

The Effectiveness of Selective Serotonin Reuptake Inhibitors for Prevention of Vestibular Migraine and Its Effect on the Quality of Life

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Abstract

Objective: This study aimed to evaluate the effect of citalopram treatment in patients with Vestibular Migraine.

Method: Three hundred and four patients with VM included in the study. 152 patients were treated with Citalopram, and 152 patients were treated with Amitriptyline for six months. Scores of Dizziness Handicap Inventory (DHI) questionnaire and number of vertigo attacks were compared for two groups.

Results: After treatment, the DHI scores decreased from $52,26 \pm 20,19$ to $12,29 \pm 8,93$ and from $55,12 \pm 9,58$ to $24,02 \pm 9,45$ ($p < 0,001$), the number of vertiginous attacks decreased from 4 to 0,4 and from 4 to 1 ($p < 0,001$) in Citalopram and Amitriptyline groups, respectively.

Conclusion: According to our findings, citalopram treatment decreases the frequency and severity of attacks and increases VM patients' quality of life.

Keywords: Vestibular Migraine; Citalopram; Vertigo

Introduction

Vestibular Migraine (VM) has been described as an episodic form of vertigo associated with migrainous symptoms. VM is the most common cause of recurrent spontaneous vertigo episodes. The reason for the difficulty in diagnosis is that the disease's signs and symptoms show a wide spectrum [1]. Patients may have episodic vertigo attacks due to spontaneous or positional vertigo, dizziness, head movements, or visual stimuli. It has a strong association with anxiety, depressive disorders, and psychiatric diseases. Since the symptomatology is quite different, diverse treatments are applied in otoneurology clinics. VM should be considered after BPPV (benign paroxysmal positional vertigo) in patients with vertigo-dizziness [2].

The prevalence of VM is 2.7%, and its 1,5 to 5 times more common in women [3]. Most of the patients are in the middle age group. Despite its high prevalence, the diagnose is exceedingly difficult.

Since a headache or other migrainous symptoms do not always accompany vertigo, the diagnostic criteria must be clearly defined. Diagnostic criteria were described by Neuhauser et al. in 2001 [4]. Barany Society and International Headache Society made a comprehensive definition of the disease in 2012 [5]. The diagnosis is made by the symptoms described by the patient and excluding other potential causes (Table 1).

Table 1: Diagnostic Criteria for Vestibular Migraine (Consensus Criteria of the Barany Society and the International Headache Society – 2012)

<i>Vestibular Migraine</i>
A. At least five episodes with vestibular symptoms of moderate or severe intensity, lasting 5 minutes to 72 hours
B. Current or previous history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD)
C. One or more migraine features with at least 50 % of the vestibular episodes: headache with at least two of the following characteristics: one sided location, pulsating quality, moderate, or severe pain intensity, aggravation by routine physical activity, photophobia and phonophobia visual aura
D. Not better accounted for by another vestibular or ICHD diagnosis.
<i>Probable Vestibular Migraine</i>
A. At least five episodes with vestibular symptoms of moderate or severe intensity, lasting 5 minutes to 72 hours
B. Only one of the criteria B and C for vestibular migraine is fulfilled (migraine history or migraine features during the episode)
C. Not better accounted for by another vestibular or ICHD diagnosis.

VM's underlying pathophysiology is not fully understood; most of the hypotheses have been made based on migraine information. The connections between the vestibular nuclei in BS and the structures that modulate the trigeminal nociceptive inputs may play a role in VM pathogenesis. It has been speculated that some neurotransmitters (dopamine, serotonin, noradrenaline) involved in the pathogenesis of migraine are also involved in VM pathogenesis.

There is no firmly accepted curative or preventative method for treatment. Prophylactic medications and treatments used for classical migraine have been adapted to VM [6]. However, there is no evidence that antimigraine therapy can cure VM. Various treatments have been proposed for prophylactic treatment: beta-blockers, calcium channel blockers, antiepileptic drugs and tricyclic antidepressants [7].

Table 2: Frequency of vertigo attacks and mean total DHI (Dizziness Handicap Inventory) scores between groups before and after treatment (istt: independent sample t test).

