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Preventive effect of citalopram on migraine headaches: a double-blinded randomized clinical trial

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Abstract

Objective: The aim of this study was to evaluate the effect of citalopram on the prevention of migraine headaches as compared to placebo.

Materials and Methods: This double-blind randomized clinical trial was conducted on patients diagnosed with migraine headaches based on the guidelines of the International Headache Society. 226 patients who met inclusion criteria were randomly allocated to two control and intervention groups. The treatment group was treated with citalopram 30 mg daily for two months and the control group was given placebo the same amount as the treatment group. All the patients were assessed at the beginning of the trial and after 1 month and 2 months and the frequency, severity and duration of their headaches were documented using the Visual Analogue Scale (VAS) and Behavioral Rating Scale (BRS-6). Data were analyzed using SPSS v.16 software.

Results: Even though initially there was no statistically significant difference between the two groups regarding the severity, duration and frequency of episodes of migraine ($P>0.05$), the same parameters had drastic changes after the first and second months of treatment and the differences between the citalopram and placebo group regarding severity, duration and frequency of migraine episodes were statistically significant ($P<0.05$).

Conclusion: The outcome of this experiment showed that citalopram, a serotonin uptake inhibitor (SSRI), possibly through a serotonin-lowering mechanism, results in less exposure of the CNS to this agent, leading to less frequent, less severe and shorter migraine episodes. This medication appears to be useful as a preventive drug used to treat and maintain episodes of migraine headaches, especially in individuals suffering from both migraine headaches and clinical depression.

Keywords: Migraine headache, Citalopram, Serotonin uptake inhibitors, Prevention

1. Introduction

More than 90% of individuals at some points in their life suffer from episodes of headaches, which makes it one of the most common complaints that patients have when visiting their physician. The most common underlying condition resulting in headaches is due to recurrent episodes of migraine (1-3). Biochemical markers and radiologic assessments rarely help with the diagnosis, therefore, the diagnosis is mainly based upon thorough history taking from the patient and ruling out other possible causes (4). Heredity plays a substantial role in pathogenesis of

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migraines and first-degree relatives of diagnosed patients have a higher probability of suffering from this disease (5). The incidence of migraine headaches in the United States is 17.6% among women and 5.7% among men and peaking at the age group of 35-45 in both genders (6), most commonly starting in the second decade of the patient's life and 90% will experience the first episode of migraine by the age of 40 (7). The incidence rate is higher in low-income societies (6). A study has reported the incidence rate of migraines in Iran to be 36.7% among women and 21.6% among men (8). Generally, each migraine episode lasts anywhere between 4 to 7 hours, and the recurrent nature of the illness directly influences the physical and psychological aspects of the patient, substantially decreasing the individual's quality of life, during daily activities, work hours, etc. Therefore, the role of proper diagnosis and treatment is crucial (9-11). Migraine sufferers often have a lower quality of life compared to the general public, and those with sever migraine have even worse conditions. The inability to perform daily activities results in impaired social and emotional well-being. Feelings of inadequacy and helplessness in reducing the pain results in more cognitive mistakes and a lowered sense of competence. Moreover, misconceptions about migraine headaches result in lowered mood and in some cases even affects the patient's self-image and confidence (11-13). Migraine's treatment plans are further categorized into two groups: symptomatic relief and prevention (14). Medication recommended for prevention of migraine headaches include tricyclic antidepressants (TCA's), Selective Serotonin Reuptake-Inhibitors (SSRI's) and Serotonin-Norepinephrine Reuptake-Inhibitors (SNRI's) (15, 16). Choosing the suitable drug from these pharmaceutical groups depends upon several factors such as undesired side effects of the drug and comorbidities of the patient. Therefore, thorough assessment of the patient is imperative (17). Citalopram is an anti-depressant drug belonging to the SSRI group which is commonly used for various conditions.

In 2013, migraine headaches were the 7th leading contributor of YLDs (Years Lived with Disability) with a reported 28,000 YLDs (6, 18, 19) Moreover, this disorder can independently operate as a risk factor for other disorders such as Multiple Sclerosis or stroke (20-22). Considering the importance of the matter at hand and the insufficiency of similar studies has led us to conduct this clinical trial with the goal of assessing the usefulness of citalopram as an SSRI in preventing migraine headaches.

