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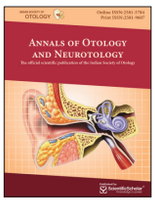

Original Article

Is Acetazolamide an Effective Drug for Vestibular Migraine?

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ABSTRACT

Objectives: To evaluate the efficacy of acetazolamide in the management of VM.

Material and Methods: A retrospective study was carried out in the ENT Department at Choithram Hospital and Research Centre, Indore, for 1 year. Seventy-four subjects of either sex were included in the study. All the participants were given acetazolamide in a 500 mg BD dose after stopping previous medications.

Results: 60 out of 74 patients who were prescribed acetazolamide were studied. 49 (81.6%) were females, and 11 (18.4%) were males. Thirty-one patients (51.6%) experienced an improvement in both headache and vertigo symptoms, 18 (30%) in vestibular symptoms only, 7 (11.6%) in headache only, and 4 (3.3%) showed no change. Overall, 56 patients (93.3%) improved with acetazolamide; the effect was more on vestibular symptoms than headache.

Conclusion: Acetazolamide can be a promising drug in selected cases of VM.

Keywords: Acetazolamide, Headache, Vestibular Migraine, Vertigo.

INTRODUCTION

Migraine is a disease characterized by periodic headaches, but patients often experience other symptoms, including dizziness and hearing loss, and in some cases, these can be the only symptoms. The association of migraine and dizziness extends back to the 19th century when Living mentioned their connection in his "On Megrim: Sick Headaches and Some Allied Health Disorders." Overall, episodic vertigo occurs in about 25% of unselected migraine patients (about as frequent as the visual aura).[1] In the general population, lifetime prevalences are estimated at 7% for vertigo and 16% for migraine.[2]

Vestibular migraine (VM) is the most common cause of recurrent spontaneous vertigo across all age groups. Neuhauser, in 2001, described the term VM in patients with the symptoms of vertigo associated with migraine. This definition was updated in 2012 in a joint statement by the International Headache Society and the Barany Society and termed VM, which is characterized by the following symptoms:

A. At least five episodes with vestibular symptoms of moderate or severe intensity lasting 5 minutes to 72 hours
B. History of migraine according to IHS classification
C. Migraine feature with >50% of attacks:
    - headache with two unilateral, throb, moderate-severe, aggravation by movement
    - photo- and phonophobia
    - visual aura
D. Not better accounted for by another disorder.[3]

The pathogenesis of VM is still unclear. Both the central and peripheral vestibular systems are associated with the pathogenesis of VM. Many studies have revealed the overlap between vestibular and migraine pathways, as the caudal parabrachial nucleus receives both afferent peripheral trigeminal nociceptive and vestibular input. So, the cause of VM may be the direct central activation of vestibular centers by the trigeminovascular system, together with its effects on the inner ear. Also, there is evidence of otolithic pathway abnormalities in individuals with VM. Moreover, studies have shown that Purkinje cells in the para flocculus could be inhibited after a migraine episode, which is an important factor leading to VM.[4]

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Received: 14 January 2024 **Accepted:** 15 March 2024 **Published:** 28 January 2025 **DOI:** 10.25259/AONO-2024-1-(206)

The management of VM encompasses various approaches to alleviate symptoms and improve overall well-being. Lifestyle modifications play a crucial role, involving the identification and avoidance of trigger factors such as specific dietary items, irregular sleep patterns, and external stressors whenever possible. Patients are encouraged to maintain consistent sleep schedules, engage in regular exercise, and have structured meal times to minimize potential triggers. Pharmacological interventions are often prescribed to prevent or alleviate symptoms. Medications like beta-blockers, antidepressants, antiepileptics, and specific migraine medications (such as triptans) may be used based on the individual's needs. Acute symptoms of vertigo can be managed with vestibular sedatives such as prochlorperazine, cyclizine, or cinnarizine. The prophylactic management of VM is provided by drugs like propranolol and topiramate.[3] Acetazolamide, a carbonic anhydrase inhibitor, has also been mentioned as a prophylactic agent. Along with being a diuretic, it is used in various neurological disorders due to the wide distribution of carbonic anhydrase in the brain and other tissues. By inhibiting carbonic anhydrase in the brain, it elevates total brain carbon dioxide levels and disrupts chloride and bicarbonate membrane transport, modulating the transmembrane chloride gradient. These actions perturb the CO_2 equilibrium and inhibit ion channels, ultimately reducing seizures.[5] It also, with its strong vasodilator properties, may reverse the cerebral vasoconstriction, which plays a role in the pathophysiology of migraine headaches, and decrease intracranial pressure by reducing increased blood flow rate and production of cerebro-spinal fluid (CSF).[6]