	Group 1 (citalopram group)n=152117 female (77 %), 35 male (23 %)average age: 34 (24-58)		Group 2 (amitriptyline group)n= 152112 female (65 %), 40 male (35 %)average age: 36 (22-56)		
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	
Number of vertigo attacks / month	4	0,4	4	1	p<0,001 ^{istt}
Mean total DHI score	52.26±20.19	12.29±8.93	55.12±9.58	24.02±9.45	p<0,001 ^{istt}

Selective serotonin reuptake inhibitors (SSRIs) are used in first-line therapy to treat depression and have made significant therapeutic progress in psychopharmacology. The treatment principle is to inhibit neurotransmitter reuptake. By blocking the serotonin presynaptic reuptake pump in somatodendritic auto-receptors and axons, they increase the serotonin effect. First, serotonin level rises only in the somatodendritic area. As the level increases, neuronal impulse current increases, and serotonin release is stimulated at the axon terminal. Consequently, serotonin concentration increases in the synaptic cleft. All SSRIs are serotonin agonists. Neurons containing serotonin in the human brain are highly localized in the brainstem and spinal cord. These neurons send their axons to terminals containing serotonin in every region of the brain. Thus, serotonin increases in critical brain areas. Because of this distribution, the dysfunction of serotonin neurons is associated with many diseases. Therefore, serotonin active drugs can have many clinical effects. Besides depression, SSRIs are also used to treat anxiety, pain disorders, panic disorders, obsessive-compulsive disorders, alcoholism, obesity, and migraine. It has been suggested that serotonin also modulates the homeostasis between dopamine-noradrenaline and GABA. SSRIs are high lipophilic molecules and accumulate in fat-rich tissues such as CNS cells. They are primarily metabolized in the liver by the cytochrome p-450 enzyme system. SSRIs are used for preventing VM attacks. However, there is insufficient data regarding the efficacy in the prophylaxis of VM.

Citalopram is an SSRI with an antidepressant effect in controlled clinical studies. Citalopram also has effects on α -1-adreno-receptors and histamine H1 receptors. It is the most reliable SSRI in terms of drug interactions. The elimination half-life is 36 hours. This study aimed to evaluate the effect of SSRI treatment in patients with VM. In this study, the effect of citalopram was compared with amitriptyline in vestibular migraine patients. This is the first trial evaluating citalopram as a prophylactic medication in adults with definitive VM.

Materials and Methods

The study was approved by the University Ethics Committee (XXXX). Informed consent of all participants was obtained in written form. Three hundred and four patients who applied to the ENT clinic and were diagnosed with definite vestibular migraine according to the Barany Society and International Headache Society criteria were included in this study. The effectiveness of SSRI - citalopram in prophylaxis and quality of daily life in patients with vestibular migraine was investigated. Patients with normal neurological examination findings and three or more vestibular migraine attacks per month were included in the study. Patients under 18 years of age, patients who received any treatment for their vestibular symptoms or received a medication that would affect the treatment results, and patients who had previously used SSRIs were not included in the study. ENT and neurology examinations were applied to the patients, VHIT and VNG tests were performed. Typical history according to BS and IHS criteria was deemed sufficient for diagnosis. Patients were randomly divided into two groups according to the admitting to the study, first patient for to first group, second patient for the second group, third patient for the first group and etc. 152 patients in the first group received citalopram treatment, and 152 patients in the second group received amitriptyline treatment. SSRI - citalopram (Cipram® 20 mg, Lundbeck Ilac, Istanbul, Turkey) was given as a single dose of 20 mg per day for six months, and amitriptyline (Laroxyl® 10

mg, Deva Holding AS, Istanbul, Turkey) was given as a single dose of 10 mg per day for six months. Dizziness Handicap Inventory (DHI) questionnaire was applied to the patients before and after treatment, and the number of vertigo attacks were evaluated before and after treatment. After six months of treatment, the patients were re-evaluated. Vestibular attack number, duration and DHI scores were compared. The disability degree was tried to be determined with DHI. DHI is a symptom-specific questionnaire. In DHI, there are a total of 25 questions questioning the physical, sensory and functional disability caused by dizziness. Answers scored as follows: no: 0 points, sometime: 2 points and yes: 4 points. Total score between 0-30 points is considered low, between 31-60 points as medium, and between 61-100 points as high. The high score indicates that the dizziness of the patient has a severe effect on his/her life. Independent sample t test was applied for statistical evaluation. The significant difference between scores before and after treatment indicates the effectiveness of the treatment.

