Journal of University of Babylon for Pure and Applied Sciences, Vol. (28), No. (3): 2020
Online ISSN: 2312-8135, Print ISSN: 1992-0652

Low Dose of Pizotifen in Migraine Prevention: A Comparison with Topiramate

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Article Information
Submission date: 18 /11 / 2020
Acceptance date: 1 /12 / 2020
Publication date: 31/ 12/ 2020

Abstract

Background & Objective: Pizotifen is an alternative option for prophylactic treatment of migraine headache. This study aims to compare the efficacy and safety of pizotifen with topiramate; one of the most-widely used drugs in migraine prevention. Methods: This was a single blind, randomized, parallel-group study. After a 4-week baseline evaluation, patients with episodic migraine were randomly assigned to get either to piramate or pizotifen for a period of 12 weeks. Patients were asked to fill a headache diary through the study. Headache characteristics and the possible side effects were evaluated throughout and at the end of trial. Results: Sixty patients aged 20 to 49 were recruited to the study. With both drugs, the frequency, intensity and duration of headaches were significantly reduced ($p < 0.05$). Except for headache duration, pizotifen was significantly superior to topiramate in the headache parameters assessed. Total reported side effects were initially higher inpatients who received pizotifen (37 vs. 22; P= 0.038); however, persistent side effects were lower for pizotifen (6 vs. 10; P= 0.22).Conclusions: The results of this study suggest that pizotifen is a safe and effective drug in migraine prevention.

Keywords: Migraine Prevention, Pizotifen, topiramate ز

Introduction

Migraine is a chronic episodic disorder characterized by recurrent headache mostly with nausea, vomiting and sensitivity to light and noise. It is the most common headache diagnosis in neurological services in Asia and is among the top 10 most disabling disorders worldwide.[1,2] However, it still remains under diagnosed and under treated. About 15–18% of women and 6% of men suffer from migraine.[3] Many patients require management of individual migraine episodes, as well as prophylactic treatment to prevent future episodes.[4]

Frequency and severity of attacks are subject to marked inter-patient and intra-patient variability. The median attack frequency is 1.5 per month although 10 percent of patients have weekly attacks. Nearly 38% of migraines need prophylactic treatment;

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Online ISSN: 2312-8135, Print ISSN: 1992-0652

nevertheless, utilization of prophylaxis continues to be low and only 3-13%of patients receive prophylactic treatment,5thismay be as a result of limited efficacy, a difficult dosage schedule or unpleasant side effects of available options; and so there is a need for an efficient prophylactic treatment with minimal side effects.6 Migraine prophylaxis involves avoidance of trigger factors, lifestyle advice followed by consideration of medications. Adequate prophylaxis is necessary to reduce the frequency and severity of migraine attacks and thereby improve the quality of life and prevent medication overuse headache.[7]

Topiramate blocks voltage-sensitive sodium channels and voltage-activated calcium channels, inhibits glutamate release, and increases GABA levels.[8] It significantly reduces the mean monthly frequency of migraine in patients receiving 50-100 mg per day.[9] The most common adverse effect with to piramate is paresthesia, followed by fatigue, weight loss, somnolence, psychomotor slowing, language problems, renal calculi, and secondary angle closure glaucoma. To piramate is similar in efficacy to propranolol and valproate.[10]

Pizotifen is a serotonin antagonist.[11] There are several studies which have shown the usefulness of pizotifen for migraine prevention.[12,13,14] Nonetheless, because of side effects of drowsiness and weight gain, it is not a first choice prophylactic agent, and is usually used as an alternative option when other medications are ineffective.[15,16] The aim of this trial was to compare the efficacy and safety of low dose pizotifen with topiramate. The primary endpoint was a decrease in headache frequency at the end of a16-week study period.17 Correct diagnosis and appropriate prescribing are essential to reduce the individual and economic impact of this disorder.

Methods

This randomized single-blind clinical trial without placebo control was carried out on patients with episodic migraine who were referred to the neurology clinic of Al Sadic teaching hospital, Babylon, Iraq, 2018. The duration of study was 12 weeks, consisting of a 4-week period for baseline assessment and a subsequent 8-week period in which intervention was given. Patients with episodic migraine who were seeking prophylactic treatment were included in a primary evaluation according to International Headache Society (IHS)criteria.18 After a comprehensive assessment for inclusion and exclusion criteria, eligible patients who gave informed consent were recruited to the study. A research assistant who was blind to the type of intervention made all evaluations.

The exclusion criteria were:

1. Anyhyper sensitivity to topiramate or pizotifen;
2. History of mental disorders;
3.Females who were pregnant, breast feeding,or planning for pregnancy;
4. Treatment with topiramate or pizotifen in the last three months before the study;
5. Concurrent prophylactic treatment for migraine;
6. Patients with headache disorders other than episodic migraine headache;
7. Suspicious to medication overdose headache;
8. Use of any drugs with potential preventive effects in migraine headache within three months before the study.