2. Materials and Methods

This study was designed as a double-blinded randomized clinical trial (IRCT registration number: IRCT20161103030680N9) to be performed on patients visiting the neurology clinic of Mostafa Khomeini General Hospital with complaints of headache. The patients went through a thorough neurological examination at first, and then those were chosen from among both genders aged 18 to 45 years who were diagnosed with migraine based on the International Headache Society (IHS) guidelines and criteria (23). Prior to the visit to the neurology clinic, patients had recurring headaches for at least 6 months and at least three episodes per month and each episode lasted a minimum of 30 minutes. Only the patients who had not received any form of treatment or prevention were chosen to participate in the study.

Other patients suffering from other forms of headaches such as tension headaches and headaches linked to sinus problems, women suffering from menstruation-related migraines, patients with active peptic ulcers and other severe gastrointestinal problems, renal failure patients, patients with a history of severe depression or asthma, patients suffering from heart problems, patients using any form of analgesic drugs, beta blockers, TCAs, anticonvulsants, Mono-amine Oxidase Inhibitors (MAO), NSAIDs, topical anesthetics, corticosteroids or botulinum toxin, patients with sensitivity to similar drugs and finally those without consent were excluded from the selection. All the information regarding the goal and process of the trial, benefits of the possible treatment and possible side effects were informed to all the patients and the costs of treatment were fully covered by the researchers. The researchers were committed to the ethical guidelines of the Declaration of Helsinki and approval for the study was obtained from the Institutional Review Board at Shahed University. Signed informed consents were also obtained from all participants.

The final pool of selected patients consisted of 226 patients (Figure 1). Available samples were marked by a number and then are assigned to two control and intervention groups randomly by use of the chart of random numbers alternatively. The selection of first patients is by lottery. The treatment group treated with citalopram 30 mg daily for two months with a slow increase in dosage over time and the control group given placebo the same amount as the treatment group. Neither the patients nor the researchers/doctors had any information regarding the status of the placebo or active agent of the drugs administered to the groups. In case of a severe migraine headache, the patient would receive an analgesic based on standard treatment protocols for the acute phase. All the patients were assessed at the beginning of the trial and after 1 month and 2 months and the frequency, severity and duration of their headaches were documented using the Visual Analogue Scale (VAS) and Behavioral Rating Scale (BRS-6) (24). The data was then put in information forms and at last, put in SPSS software (SPSS v.16, IBM SPSS, USA) and underwent Chi-Square test and independent t test. Significant value for all analyses were appointed at $P<0.05$.

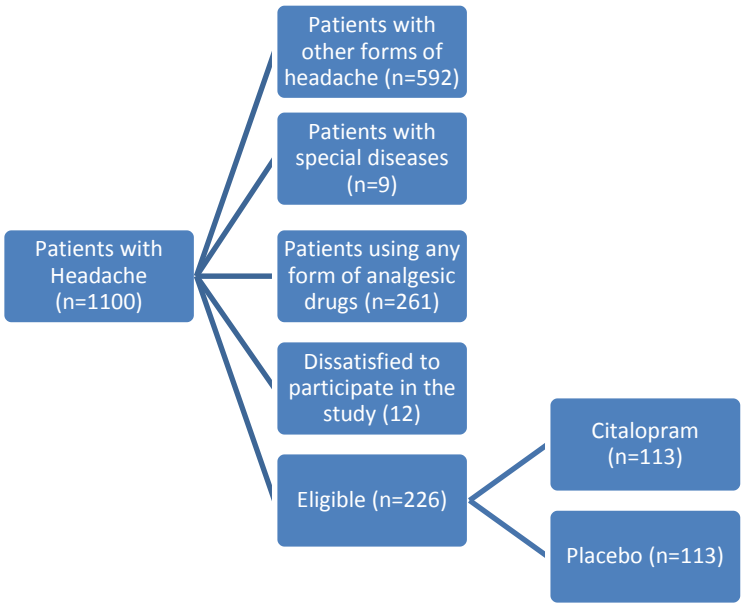

Figure 1: Sampling flowchart

3. Results

After equalizing gender and age variables, the mean age in the placebo group was calculated to be 31.97±8.82 and in the Citalopram group was 32.61±8.01 and the difference between the two groups were statistically insignificant (P>0.05). 24 patients (31.6%) in the placebo group and 50 patients (32.9%) in the Citalopram group were men and 52 patients (68.4%) in the placebo group and 102 patients in the Citalopram group (67.1%) were women. The difference between gender distribution among the two group were statistically insignificant (P>0.05).