The role of acetazolamide is well-established in the treatment of Meniere's disease, but its role in VM is yet to be studied. Currently, all drugs are aimed at the management of migrainous headaches rather than vestibular components of VM. Our study here aims at evaluating the efficacy of acetazolamide in the management of VM.

MATERIAL AND METHODS

It is a retrospective study carried out in the department of ear nose throat (ENT) at Choithram Hospital and Research Centre, Indore. The duration of the study was 1 year. Two hundred nineteen patients were diagnosed with VM. Seventy-four patients of either sex were included in the study after taking proper informed consent. A detailed history was taken, and vertigo and headache frequency and severity were assessed. All the patients were given instructions to withhold vestibular suppressants and other anti-migraine drugs. Acetazolamide was prescribed after a detailed discussion with the patient about the possible effects and side effects of the drug. The dosage was 500 mg/day in two divided doses at 8 am and 3 pm to avoid nocturnal diuresis. The response was assessed at the end of 3 months of treatment.

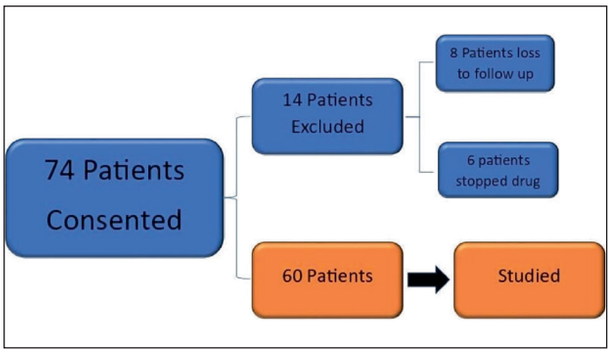


Figure 1: Number of patients studied.

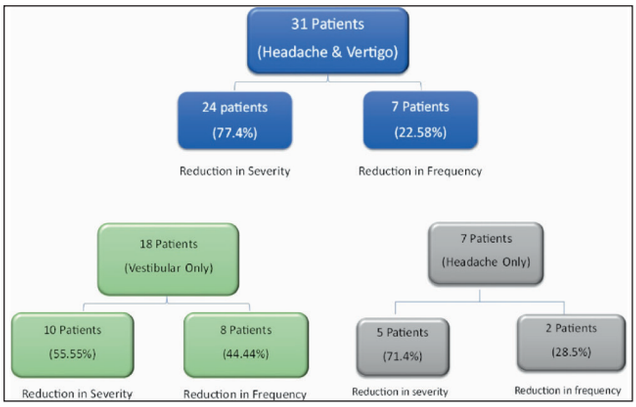


Figure 2: Reduction infrequency and severity of vestibular and headache symptoms.

RESULTS

Out of the total 74 patients prescribed acetazolamide, 60 patients were studied. The remaining 14 patients were excluded from the analysis, with 6 of them stopping the drug and 8 patients being lost to follow-up during the study period [Figure 1].

The study assessed the treatment response based on improvements in headache and vertigo symptoms. Results showed that 31 patients (51.6%) experienced improvement in both headache and vertigo symptoms. These patients reported a reduction in the frequency and severity of both headache attacks and vertigo episodes, indicating a positive response to acetazolamide treatment for the combination of symptoms. In addition to the patients with improvements in both headache and vertigo, there were subgroups within the studied population. Eighteen patients (30%) reported improvement in only vestibular symptoms and a reduction in the frequency and severity of vertigo episodes without a significant effect on headache frequency and severity. On the other hand, 7 patients (11.6%) experienced improvement in headache only. Four patients (3.3%) showed no change in their condition [Figure 2].

Table 1: Gender distribution.