Data Availability: the data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results and Analysis

In the citalopram group, there were 152 patients, 117 were female (77 %), and 35 were male (23 %). The average age was 34 (24-58). In the amitriptyline group, there were 152 patients, 112 were female (65 %), and 40 were male (35 %). The average age was 36 (22-56). The average number of vertigo attacks before treatment was 4/month for both groups. After treatment, the average number of attacks 0,4/month in citalopram group, and 1/month in amitriptyline group. The difference was found to be statistically significant ($p<0,001$). Treatment success was evaluated as no attacks in two months or a reduction of more than 50 % for attacks. Accordingly, success was achieved in 133 patients in citalopram group (88 %). No attack was observed in 121 patients (80 %). More than 50 % reduction was achieved in 12 patients (9 %), and moderate control was achieved in 13 patients (9 %). Less than 25 % improvement (minimal control) was achieved in only four patient (3 %). In amitriptyline group, the success rate was 65 % (98 patients). No attack was observed in 80 patients (53 %), and more than 50 % reduction was achieved in 18 patients (12 %). In citalopram group, mean total DHI score before treatment was 52.26 ± 20.19 , it was 12.29 ± 8.93 after treatment. In amitriptyline group, the scores were 55.12 ± 9.58 and 24.02 ± 9.45 , respectively. The difference between the two groups provided with treatment was statistically significant ($p<0.001$) (Table 2). In citalopram group, fatigue and insomnia were observed in two patients (6 %), and there was no patient discontinued the treatment due to drug side effect.

Discussion

All dizziness forms (rotational vertigo, positional vertigo, imbalance, dizziness, and Meniere's disease) are more common in patients with migraine than in the general population [8-9]. Vertigo is observed in up to 50% of patients during headache-free periods. There is no definitive accepted definition for these patients. Definitions of migraine-associated vertigo, migraine-related vestibulopathy, migrainous vertigo, vestibular migraine (VM) were used. Dieterich and Brandt are the first to use the VM definition [10]. VM is the most common cause of spontaneous episodic vertigo and is the second most common cause of vertigo [11]. Lifetime prevalence in the general population is 1 %. It is seen with spontaneous or positional vertigo attacks; attacks can last for seconds-hours to days. Diagnosis is made by a description of symptoms and exclusion of other possible causes. There is no objective diagnostic test or biomarker. Barany Society and International Headache Society have published diagnostic criteria⁵. Pathophysiology is not clear; many authors think VM is derived from migraine. The comorbid psychiatric disease was found in 50% of VM patients [12]. Anxiety, panic attacks, phobic behaviors, and depression are common in these patients [13].

It is not easy to evaluate the response to treatment due to fluctuation in symptoms in VM. Improvement in symptoms may be due to treatment or the natural course of the disease. To decide this, the duration of treatment must be long. However, in this case, patients have problems in compliance with treatment due to drug side effects. There are few studies on VM treatment in the litera-

ture. VM therapy is mostly based on data from observational studies. Pharmacological treatment applied to VM patients is divided into two; 1) treatment of the attacks and 2) prophylactic treatment to reduce the frequency and severity of attacks. Patients with migraine need both treatments. Preventive therapy is used to reduce the frequency, severity, and duration of attacks. Drugs used to prevent VM attack; beta-blockers, calcium antagonists, anticonvulsants, antidepressants, selective 5-HT₁ agonists, serotonin antagonists, NSAIDs, riboflavin, coenzyme Q10, magnesium, angiotensin-converting-enzyme (ACE) inhibitors, calcitonin gene-related peptide, monoclonal antibodies, SSRIs, and SNRIs. However, there are very few randomized controlled studies to evaluate the prophylactic effects of these drugs. In the literature, there is no definite consensus on the evaluation of the effect of treatment. The frequency of attacks, duration of symptoms, and DHI scores were used in Çelik's study [1]. To evaluate the effect of drugs used in prophylaxis, treatment should continue for at least six months. However, patients' compliance with preventive treatments is low. Efficacy, tolerability, patient priority, purchasing power, and comorbid conditions are factors that should be considered in treatment selection. Because of the side effects of these drugs, patients discontinue the treatment early and show resistance to a new drug. For this reason, the drug to be applied should be selected very carefully and should be given at the optimum dose.

