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Acamprosate as the Remedial Molecule in Sensorineural Tinnitus

Mukesh Chandra Das[1], Abhinav Paul Minj[2]

[1]Assistant Professor, Department of Pharmacology, Medini Rai Medical College, Palamu, Jharkhand, India

[2]Assistant Professor, Department of ENT, Medini Rai Medical College, Palamu, Jharkhand, India

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Corresponding Author: Abhinav Paul Minj

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Abstract:

Background: The management of tinnitus remains a significant clinical hurdle for otolaryngologists in the field. Numerous aspects pertaining to the pathophysiology of this condition still remain elusive, giving rise to a diverse array of therapeutic approaches, yielding inconsistent outcomes. Acamprosate, a pharmacological agent, is commonly employed in the therapeutic management of alcohol use disorder. This drug exerts its effects by modulating glutamatergic and GABAergic neurotransmission. Notably, acamprosate has not been previously utilised in the treatment of tinnitus. To assess the effectiveness and safety of acamprosate in the management of sensorineural tinnitus.

Methods: A cohort of 50 individuals diagnosed with sensorineural tinnitus were enrolled in a three-month prospective double-blind study. The primary objective of this study was to evaluate the effectiveness and safety of a specific intervention. The subjective score, ranging from 1 to 10, provided by each patient was utilised as a measure of efficacy.

Results: A significant success rate of approximately 86.9% was observed in the alleviation of tinnitus. In 47.8% of the observed instances, a significant reduction of more than 50% in symptoms was observed. The prevalence of adverse reactions was found to be minimal, specifically 12%, with all reported cases being of a mild nature.

Conclusion: Acamprosate, a drug used in the treatment of alcoholism, is a safe and successful alternative for sensorineural tinnitus' treatment.

Keywords: Acamprosate, Audiometry, Sensorineural Tinnitus, Tinnitus Matching.

Introduction

Tinnitus is clinically characterised as an auditory perception that lacks an identifiable external origin [1]. Epidemiological data indicate that approximately 10-15% of the overall population experience tinnitus, however, only 2% perceive it as a significant issue that significantly impacts their overall well-being and quality of life (QoL) [2]. There has been a proposed correlation between an elevation in the secretion of glutamate, the primary neurotransmitter found in both the cochlea and central auditory pathways, and the development and persistence of sensorineural tinnitus. This correlation is believed to occur due to the occurrence of "excitotoxicity" and subsequent upregulation of NMDA receptors [2]. The therapeutic approach for tinnitus primarily revolves around pharmacological interventions that target central nervous system (CNS) neurotransmitters, such as glutamate, gamma-aminobutyric acid (GABA), serotonin, acetylcholine, and dopamine. Glutamate receptor antagonists, which inhibit the binding of glutamate to its receptors and subsequently hinder or reduce the entry of calcium ions, have demonstrated potential efficacy in the management of the aforementioned condition [3].

Numerous treatment modalities have been suggested for central and sensorineural tinnitus; however, none of them have consistently exhibited favourable outcomes across all individuals [5].

Acamprosate, a pharmacological agent utilised in the management of alcohol dependence, was initially documented as a prospective therapeutic intervention for tinnitus in the year 2005 [6, 7]. The pharmaceutical compound exhibits a dual mechanism of action, functioning as both a glutamate antagonist and a GABA agonist. Acamprosate exerts its pharmacological effects on the glutamatergic system, which is responsible for excitatory neurotransmission, as well as on the inhibitory GABA system. This dual mechanism of action is utilised in the treatment of tinnitus. No other pharmaceutical agent employed in the therapeutic management of tinnitus exhibits a concurrent mechanism of action in both physiological systems [8]. Acamprosate induces an upregulation of gamma-aminobutyric acid (GABA)

reuptake sites and alters GABA reuptake in rodent models, resulting in widespread enhancements of GABAergic transmission. This ultimately leads to the inhibition of auditory pathway excitation [9, 10]. Acamprosate mitigates the impact of excitatory amino acids, specifically glutamate, within the central nervous system. Its primary mechanism involves reducing the excitatory effects exerted on NMDA receptors, likely through its interaction with calcium channel blockers [3, 11].

Our objective was to evaluate the effectiveness and safety of acamprosate in managing sensorineural tinnitus through the implementation of a double-blind randomised clinical study.

Methods

We selected 50 patients with tinnitus seen at Medini Rai Medical College, Palamu, India for one year.

The study's inclusion criteria consisted of individuals with sensorineural tinnitus, while excluding cases of external and middle ear pathology, as well as concurrent temporomandibular joint disorders. Pure tone audiometry, vocal audiometry, and immittanciometry were conducted on all participants, and individuals with conductive and mixed hearing impairments, as well as those with tympanogram curve types A-r, A-d, C, and B, were excluded from the study. The audiometer employed in the study was the AMPLAID A 177 PLUS, while the Immittanciometer utilised was the AMPLAID 750. The thresholds were evaluated within the range of 25 dB (representing normal hearing), 26 to 40 dB (indicating mild hearing loss), 41 to 70 dB (suggesting moderate hearing loss), 71 to 90 dB (indicating severe hearing loss), and exceeding 90 dB (indicating profound hearing loss).