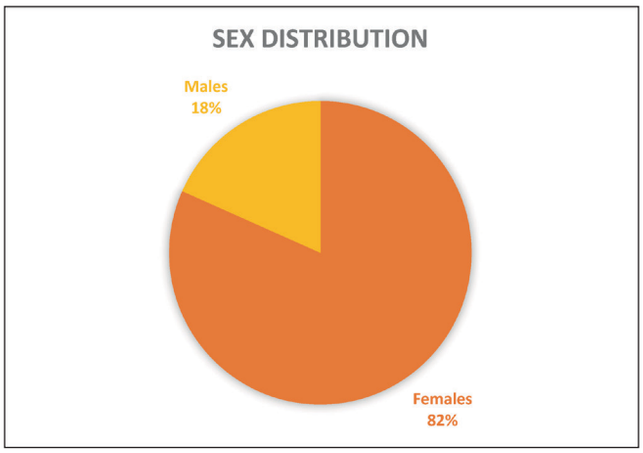
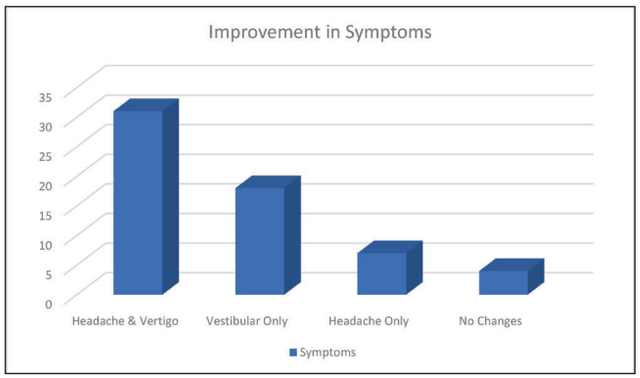


Table 2: Improvement in symptoms of vestibular migraine (VM).



Among the 60 studied patients, 49 (81.6%) were females and 11 (18.4%) were males. This gender distribution indicates a higher prevalence of VM among females in this particular group [Table 1].

Overall, 56 patients (93.3%) showed some form of improvement with acetazolamide treatment. Among these patients, 30 reported an improvement in the severity of their symptoms, while 26 reported a reduction in the frequency of their symptoms [Table 2].

Interestingly, the study found that the reduction in vestibular symptoms (both frequency and severity) was more pronounced as compared to the reduction in headache symptoms (both severity and frequency). This suggests that acetazolamide is more effective in managing vestibular symptoms in VM patients.

Regarding side effects, the most common ones reported were tingling and paresthesia. Other reported side effects included sedation, nausea, and fatigue.

DISCUSSION

VM is an underdiagnosed but increasingly recognized condition that causes episodic vertigo, often accompanied by headache. A condition first clearly described by Boenheim in 1917, it is now thought to be the most common cause of spontaneous (non-positional) episodic vertigo, affecting between 1% and 2.7% of the general population. Previously known variously as "migrainous vertigo," "migraine-associated vertigo," "migraine-associated dizziness," "migraine-anxiety-associated dizziness," and "migraine-related vestibulopathy," VM has been accepted by the International Classification of Headache Disorders (ICHD) as the unifying term that identifies both the vestibular and migrainous symptoms. The current diagnostic criteria, first proposed by Neuhauser et al.[7] and ratified by the International Headache Society and the committee for the International Classification of Vestibular Disorders (ICVD) of the Bárány Society, mandate a history of migraine and the temporal overlap of vestibular and migrainous symptoms in at least 50% of episodes and allow for the possibility of probable VM.[8]

The pathophysiology of VM is not fully known; however, the growing body of knowledge regarding migraine in general points to possible central as well as peripheral mechanisms. In the cerebral cortex, evidence suggests that visual auras are due to cortical spreading depression (CSD). Lon channels in the neuronal membrane confer susceptibility to CSD but also sensory hypersensitivity at baseline. The sensory hypersensitivity and lack of habituation to repetitive stimuli are often seen in VM. The "vascular theory" of migraine held that ischemia was caused by vasospasm. Current evidence favours peripheral involvement through a more complex mediation by the trigeminovascular system (TVS). CSD activates meningeal nociceptors of the TVS, comprising trigeminal nuclei, ganglion, nerve, and meningeal vasculature. The release of vasoactive neuropeptides such as neurokinin A, substance P, and calcitonin gene-related peptide (CGRP) induces sterile neurogenic inflammation, inducing TG excitation, causing throbbing pain and central sensitization, resulting in allodynia. The same TG excitation may reach the inner ear as well as the cochlear nucleus and superior olivary complex, a possible link from central to peripheral cochlear and vestibular dysfunction.[9]

