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Assessment of the Middle Dose of Topiramate in Comparison with Sodium Valproate for Migraine Prophylaxis: A Randomized-Double-Blind Study

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Abstract: This randomized-double-blind aimed to show the effect of middle dose of topiramate and monitor the sodium valproate as a treatment quite acceptable in migraine prophylaxis as well as compare health and treatment effects in reducing both frequency and the severity of headache. Seventy-three females patients filled questionnaire based on the migraine disability assessment score (MIDAS) in the beginning and end of the study. Frequency, severity, duration of headache attacks and symptoms of drug in each of the patients are listed in his file. The effects of middle dose of topiramate (50-75 mg) and sodium valproate (400-600 mg) in the prevention of migraine headache was compared. Out of the 73 patients three cases were excluded due to unwanted and adverse events. Although, both drugs have been successful in reducing headache frequency more than 50% within the study, but there was no significant difference. The MIDAS score in topiramate group reduced more than the group receiving valproate sodium, which indicates changes, was statistically significant in both groups before treatment. The most common complications recorded in the group receiving topiramate were, paresthesia followed by weight loss, drowsiness and dizziness in topiramate group. While, the most common complications recorded in the group receiving sodium valproate were, drowsiness, weight gain, hair loss, nausea and Tremor. This trial demonstrates that topiramate significantly reduced mean monthly migraine and was a safe and well-tolerated preventive therapy in this group of subjects with migraine, a therapeutic area in which profound clinical needs exist.

Key words: Prophylaxis, migraine, frequency, severity, headache, sodium valproate, topiramate

INTRODUCTION

Migraine is a common primary headache disorder characterized by severe, pulsating, mostly unilateral headaches accompanied by vomiting, nausea and autonomic dysfunctions. Studies proven that about 5% of males, 18-16% of females and 10-5% of children are affected with migraine (Hämäläinen, 2006; Lipton *et al*., 2007). In the United States alone, about 18% of the female population and 6% of the male population have migraine headaches (Bigal and Lipton, 2009). Currently based on studies in other parts of the world ß-blockers are considered as the first line preventive therapy for migraine, but still is not clear how these drugs reduce the frequency and severity of migraine attacks (Silberstein, 2009; Evers, 2008). In the past few years various studies attempts to replace ß-blockers with new generation of drugs with fewer side effects and more treatmental effects as propranalol (Buchanan and Ramadan, 2006; Diener and Limmroth, 2005).

Recent studies tend to compare the effects of new generation antiepileptic drugs compared with the old generation of these drugs, because it seems the side effects is higher than the old generation as well as the patients are more tolerant of these drugs. Sodium valproate as a group of anticonvulsant drugs examined and its primary preventive effects in the headaches resistant to ß-blockers have been proven (Shimizu, 2009; Nejad *et al*., 2009). These new generation include new drugs such as topiramate that been widely used in recent studies (Diener *et al*., 2004; Brandes *et al*., 2004; Dodick *et al*., 2009; Silberstein *et al*., 2009).

The topiramate Mechanism of action is widespread on the central nervous system that can accentuate the inhibitory effects of Gamma-Amino Butyric Acid (GABA) and reduce the excitability effects of glutamate (Chen and Holmes, 2009). This drug inhibits sodium channel activity and decreased function of calcium channels as well as inhibits the enzyme carbonic Anhydrase (Diener *et al*., 2004; Silberstein *et al*., 2009). In earlier studies high

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dosage topiramate (150-200 mg), have been used repeatedly. Although, there is the favorable treatment response in patients to reduce the frequency of headache attacks, but had not been preferred by the physicians and patients due to the complications including the sense of disorder, fatigue, impaired memory, decreased appetite, nausea and weight loss (Bussone *et al*., 2006).

In this sequel, the present study aimed to show the effect of middle dose of topiramate (50-75 mg) and observed the response rate in patients. Furthermore, monitor the sodium valproate as a treatment quite acceptable in migraine prophylaxis (400-600 mg) used to compare health and treatment effects in reducing both frequency and the severity of headache.