Byun et al. compared the efficacy of treatments for VM prophylaxis. In this analysis, studies using antiepileptics, calcium channel blockers, tricyclic antidepressants, beta-blockers, SSRIs, and SNRIs, and vestibular rehabilitation were evaluated [14]. With all treatment options, there was an improvement in DHI scores and vestibular attack frequency (number of attacks per month), but none of these treatments was superior to others. According to Byun's meta-analysis, the most improvement in DHI was seen with beta-blockers (propranolol), SNRI (venlafaxine) took the second place. Studies using calcium channel blockers (flunarizine, cinnarizine, lomerizine) were also evaluated in the same analysis, and improvement was reported in all parameters, including DHI and vestibular attack frequency.

Antiepileptic drugs are also used in prophylaxis. These drugs modulate neural systems through different mechanisms. Byun reported that with valproic acid, DHI scores improved, and the frequency of vestibular symptoms decreased, but only the frequency of vestibular symptoms decreased with lamotrigine [14]. However, due to the side effects of these drugs, their use has been limited. Bayer et al. reported that in the study in which they used metoprolol for VM prophylaxis, the frequency of vertigo attacks decreased significantly, but it was not superior to placebo. Besides, they stated that the treatment benefit evaluated by the DHI total score was low. Çelik et al. stated that the number, severity, and duration of attacks decreased, and the quality of life increased with propranolol treatment in VM patients [1].

SSRIs and SNRIs have replaced other drugs in both migraine and vestibular migraine prophylaxis in recent years. SSRIs and SNRIs block the reuptake of serotonin and norepinephrine and are widely used in anxiety and depression. Serotonin has been shown to have an important role in migraine pathophysiology [15]. Serotonin levels are low during attacks, and there is a temporary increase during attacks. Decreased serotonin levels may decrease the migraine attack trigger threshold for internal or external stimuli [16]. Serotonin changes reactions in movement-sensitive neurons in the central nervous system [17-18]. It has been speculated that serotonin regulates neural activity in the central nucleus of Amygdala, which is linked to the central vestibular nuclei and autonomic centers in the brainstem [19]. In animal studies, norepinephrine has also been shown to be particularly important in the inhibition of pain [20]. Vasoactive neurotransmitters (serotonin 1B and 1D) in the perivascular afferent terminations of the trigeminal nerve in the labyrinth are involved in migraine's pathogenesis. Serotonin and norepinephrine play a role in regulating neuropathic pain such as migraine, they regulate the activity of central and peripheral vestibular neurons and may be involved in VM pathogenesis [21-22]. Serotonin and norepinephrine are also important neurotransmitters in the pathophysiology of anxiety and depression. The comorbid psychiatric disease was found in 50% of VM patients [12]. Central vestibular and afferent interoceptive projections network (serotonergic pathway) and coeruleo-vestibular network (noradrenergic pathway) may explain some associations in the connection between vertigo-anxiety [23]. For these reasons, it is thought that drugs that affect serotonin and norepinephrine levels (SSRIs and SNRIs) may be effective in migraine prophylaxis. These drugs target serotonergic and noradrenergic systems and the nociceptive properties of these systems. Among the SNRIs, venlafaxine, duloxetine, and milnacipran have been the most studied molecules [24-25]. Studies are reporting that venlafaxine is effective in preventing migraine [26]. Some authors re-

commend venlafaxine as the first-line treatment because they consider strong psychiatric comorbidity in VM. SSRIs increase serotonin levels in the synaptic cleft. Among the SSRIs, fluoxetine, sertraline, and paroxetine were studied in migraine prophylaxis, and the most studied molecule was fluoxetine. Animal studies have shown that fluoxetine is effective on central opioid receptors as well as on serotonergic pathways. SSRIs have been the most preferred antidepressant in treating depression due to their fewer side effects and relatively lower toxicity.