The current treatment strategies devised by von Brevern and Lempert include pharmacological management for acute cases and long-term prophylaxis, rehabilitative exercises, and psychological assurance. The first therapeutic step is explanation and reassurance. Many patients do not need

pharmacological treatment, as attacks may be infrequent and tolerable. Acute attacks can be ameliorated in some patients with antiemetic drugs such as diphenhydramine, meclizine, and metoclopramide. Frequent attacks may warrant pharmacological prophylaxis with metoprolol, amitriptyline, topiramate, valproic acid, flunarizine, or acetazolamide. Non-pharmacological measures, including regular exercise, relaxation techniques, stress management, and biofeedback, may be similarly effective and can be combined with a pharmacological approach.[10]

Acetazolamide works by inhibiting carbonic anhydrase, an enzyme distributed throughout tissue in the body and glial cells of the brain. The resulting effect of raised carbon dioxide concentration and blockade of chloride and bicarbonate membrane transport has led to its use in promoting diuresis, reducing intraocular pressure, and limiting seizures.[5,11] It also has strong vasodilator properties, which reverse the cerebral vasoconstriction, which plays a role in the pathophysiology of migraine headaches and decreases intracranial pressure by reducing increased blood flow rate and production of CSF. It does this by inhibiting carbonic anhydrase after passing the blood-brain barrier, thus producing acidosis. Due to acidosis, cerebral vessels undergo vasodilation, which increases cerebral blood flow. This vasodilating effect of acetazolamide was observed only on constricted arterioles. It has been shown that no vasodilation occurs in the carotid and vertebral arteries when 250 mg of acetazolamide is given intravenously but that a higher 500 mg of intravenous acetazolamide is effective.[6]

The earliest account of the use of acetazolamide was mentioned by Robert Baloh in 1997. He has suggested the use of this drug in prophylaxis of migraine after finding it particularly effective in controlling vertigo and motion sickness in patients with migraine and episodic ataxia type 2.[1]

The study done by Vahedi et al. (2002) on the efficacy and tolerability of acetazolamide in migraine prophylaxis did not show much improvement in symptoms. According to their study, poor tolerance was found to carbonic anhydrase inhibitors in migrainous subjects, suggesting hypersensitivity to metabolic acidosis.[12] In contrast to these results, the clinical study done by De Simone et al. (2005) reported a reduction in the frequency of attacks in both migraine types with and without aura with acetazolamide, which is consistent with our findings.[13]

The results of our study closely align with the findings of Celebisoy et al. (2016).[5] Both studies reveal a female preponderance and significant improvement in vestibular symptoms as compared to headaches.

The use of acetazolamide was further supported in the studies done by Furman and Balban et al. (2015),[14] Oberman and Strupp et al. (2015),[15] John-hee Sohn et al. (2016),[16] A. Lapira et al. (2019),[17] von Breveren and Lempert et al. (2019),[18] Magdalena Nowaczewska et al. (2020),[19] Vyawahare and Chakole et al. (2021),[20] and Koukoulithras et al. (2022).[4] Teelucksingh et al. (2023) studied the use of acetazolamide in VM in pregnant patients. Their research also concluded the safe use of this drug. Their recommendation was the usage of acetazolamide as a second line of prophylaxis, as there were some intolerances seen due to side effects.[21]

CONCLUSION

In conclusion, our research demonstrated a favorable impact of acetazolamide. There was a significant reduction in frequency and severity of attacks. Both headache and vestibular symptoms were remarkably improved; the effect was more prominent over vestibular symptoms than headache. This suggests that acetazolamide is a promising therapeutic option for selected VM patients, while also highlighting limited occurrence of side effects.