The patients were classified according to the following parameters:

- Age
- Gender
- continuous or intermittent tinnitus
- uni or bilateral tinnitus
- tinnitus characteristics (type of associated noise)
- time of tinnitus
- associated symptoms (hypo and hyper loss, dizziness, ear fullness)
- probable tinnitus Etiology
- previous use of drugs to treat tinnitus
- baseline tinnitus score, given by the patient, ranging from 0 to 10, according to how much it disturbed the patient

The participants were requested to rate the severity of their tinnitus on a scale ranging from 1 to 10, based on the level of distress it caused them. We permitted scores of 0.5 as well. The assistant physician provided comprehensive explanations of all aspects of the study to the patients, ensuring their understanding. Subsequently, the patients provided their informed consent by signing the appropriate documentation.

Statistical Analysis

The statistical analysis was performed based on the following methods:

- to evaluate quantitative data we used t Student test for independent samples or the Mann-Whitney test.
- to evaluate qualitative data we applied the chi-square test ($\chi 2$) or Fisher exact test.
- to analyze the progression of tinnitus scale (quantitative data) throughout time (four assessments within 3 months) with the treatment we performed Friedman Variance Analysis. The test of multiple comparisons based on the statistics of Friedman was applied to identify which moments were different. The test of multiple comparisons is a test complementary to Variance Analysis.

The criterion for determination of significance was adopted as 5%, that is, when p value of the statistical test was smaller or equal to 0.05, meaning there was statistical significance. The statistical analysis was processed by the statistical software SAS System.

Results

The age distribution of the study participants encompassed a range of 35 to 82 years, with a calculated mean age of 60 years and a median age of 60.5 years. The duration of symptoms in months varied from 1 to 420, with a mean of 101.78 months and a median of 60 months.

Our study revealed that 58% of the participants were male individuals, while 42% were female individuals. The most commonly reported type of tinnitus among patients was characterised by a wheezing sound, which was reported by 62% of the individuals. Additionally, a significant proportion of patients (46%) reported experiencing a whistle-like sound as their tinnitus symptom. Additionally, the patients also documented auditory sensations resembling engine noises, pain akin to pressure-cooking, and the sound of cicadas. It is noteworthy that 16% of the individuals experienced multiple forms of tinnitus simultaneously. Regarding the temporal manifestation of symptomatology, it was observed that 9.76% of the individuals exhibited recent tinnitus (within a duration of less than 1 year), 53.65% presented with intermediate tinnitus (occurring between 1 and 7 years), and 36.59% displayed chronic cases of tinnitus (persisting for

more than 7 years). A study revealed that 58% of the patients exhibited bilateral tinnitus, while 72% experienced persistent tinnitus, and 64% reported concurrent symptoms. Among the entire sample, a notable proportion of 59.4% indicated experiencing hearing loss, while 46.9% reported episodes of dizziness. Additionally, 15% of participants reported instances of ear fullness, and 9.3% disclosed the presence of hyperacusis. Furthermore, a significant proportion of the patient cohort, specifically 52%, had previously undergone pharmacological interventions for the management of tinnitus.

A potential etiological factor, namely exposure to noise, was observed in 60% of the cases. Approximately 20% of the individuals exhibited a likely multifactorial origin for the occurrence of tinnitus. Regarding auditory thresholds, our observations revealed a normal audiogram in two patients, accounting for 4% of the sample. Mild hearing loss was observed in 30 individuals, representing 60% of the cohort. Additionally, 10 participants (20%) exhibited moderate hearing loss, while six individuals (12%) displayed severe hearing loss. Lastly, two patients (4%) were found to have profound hearing loss. Among the cohort of patients exhibiting threshold abnormalities, there was observed a varied distribution of audiometric curves. In light of the cohort of 50 individuals, it is noteworthy that 9 subjects prematurely discontinued their therapeutic intervention prior to the completion of the assessment period. Six patients discontinued their treatment due to adverse effects. Three additional patients, accounting for 6% of the total sample size of 50, discontinued their treatment regimen due to familial influence.

The observed percentage of improvement at day 90, as indicated by any discernible increase in scores, was significantly higher with the administration of acamprosate (p=0.004). There was no observed deterioration in the patients' scores. Three participants (13.04%) did not exhibit any signs of improvement, while 9 participants (39.13%) reported experiencing improvement below 50%. On the other hand, 11 participants (47.83%) reported improvement exceeding the 50% threshold. Three participants (13.04%) reported the cessation of tinnitus symptoms. In order to evaluate the temporal evolution of tinnitus severity, we conducted a Friedman Variance Analysis. This study examines whether there is statistically significant temporal variation, either in the form of decline or increase. The tests of multiple comparisons based on Friedman statistics were utilised to ascertain the temporal variations that existed.

