensorineural origin. In the present study, the group of patients that received acamprosate with TRT (Group B), there was reduction in the VAS score of patients which is similar to other studies.[13] In our study, the baseline VAS score in group B was 55.00 mm and at 6 week the mean VAS score was 16.67 mm, which was statistically significant. The baseline demographic characteristics and VAS score was similar as other study but the duration of study was different.[13] In our study the assessment of VAS scale done at baseline, 2, 4 and 6 weeks but in Sharma *et al* (2012) study the assessment was done at baseline, 45th day, 52th day and 97th day of the study.[13]

In our study in group B patients, there was reduction in the THI score, which is almost similar to other studies.[11] In our study the assessment of THI score done at baseline, 2, 4 and at 6 weeks but in Azevedo AA *et al* (2005) study, the assessment was done at baseline, 30th, 60th, and at 90th day of the study.[11] So our study differs in terms of duration of study as our study duration was 6 weeks whereas in Azevedo AA *et al* (2005), the study duration was 90 days. In Azavedo *et al* (2005) study, there was significant decrease in the tinnitus scale after the first month of treatment but in our study, there was significant decrease in tinnitus scale after the 2 week of treatment but in both the studies the patients reported relief in tinnitus, which was also statistically significant. In our study, the baseline THI score in group B was 24.40 and, the mean THI score was 7.27, at 6 weeks which is statistically significant. In our study, the mean decline of THI scores was 17.13 in group B but in another study by Rukma Bhandary *et al* (2013), the mean decline of the THI scores was 14 after 2 months of treatment, in which *Ginkgo biloba* was the study drug. The difference in THI scores from Rukma Bhandary *et al* (2013) study may be due to different study drug and the duration of treatment in that study.[14]

In our study, in the control group (Group A) patients who received only TRT, there was reduction in the THI and VAS scores of patients which is almost similar to other studies. [15,14] In our study the baseline THI score in Group A was 23.93 and after 6 weeks the mean THI score was 14.40, which is also statistically significant. In our study, the

mean decline of the THI score was 9.53 in group A after 6 weeks from baseline but in another study by Hashir A *et al* (2008) [15] the mean THI scores significantly decreased after 3 to 23 months of treatment and the mean decline of the THI score were 45 and the difference between pre and post treatment scores was statistically significant. So in both the studies the difference between pre and post treatment THI scores were statistically significant despite difference in the duration of study and baseline characteristics.

In our study, it is important to point out that p value is not statistically significant at 2 and 4 week but it is statistically significant at 6 week, between the two groups (Group A and group B) on THI scale.

However, the present study has few limitations too. The study was not blinded and therefore possibility of bias could not be excluded. Other limitation of our study is that the drug acamprosate (In group B) was given for 6 weeks only. Thus, long term efficacy and safety of TRT with acamprosate could not be assessed. Acamprosate drug was well tolerated and did not show any serious adverse drug reaction (ADRs)which was similar to previous studies.[13] The ADRs reported in our study were mild and no discontinuation was needed.

Conclusion

On the basis of the findings of this study, it may be concluded that acamprosate as add-on to tinnitus retraining therapy is more efficacious as compared to tinnitus retraining therapy alone in subjective tinnitus of sensorineural origin and has reported fewer adverse drug reactions for the treatment of subjective tinnitus.

Acknowledgement Thanks to all senior faculty of pharmacology and ENT department of CMC and hospital, Ludhiana.

References

1. Vesterager V. Tinnitus-investigation and management. Br Med J. 1997;314:728-31.
2. Ceranic B, Luxon LM. Tinnitus and other dysacuses. In: Gleeson M, Browning GG, Burton MJ, Clarke R, Hibbert J, Jones NS, *et al* editors. Scott-Brown's Otorhinolaryngology, Head and Neck Surgery. 7th ed. Chicago: Hodder Arnold. 2008; 3594-628.
3. Moller AR. Pathophysiology of tinnitus. Otolaryngol Clin North Am. 2003; 36: 249-66.
4. Schleuning AJ. Management of the patient with tinnitus. Med Clin North Am. 1991;75:1225–37.
5. Ergemmont JJ. Central tinnitus. Auris Nasus Larynx 2003;30: S7-12.
6. Weber PC, Klein AJ. Hearing loss. Med Clin North Am. 1999;83:125–37.
7. Fioretti A, Eibenstein A, Fusetti M. New trends in tinnitus management. Open Neurol J. 2011;5:12-7.
8. Baldo P, Doree C, Lazzarini R, Molin P, McFerran D. Antidepressants for patients with tinnitus. Cochrane Database Syst Rev. 2006;4:CD003853.
9. Gananca MM, Caovilla HH, Gananca FF, Ganança CF, Lei Munhoz MS, da Silva ML *et al*. Clonazepam in the pharmacological treatment of vertigo and tinnitus. Int Tinnitus J. 2002;8:50-3.
10. Lopez-Gonzalez MA, Santiago AM, Esteban-Ortega F. Sulpiride and melatonin decrease tinnitus perception modulating the auditolimbic dopaminergic pathway. J Otolaryngol. 2007;36:213-9.
11. Azevedo AA, Figueiredo RR. Tinnitus treatment with acamprosate: double-blind study. Braz J Otorhinolaryngol .2005;71:618-23.
12. Gillespie DC, Kim G, Kndler K. Inhibitory synapses in the developing auditory system are glutaminergic. Nat Neurosci. 2005;55:332-8.

13. Sharma DK, Kaur S, Singh J, Kaur I. Role of acamprosate in sensorineural tinnitus. Indian J pharmacol .2012;44:93-6.
14. Bhandary R, Kudva A, D'Silva R, Devan PP, Thantry D, Ashok K. Comparison of efficacy of tinnitus retraining therapy versus ginkgo biloba in the management of tinnitus. Res Rev: J Med health Sci. 2014;3:1-6.
15. Aazh H, Moore BCJ, Glasberg BR. Simplified form of tinnitus retraining therapy in adults: a retrospective study. BMC Ear Nose and Throat Disorders. 2008;8:1-7.