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Online ISSN: 2312-8135, Print ISSN: 1992-0652

The inclusion criteria were:

1. Male or female with age of entry between 19 to 50 years;
2. Age of migraine onset should be less than 50 years old;
3. Willing and able to be available in the following three months;
4. Migraine headache frequency of 4 to 14 moderate-to-severe at tacks per month during the past three months before the study; Migraine attacks should be separated at least by a one-day headache-free period;
5. History of migraine at least one year before entry;
6. To have signed the informed consent.

The baseline assessment was based on the headache diary completed by the patients during the first eight weeks of the study. The following were recorded:

1-Demographic data; 2- Frequency of migraine headache (attacks/month);3- Intensity of migraine headache measured by a10- point Visual Analog Scale (mean± SD, VAS)19;

4- Duration of migraine headache (mean ± SD);which is the time between starting to cessation of each attack.

After the baseline assessment, patients were randomized to two treatment groups of topiramate(n = 30) or pizotifen (n = 30) for a12-week period. The prescribed dose of topiramate was 25 mg twice a day. Pizotifenwas started as a 0.125 mg bedtime dose. During the baseline assessment and intervention periods, the patients were allowed the use of acute medication as they had used before the study. For observations and outcome measurements, the patients asked to fill in a headache diary through the study. The efficacy of treatment was evaluated by assessing headache parameters during weeks 8 to 12 from randomization relative to baseline assessment. The headache diaries were interpreted by an expert neurologist in migraine(me).The primary endpoint was a reduction in the frequency of migraine attacks, and secondary end points were: (1) Headache intensity (mean±SD, VAS); (2) Headache duration (although it has a low value in parallel clinical trials of migraine prevention 20; (3) Response to treatment, defined as 50% or greater reduction in attacks; (4) Safety as assessed by: Side effects that listed in a diary and were checked at the end of weeks 2,4, 8 and 12 from randomization by a neurologist. For ethical approval, doctrines of current version of the declaration of Helsinki wereobserved.21 The Ethics Committee of Babylon University of medicine approved the study, and the patients were informed regarding the trialed sign and potential side effects.

For statistical Analysis, results are presented as mean ± standard deviation. Computerized data were analyzed using SPSS 18 software. Mann-Whitney, independent T-test, and chi-square tests were used in the statistical analysis. P values of less than 0.05 considered significant.22

Results

Sixty patients enrolled into the study; 67.1% were female. The mean age of entry was 33.4±7.9 years (range = 20-49) and the mean age of migraine onset was 26 ± 6.3 years old. Twenty patients had classic and 40 had common migraines. They had between 4-13 attacks of migraine per month. The treatment groups were similar with

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respect to the migraine characteristics and demographic data. The baseline characteristics of both treatment groups are listed in Table 1. After a 12-week period, a considerable improvement for all headache characteristics was observed within groups compared to the baseline. A statistically significant reduction was observed in headache frequency, intensity and response to treatment for pizotifen compared to topiramate. The change in headache characteristics after interventions is listed in table 2. Regarding safety, 30 patients reported one or more side effects during the study, 18 in the pizotifen group and 12 in the topiramate group. No patients discontinued prophylactic treatment because of adverse side effects. The side effects of topiramate and pizotifen are listed in table 3 and 4. The comparison between common side effects of pizotifen and topiramate is listed in table 5. The most frequently reported side effects of topiramate were increased appetite (9 patients), weight gain (6 patients) and sedation(4 patients). For pizotifen, the most frequently reported side effects were drowsiness (14 patients), dizziness (6 patients), increased appetite (6 patients) and weight gain (5 patients). Reported side effects by pizotifen were lessened as the study progressed and nevertheless, the total reported side effects were statistically higher in patients who received pizotifen (37 vs. 22; P=0.038, independent T test); at the end of trial, persistent side effects were numerically lower for the pizotifen group (6 vs. 10; P= 0.22, Mann-Whitney).

Table 1: Baseline headache characteristics of the study subjects

Baseline characteristics		Topiramate	Pizotifen	P values
Age at entry (mean ± SD, years)		29.8± 7.8 (20-49)	32.7 ± 7.6 (20-48)	0.24*
Age at migraine onset(mean ± SD, years)		24.5 ± 6.4 (17-42)	25.2 ±6.1 (17-38)	0.7*
Migraine history (mean ± SD, years)		5.2±3.5	7.4±6	0.2*
Female		61.8%	52.3%	0.4**
Type of migraine(number)	classic	5	6	0.72**
	common	16	15	
Headache frequency (mean ± SD, attack/month)		8 ± 3.5	9.8 ± 2.8	0.06*
Headache Severity (mean ± SD, VAS)		6.6 ± 2	7.7 ± 1.6	0.2#
Headache Duration (mean ± SD, hour)		14.2 ± 4.4	14.2 ± 4.7	0.9*
Positive family history for migraine		28.5%	33.2%	0.8**
Low or Uneducated		0%	10%	0.5#

SD: Standard Deviation; VAS: Visual Analog Scale.

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The weight gains of more than two kg observed in five patients who received pizotifen and in six patients who received topiramate. Weight gains decreased as the study progressed, and most patients were able to return to theirinitial weight. There was no significant difference between pizotifen and topiramateregarding the side effects of drowsiness, nausea, weight gain and increased appetite. No pathological findings were encountered in the laboratory tests (CBC and LFT).