Table 1: Longitudinal analysis of tinnitus scale

Tinnitus scale	n	Mean	SD	Median	p value
Baseline	41	20.5	2.53	13	0.0001
Score – 30d	41	20.5	2.29	10.5	
Score – 60d	41	20.5	2.62	9.5	
Score – 90d	41	20.5	2.70	26.5	

Table 1 presents the statistical measures of central tendency and dispersion, including the mean, standard deviation (SD), median, minimum, and maximum values of the scale at four distinct time points. Additionally, the table includes the corresponding level of significance (p value) obtained from the Friedman test, a statistical test used to analyse repeated measures data. The instances that exhibited variations, as determined by the test of multiple comparisons, were indicated in the column denoting statistically significant disparities, at a significance level of 5%.

Discussion

Tinnitus is a highly prevalent symptom that impacts a substantial proportion of the overall population, as indicated by numerous empirical investigations, with prevalence rates ranging from 14% to 32% [12, 13]. In a study conducted by researchers, it was found that tinnitus had a significant impact on the lives of patients in approximately 20% of cases. This impact was found to be particularly severe, leading to disabling effects in around 5% of cases [13].

The management of tinnitus utilising carbamazepine, administered in a gradually escalating manner ranging from 50 to 600 mg per day, as determined by a positive lidocaine test, has demonstrated potential for ameliorating 50% of tinnitus cases [14]. Several pharmaceutical agents have been previously investigated for their potential in treating tinnitus. These include baclofen, which demonstrated a modest improvement rate of approximately 9.7% [15]. Caroverine exhibited a more substantial improvement rate of 63.3% [16]. Piribedil, another drug under investigation, showed a promising improvement rate of 92.6% [17]. Nimodipine, on the other hand, demonstrated a modest improvement rate of 16.13% [18]. Clonazepam exhibited a 32% improvement rate [19], while trimetazidine showed a notable improvement rate of 89% [20, 21]. Only the clinical trials that examined the effects of baclofen and caroverine were conducted using a double-blind methodology. Trimetazidine, a pharmacological agent with antiischemic properties, is commonly prescribed in Europe for the management of tinnitus and vertigo.

It has been observed to exhibit enhanced efficacy in cases of tinnitus that have manifested within the past year [21]. In a retrospective study conducted by Murai et al. [22], the researchers evaluated the efficacy of various pharmacological interventions for tinnitus. These interventions encompassed the administration of clonazepam and flunarizine, among other drugs. The study findings revealed a range of 33% to 56% in terms of symptom improvement rates.

No literature review yielded any evidence regarding the utilisation of acamprosate for the management of tinnitus. The drug's dual action mechanism, characterised by the reduction of glutamatergic transmission (excitatory) and the enhancement of GABA activity (inhibitory), coupled with its exceptional tolerability, positions it as a highly promising pharmaceutical intervention for the treatment of tinnitus.

In our research investigation, a noteworthy proportion of tinnitus amelioration was observed, amounting to 86.9%. Furthermore, in 47.8% of the instances, the degree of improvement surpassed 50%. A progressive decline in the tinnitus severity rating was noted over the course of 90 days. The rate of improvement exhibited a higher magnitude compared to alternative pharmaceutical interventions. Notably, for trimetazidine, data pertaining to its efficacy (89%) and piribedil (92.6%) were not obtained from studies employing the rigorous double-blind placebo controlled methodology. The clinical investigation involving piribedil was conducted by medical professionals specialising in general medicine. These clinicians also evaluated additional symptoms, including vertigo and memory impairment [23]. It is imperative to highlight that there was no statistically significant disparity in improvement when comparing variables such as age, gender, aetiology, type and duration of tinnitus, as well as severity of hearing loss and type of audiometric curve. This finding opens up a promising avenue for the treatment of all instances of sensorineural tinnitus. There was no statistically significant difference observed in the outcomes pertaining to variables such as age, gender, aetiology, duration and classification of tinnitus, degree of hearing impairment, and configuration of audiometric curve.

Conclusion

Within the realm of tinnitus, a complex condition characterised by multiple causative factors and varying treatment outcomes, it is imperative to explore all potential therapeutic interventions that may provide relief to affected individuals. Due to this rationale, it is imperative to consider the inclusion of acamprosate, a pharmacological agent utilised in the management of alcohol use disorder. This medication exhibits a dual mechanism of action, targeting both the inner ear and auditory pathways. Furthermore, it demonstrates commendable tolerability, thus warranting its incorporation into our therapeutic armamentarium.

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