Even though initially there was no statistically significant difference between the two groups regarding the severity, duration and frequency of episodes of migraine (P>0.05), the same parameters had drastically changed after the first and second month of treatment and the differences between the Citalopram and placebo group regarding severity, duration and frequency of migraine episodes were statistically significant (P<0.05) (Table 1 and Figures 1-2).

Table 1: The quality of migraine attacks among patients in different phases of treatment

		Initial Phase (Pre-Trial)		First Phase: 1 month after treatment initiation		Second Phase: 2 months after treatment initiation	
Index	Group	Mean±SD	P Value	Mean±SD	P Value	Mean±SD	P Value
Pain Duration (hour)	Placebo	16.96±15.38	0.493	15.13±12.57	0.0001		
	Citalopram	15.66±12.36		9.35±5.37			
Frequency of Episodes	Placebo	7.82±2.78	0.772	7.87±3.71	0.0001		
	Citalopram	7.94±3.19		3.47±3.62			
VAS	Placebo	64.01±19.45	0.952	61.63±19.06	0.0001	61.17±21.82	0.0001
	Citalopram	63.84±20.34		46.68±22.19		29.67±24.64	
BRS-6	Placebo	3.59±1.08	0.966	3.51±1.05	0.0001	3.49±1.20	0.0001
	Citalopram	3.60±1.12		2.72±1.26		1.70±1.50	