SSRIs and SNRIs are better tolerated than other antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors, benzodiazepines), are easy to use, have high dose confidence intervals, no need to monitor serum levels, and have fewer side effects [13]. Wang et al. evaluated the effect and tolerability of SNRIs in VM prophylaxis in their meta-analysis study. They analyzed the results of a total of 418 patients in 6 studies. They found that venlafaxine had a distinct advantage over other agents in improving DHI scores and decreasing the frequency of vertigo attacks. They decided that SNRIs were clinically safer than placebo in VM prophylaxis and could be recommended in VM with psychiatric patients [27]. In Cochrane study, Banzi reported that SSRI-SNRIs used in migraine prophylaxis were better tolerated than amitriptyline and found that it was significantly superior to placebo in reducing the frequency of migraine [28]. Tarlacı reported that three-month escitalopram treatment was successful in migraine headache prophylaxis [26]. Staab reported that SSRI use in patients with dizziness and psychiatric symptoms was successful compared to other treatments in reducing migraine headache and dizziness complaints [13]. Studies are showing that the use of SSRIs decreases vertigo attacks in Meniere's disease [29]. It has been reported that SSRIs are beneficial in the treatment of panic disorders and chronic subjective dizziness (CSD) that cause vestibular symptoms [13]. SSRIs have been shown to reduce PPPD (persistent postural perceptual dizziness) symptoms [30]. According to Staab's study, symptoms and DHI scores decreased significantly with sertraline in patients with CSD. According to Staab, sertraline may affect serotonin-dependent systems in the brain that control mood and anxiety [19]. Some clinical studies conducted in recent years suggested that the antimigraine and antivertigo effects of SSRIs and SNRIs are independent of their antidepressant activities [26]. The mechanism of action of these drugs is still unknown.

Side effects of the drugs used in vestibular migraine prophylaxis may cause patients to discontinue the treatment. It has been reported that treatment was discontinued due to side effects in 24% of patients in whom topiramate was used and in 13% of patients in whom nortriptyline was used in prophylaxis [7,31]. Patients may discontinue treatment with propranolol due to bronchospasm, hypotension, and syncope, and calcium channel blockers due to weight gain, somnolence, gastrointestinal upset, and valproic acid due to nausea, somnolence, and indigestion [32].

Compared to placebo, patients are more likely to quit SNRIs because of their side effects [27]. On the other hand, SSRIs have advantages such as good tolerability, easy prescription, and low complication rates. 20% of the patients may have temporary nausea, dizziness, fatigue, and mental slowing, but these side effects are not enough to require discontinuation of the drug as in SNRIs. Sobieraj et al. found the rate of side effects close to placebo with SSRIs while reported more side effects with SNRIs [33]. Moja reported that there was no difference in the rate of discontinuing treatment in migraine patients due to side effects between SSRIs and placebo, and SSRIs were better tolerated than tricyclic antidepressants [34].

In the present study, the difference between the vertigo attack scores between two groups was statistically significant (88 % for the citalopram group and 65 % for the amitriptyline group). Also, the difference between the DHI scores evaluated before and after treatment was significantly significant. With these prominent results and the lower side effects, citalopram can be used as a first choice treatment for vestibular migraine patients.

Conclusion

This study is the first to evaluate the effect of citalopram on VM prophylaxis and DHI scores to the best of our knowledge. Our results showed that SSRIs are clinically safe and effective for the prophylaxis of VM. According to our findings, citalopram treatment decreases the frequency and severity of attacks and increases VM patients' quality of life. SSRIs' central effects on serotonin's level

may change the reactions of motion-sensitive neurons in vestibular nuclei and autonomic centers in the brainstem. However, randomized, double-blind, placebo-controlled studies must be done to assess SSRIs' effect in the prophylaxis of VM. SSRIs such as citalopram can be used as the drug of choice in first-line treatment in VM prophylaxis because they both reduce the frequency and severity of attacks and have fewer side effects.

Conflict of Interest

None

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