Table 2: Change in headache characteristics after intervention of the study subjects

characteristics	topiramate	Pizotifen	P value
Headache frequency reduction (mean ± SD, attack/month)	4 ± 2.3	6.7 ± 3.2	0.002*
Headache severity reduction (mean ± SD, VAS)	1.7 ± 1.3	3 ± 1.3	0.002#
Headache duration reduction (mean ± SD, hour)	4.1 ± 3.3	5.2 ± 6.2	NS*
Response to treatment (> 50% fall in headache frequency)	42.7%	81%	0.012#

SD: Standard Deviation; VAS: Visual Analog Scale; NS: not significant
*Independent t-test; #Mann-Whitney

Table 3: Reported side effects in topiramate group

Side effects	End of week 2		End of week 4		End of week 8		End of week 12		Total reported	
	frequency	%	frequency	%	frequency	%	frequency	%	frequency	%
Increased appetite	4	19	8	38.1	8	38.1	5	23.8	9	42.9
Weight gain	2	9.5	3	14.3	4	19	3	14. 3	6	28.6
Sedation	4	19	2	9.5	1	4.8	1	4.8	4	19
Nausea	2	9.5	1	4.8	0	0	1	4.8	2	9.5
Vomiting	1	4.8	0	0	0	0	0	0	1	4.8

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Table 4: Reported side effects in pizotifen group

Side effects	End of week 2		End of week 4		End of week 8		End of week 12		Total reported	
	frequency	%	frequency	%	frequency	%	frequency	%	frequency	%
Drowsiness	14	66.7	12	57.1	3	14.3	0	0	14	66.7
Increased appetite	6	28.6	6	28.6	6	28.6	3	14.3	6	28.6
Dizziness	5	23.8	1	4.8	1	4.8	0	0	6	28.6
Weight gain	4	19	5	23.8	3	14.3	1	4.8	5	23.8
Dry Mouth	3	14.3	3	14.3	1	4.8	0	0	3	14.3
Nausea	2	9.5	2	9.5	0	0	0	0	2	9.5
Fatigue	1	4.8	1	4.8	0	0	0	0	1	4.8
Mood Change	1	4.8	0	0	0	0	0	0	1	4.8
Anxiety	1	4.8	1	4.8	0	0	0	0	1	4.8

Table 5: Comparison between common side effects of pizotifen and topiramate

Side effects		Total reported	P value*	Persistent at the end of trial	P value*
Drowsiness or sedation	Pizotifen	14	0.012	0	NS
	topiramate	4		1	
Increased Appetite	Pizotifen	9	NS	3	NS
	topiramate	6		5	
Weight Gain	Pizotifen	5	NS	1	NS
	topiramate	6		3	
Nausea	Pizotifen	2	NS	0	NS
	topiramate	2		1	

*Chi-square, Fisher's exact test, Yate's correction; NS: not significant

Discussion

There are several studies of pizotifen for migraine prevention; some compared its efficacy with placebo23, and some with other drugs.24 In the present study, we compared the efficacy of the pizotifen with topiramate, a widely used drug for migraine prevention. Both drugs were useful and there was a significant improvement for all evaluated headache parameters, compared to baseline. In some patients even complete

remission of symptoms observed. On the other hand, except for headache duration, pizotifen was more effective than topiramate regarding the headache characteristics evaluated. The present study confirms the efficacy of pizotifen(in low dose) as evaluable choice in migraine prevention. Concerning the safety of both drugs, although more than two third of patients reported one or more side effects, all were mild and non-serious. The total reported side effects was statically higher for pizotifen, however, the side effects of pizotifen decreased as the study progressed and at the end of trial the numbers of patients with persistent side effects were lower for pizotifen. Drowsiness is the most worrisome side effect of pizotifen; however, it is suggested that can be reduced by careful dose titration.25 In this study, a third of patients in pizotifen group initially developed drowsiness. However, at the end of trial, no patient complained of drowsiness. For both drugs, the weight gain paralleled increased appetite. However, similar to the findings of otherinvestigators26, for pizotifen with time most of them returned to their initial weight. In this study we used a single nighttime dosage for pizotifen. Itis suggested by other investigators 27that a single nighttime dosage might be preferred to the three times a day dosage for reduction of weight gain.Based on previous studies, pizotifen has been a second line drug in migraine prevention28-31because of major side effects (drowsiness and weight gain). However, we find that these side effects are not persistent if patients can to leratethem for a few weeks especially in low dose.32 The limitation of this trial was the absence of placebo-control; hence, the efficacy of drugs may be caused by the natural history of migraine or regression to the mean.In conclusion, the results of the present study suggest that, in short-term, pizotifen with the advantage of simple dosage schedule is a safe and effective option in migraine prevention that is superior to topiramate.

Acknowledgements

The author wish to acknowledge the contribution of Dr. Mahmoud Jasem for the statistical analyses.

Conflict of Interests.

There are non-conflicts of interest .

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