Neurology Asia 2012; 17(4) : 319 – 324

Pizotifen in migraine prevention: A comparison with sodium valproate

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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 sodium valproate; 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 sodium valproate 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:* Forty two 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 sodium valproate in the headache parameters assessed. Total reported side effects were initially higher in patients 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.

INTRODUCTION

About 15–18% of women and 6% of men suffer from migraine.[1, 2] Nearly 38% of migraineurs need prophylactic treatment; nevertheless, utilization of prophylaxis continues to be low[3] and only 3-13% of patients receive prophylactic treatment.[4] This may 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.

Sodium valproate is proven to be effective in migraine prevention.[5, 6] However, it may cause several serious adverse events such as liver failure, pancreatitis and teratogenicity which need follow up and laboratory tests.[7] Other common adverse effects which may limit sodium valproate are nausea, vomiting, hair loss, tremor, and especially weight gain.[8,9] Pizotifen is a serotonin antagonist.[10] There are several studies which have shown the usefulness of pizotifen for migraine prevention.[11-17] 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.[18-20] The aim of this trial was to compare the efficacy and safety of pizotifen with sodium valproate. The primary endpoint was a decrease in headache frequency at the end of a 16-week study period.

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 Alzahra hospital, Isfahan, Iran, 2011. The duration of study was 16 weeks, consisting of a 4-week period for baseline assessment and a subsequent 12-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.[21] 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) Any hypersensitivity to sodium valproate or pizotifen;

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(2) History of mental disorders; (3) History of advanced cardiac, renal or any unstable medical condition; (4) History of any liver disease; (5) Females who were pregnant, breast feeding, or planning for pregnancy; (6) Treatment with sodium valproate or pizotifen in the last three months before the study; (7) Concurrent prophylactic treatment for migraine; (8) Patients with headache disorders other than episodic migraine headache; (9) Suspicious to medication overdose headache; (10) Use of any drugs with potential preventive effects in migraine headache within three months before the study.

The inclusion criteria were: (1) Male or female with age of entry between 18 to 65 years; (2) Age of migraine onset should be less than 50 years old; (3) Willing and able to be available in the following four months; (4) Migraine headache frequency of 4 to 14 moderate-to-severe attacks 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 four weeks of the study. The following were recorded: (1) Demographic data; (2) Frequency of migraine headache (attacks/4-week); (3) Intensity of migraine headache measured by a 10- point Visual Analog Scale (mean± SD, VAS)[22]; (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 sodium valproate (n = 21) or pizotifen (n = 21) for a 12-week period. The prescribed dose of sodium valproate was 200 mg twice a day. Pizotifen was started as a 0.5 mg bedtime dose in the first week and titrated to a 1.5 mg bedtime dose in the second and subsequent weeks. 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 9 to 12 from randomization relative to baseline assessment. The headache diaries were interpreted by an expert neurologist in migraine. The primary endpoint was a reduction in the frequency of migraine attacks, and secondary endpoints were: (1) Headache intensity (mean± SD, VAS); (2) Headache duration (although it has a low value in parallel clinical trials of migraine prevention [23]; (3) Response to treatment, defined as 50% or greater reduction in attacks; (4) Safety as assessed by: (a) 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; (b) Laboratory tests, including liver function tests (LFT) and complete blood count (CBC) which assessed at the beginning, after one month, and at the end of the trial.

For ethical approval, doctrines of current version of the declaration of Helsinki were observed.[24] The Ethics Committee of Isfahan University of medical science approved the study, and the patients were informed regarding the trial design 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.

RESULTS

Forty two patients enrolled into the study; 57.1% were female. The mean age of entry was 31.4±7.9 years (range = 20-49) and the mean age of migraine onset was 25 ± 6.3 years old. Eleven patients had classic and 31 had common migraines. They had between 4-14 attacks of migraine per month. The treatment groups were similar with respect to the migraine characteristics and demographic data. The baseline characteristics of both treatment groups are listed in Table 1.

After a 16-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 sodium valproate. 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 sodium valproate group. No patients discontinued prophylactic treatment because of adverse side effects.

The side effects of sodium valproate and pizotifen are listed in Table 3 and 4. The comparison between common side effects of pizotifen and sodium valproate is listed in Table 5. The most frequently reported side effects of sodium valproate were increased appetite (9

Table 1: Baseline headache characteristics of the study subjects

		Sodium valproate	Pizotifen	P values
Age at entry (mean ± SD, years)		29.9 ± 7.9 (20-49)	32.8 ± 7.8 (20-48)	0.24*
Age at migraine onset(mean ± SD, years)		24.6 ± 6.5 (17-42)	25.3 ±6.2 (17-38)	0.7*
Migraine history (mean ± SD, years)		5.3±3.6	7.5±6	0.2*
Female		61.9%	52.4%	0.4**
Type of migraine(number)	classic common	5 16	6 15	0.72**
Headache frequency (mean ± SD, attack/month)		8 ± 3.6	9.9 ± 2.9	0.06*
Headache Severity (mean ± SD, VAS)		6.7 ± 2	7.7 ± 1.7	0.2#
Headache Duration (mean ± SD, hour)		14.2 ± 4.5	14.3 ± 4.8	0.9*
Positive family history for migraine		28.6%	33.3%	0.8**
Not married or single		52.4%	28.6%	0.1**
Low or Uneducated		0%	10%	0.5#

SD: Standard Deviation; VAS: Visual Analog Scale.
*Independent t-test; **Chi-square; #Mann-whitney

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

DISCUSSION

There are several studies of pizotifen for migraine prevention; some compared its efficacy with placebo[25-29], and some with other drugs.[30-36] In the present study, we compared the efficacy of the pizotifen with sodium valproate, a widely used drug for migraine prevention. Both drugs were useful and there was a significant improvement for all evaluated headache parameters, compared

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

	Sodium valproate	Pizotifen	P value
Headache frequency reduction (mean ± SD, attack/month)	4 ± 2.4	6.8 ± 3.1	0.002*
Headache severity reduction (mean ± SD, VAS)	1.7 ± 1.3	3 ± 1.2	0.002#
Headache duration reduction (mean ± SD, hour)	4.2 ± 3.3	5.3 ± 6.3	NS*
Response to treatment (> 50% fall in headache frequency)	42.9%	81%	0.012#

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

Table 3: Reported side effects in sodium valproate 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

to baseline. In some patients even complete remission of symptoms observed. On the other hand, except for headache duration, pizotifen was more effective than sodium valproate regarding the headache characteristics evaluated. The present study confirms the efficacy of pizotifen as a valuable 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.[37] 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 other investigators[17,38], for pizotifen with time most of them returned to their initial weight. In this study we used a single nighttime dosage for pizotifen. It is suggested by other investigators[12,39] that 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 prevention[25,40-43] because of major side effects (drowsiness and weight gain). However, we find that these side effects are not persistent if patients can tolerate them for a few weeks. 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 sodium valproate.

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 sodium valproate

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

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

DISCLOSURE

Conflict of interest: None

ACKNOWLEDGEMENTS

The authors wish to acknowledge the contribution of Dr.Tazhibi for the statistical analyses. This study supported by Isfahan University of Medical Sciences [grant number 389415].

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