Acknowledgment: This paper was presented in NESCON 2022 in AIIMS, New Delhi. It was awarded 2nd prize under the category of Faculty Paper Presentation.
Ethical approval: The research/study approved by the Institutional Ethics Committee at Choithram hospital and Research Centre, number EC/JAN/24/24, dated 12th January 2024.
Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.
Financial support and sponsorship: Nil.
Conflicts of interest: There are no conflicts of interest.
Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Baloh RWJHTJoH, Pain F. Neurotology of Migraine. Headache 1997;37:615–21.
2. Neuhauser H, Radtke A, Von Brevern M, Feldmann M, Lezius F, Ziese T, et al. Migrainous Vertigo: Prevalence and Impact on Quality of Life. Neurology 2006;67:1028–33.
3. Murdin L, Luxon LM. Vestibular migraine. In: Scott-Brown's Otorhinolaryngology Head and Neck Surgery: CRC Press; 2018. p. 855–61.
4. Koukoulithras I, Drousia G, Kolokotsios S, Plexousakis M, Stamouli A, Roussos C, et al. A Holistic Approach to a Dizzy Patient: A Practical Update. Cureus 2022;14:e27681.
5. Çelebisoy N, Gökçay F, Karahan C, Bilgen C, Kirazlı T, Karapolat H, et al. Acetazolamide in Vestibular Migraine

Prophylaxis: A Retrospective Study. Eur Arch Otorhinolaryngol 2016;273:2947–51.
6. Çetin G, Ak AK, Özyurt BC, Selçuki DJNA. Role of Acetazolamide in Treatment of Patients with Menstrual Migraine. Neurol Asia 2021;26:751–9.
7. Neuhauser H, Leopold M, Von Brevern M, Arnold G, Lempert TJN. The Interrelations of Migraine, Vertigo, and Migrainous Vertigo. Neurology 2001;56:436–41.
8. Smyth D, Britton Z, Murdin L, Arshad Q, Kaski DJB. Vestibular Migraine Treatment: A Comprehensive Practical Review. Brain 2022;145:3741–54.
9. Krishnan PS, Carey JPJOCoNA. Vestibular Migraine: Clinical Aspects and Pathophysiology. Lancet Neurol 2022;55:531–47.
10. Von Brevern M, Lempert T, Editors. Vestibular Migraine: Treatment and Prognosis. In: Seminars in Neurology. Thieme Medical Publishers; 2020.
11. Schettino, A., Navaratnam, D. (2019). Vestibular Migraine. In: Babu, S., Schutt, C., Bojrab, D. (eds) Diagnosis and Treatment of Vestibular Disorders. Springer, Cham. https://doi.org/10.1007/978-3-319-97858-1_18.
12. Vahedi K, Taupin P, Djomby Rf, El-Amrani M, Lutz G, Filipetti V, et al. Efficacy and Tolerability of Acetazolamide in Migraine Prophylaxis: A Randomized Placebo-Controlled Trial 2002;249:206–11.
13. De Simone R, Marano E, Di Stasio E, Bonuso S, Fiorillo C, Bonavita VJHTJoH, et al. Acetazolamide Eficacy and Tolerability in Migraine with Aura: A Pilot Study. J Neurol 2005;45:385–6.
14. Furman JM, Balaban CDJAotNYAoS. Vestibular Migraine. Ann N Y Acad Sci 2015;1343:90–6.
15. Obermann M, Strupp MJFin. Current Treatment Options in Vestibular Migraine. Curr Treat Options Neurol 2014;5:257.
16. Sohn J-HJBn. Recent Advances in the Understanding of Vestibular Migraine. Behav Neurol 2016;2016:1801845.
17. Lapira AJH. Vestibular Migraine Treatment and Prevention. HNO 2019;67:425–8.
18. Lempert T, von Brevern MJNC. Vestibular Migraine. Neurol Clin 2019;37:695–706.
19. Nowaczewska MJNiNP. Vestibular Migraine—An underdiagnosed Cause of Vertigo. Diagn Treat 2020;54:106–15.
20. Vyawahare A, Chakole SJJoPRI. Vestibular Migraine in Adolescents. J Pharm Res Int 2021;33:2013–9.
21. Teelucksingh S, Murali Govind R, Dobson R, Nelson-Piercy C, Ovadia CJIJoWsH. Treating Vestibular Migraine when Pregnant and Postpartum: Progress, Challenges and Innovations. Int J Womens Health 2023:321–38.

How to cite this article: Khan S, Agrawal R, Nivsarkar S, Sikdar A, Phatak S. Is Acetazolamide an Effective Drug for Vestibular Migraine? Ann Otol Neurotol. 2025;6:e002. doi: 10.25259/AONO-2024-1-(206)