SD: Standard Deviation, VAS: Visual Analogue Scale, BRS: Behavioral Rating Scale

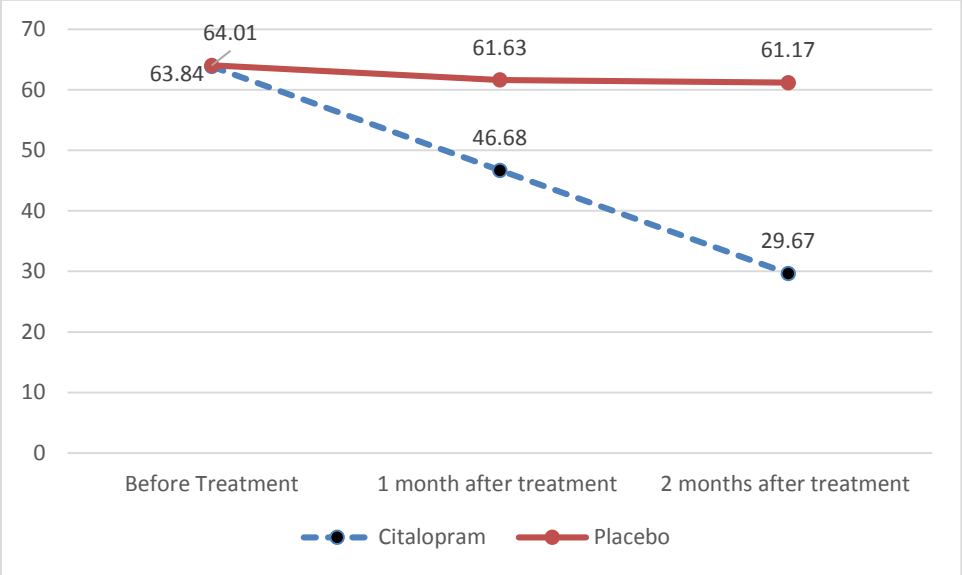

Figure 1: VAS changes before, 1 month after and 2 months after treatment

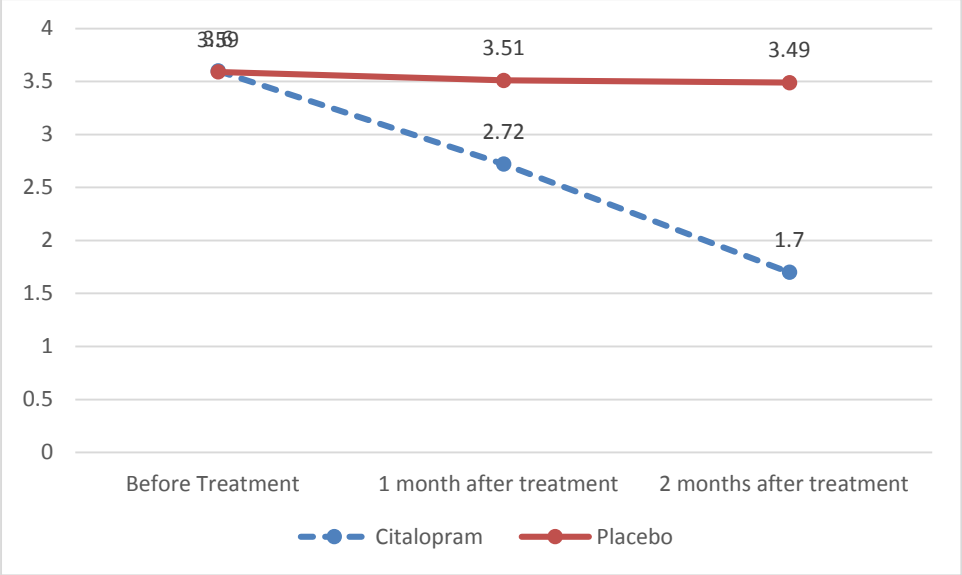

Figure 2: BRS-6 changes before, 1 month after and 2 months after treatment

4. Discussion

This study was conducted in order to assess the preventative effectiveness of Citalopram on migraine headaches. The results achieved through this experiment show that administering Citalopram for 1 and 2 months will result in less frequent, less severe and shorter migraine episodes and none of the participants suffered from any serious side effects.

Even after years and years of research, the exact cause of migraines still eludes us (25). It appears so that serotonin in the CNS plays a significant role in the pathogenesis of this disease, despite the fact that the reason behind these changes in the brainstem and the function of serotonin is not yet well understood (26). During a migraine episode, serotonin levels decrease in the brain. Other studies show that serotonin promotes the Trigeminal nerve to produce a certain kind of neuropeptide which moves to the outer layers of the brain and at those sites cause a vasodilation after which inflammatory response ensues, and an episode of migraine occurs (25, 26). Treatment for migraine episodes is divided into acute phase medication and preventative pharmaceuticals (14). Various drugs are used to prevent migraines. Considering serotonin's role in the pathogenesis of

this illness, possible groups of candidates for preventative treatment of migraines may include serotonin antagonists and SSRIs (27). Citalopram is an SSRI drug aimed at relieving symptoms of depression, panic disorder and general anxiety disorder (GAD). Moreover, this medication is sometimes used to treat diabetic neuropathy and premature ejaculation and has a lower rate of drug cross reaction and lower risks in the events of an overdose compared to other SSRIs (28). Despite the usage of SSRIs in treating migraine headaches, there is a lack of studies conducted on the effectiveness of citalopram on treating this illness.

Ittner reported a case who had been suffering from both migraine headaches and clinical depression and had started receiving Sumatriptan and Citalopram which resulted in a favorable outcome (29). Rampello et al assessed the effectiveness of Citalopram and Amitriptyline both together and alone on incidence of migraine headaches which resulted in the combination of both drugs carrying the most favorable effectiveness in preventing migraine headaches (30). Even though in this study Citalopram's effectiveness was assessed individually, the results were still favorable. All in all, both studies mentioned have had similar outcomes.

Conclusion

The outcome of this experiment showed that Citalopram, an SSRI, possibly through a serotonin-lowering mechanism, results in less exposure of the CNS to this drug leading to less frequent, less severe and shorter migraine episodes. This medication appears to be useful as a preventative drug used to treat and maintain episodes of migraine headaches, especially in individuals suffering from both migraine headaches and clinical depression.

Conflict of Interest:

The authors declared no conflict of interest.

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