MATERIALS AND METHODS

Study design and population: This study conducted in 73 female patients from the more than 250 clinics, which conducted from November 2008 to February 2009. The patients carefully filled questionnaire based on the assessment of disability caused by migraine disability assessment score (MIDAS) (Hung *et al*., 2006) in the beginning and end of the study. Furthermore, according to the severity of the headache patients, patients described the severity between zero to 10 (10 indicates the highest intensity is the headache). In addition, while reference fortnightly frequency, severity, duration of headache attacks and symptoms of drug in each of the patients are listed in his file. During the study, the effects of middle dose of topiramate 50-75 mg (Sobhan Darou Co., Iran) and sodium valproate with dosage 400-600 mg (Rouzdarou Pharmaceutical Co., Iran**)** in the prevention of migraine headache was compared. The patients according the age criteria divided into two groups of young, 20 to 30 year and middle, 31 to 50 year.

The study was approved by the University Hospital and Ahwaz Jondishapour University of Medical Sciences Ethics Committees and all subjects granted informed consent to participate.

Inclusion criteria: The patients fulfilled the criteria include: migraine, according to the criteria International Headache Society (HIS) (Evers, 2004) with 1-6 attacks per month for at least 1 year, age between 20 and 50 years, body mass index within the range 19-29 kg m^{-2}, weight range 45-85 kg, good general health determined by medical history, physical examination, ECG and urine and blood screening tests including test for hepatitis B and C, females of child-bearing potential could participate provided, they had a negative pregnancy test and used reliable contraceptive, were included in this study.

Exclusion criteria included: Tension type headache more than 2 days a month, known allergy to the drugs used, blood donation within the previous month, breastfeeding, migraine prophylaxis within 2 months of study start, previous proven inefficacy of sodium valproate prophylaxis, drug overuse (urine screen for drugs of abuse), regular use of prescribed or over-the-counter medication except oral contraceptive pill and usual acute migraine treatment.

Intervention: First topiramate has been given in 25 mg day^{-1} does during the first week and gradually was increased within weeks after the patients admitted to the maximum dose of 75 mg day^{-1}. Furthermore, sodium valproate has given in the dose of 200 mg day^{-1} first and within 2 to 4 weeks, based on the patient's response to treatment and severity of the complications the dose was increased to 600 mg day^{-1}. Drug delivery in patients has done using a significant closed container without a name which has the separate code for each patient. Initial examination, drug delivery and dosage control has done by a group including two physicians and secondary examinations and data record a week later has done by another group, including two physicians. File for each patient has specific code, so the next reference (after reaching the goal dosage), patient and examination takes no notice and each of the patients were followed up for 12 weeks from the time of reaching the goal Dosage.

Statistical analysis: Randomization was performed by GlaxoWellcome and the code was not known to the investigators until after the database was closed. Comparison of the number of patients experiencing headache/migraine attacks on the study days was investigated with a sign test and differences in peak headache intensity were investigated with paired t-test. The changes were analyzed over time with ANOVA. For all analyses, a p-value$<$0.05 was considered statistically significant. The statistical program SPSS 13.0 was used to analyze the data.

RESULTS

Out of the 73 patients three cases were excluded including a case severe complication Paresthesia due to topiramate, a case due to severe drowsiness and nausea due to taking sodium valproate and an unwanted pregnancy. Finally, 70 females were continued in the total full course of study within 8 months. The average age of patients receiving topiramate group was 30.1±6 years and the average age of patients in the group receiving sodium valproate was 31.2±5 years respectively (p = 0.438) (Table 1). Monthly headache frequency before treatment

Table 1: Demographics and baseline characteristics in 70 patients affected by migraine

Variables	Topiramate group (n = 35)	Sodium valproate group (n = 35)	Total (n = 70)	p-value
Age (years): Mean±SD	30.1±6.0	31.2±5.0	41.3±9.98	0.438
Episodic migraine: n (%)	34 (97.1%)	33 (94.2%)	67 (95.71%)	0.781
MIDAS scores: Mean±SD	53.23±6.52	46.76±4.29	48.71±12.1	0.025*
No. of headache days per month: Mean±SD	10.07± 2.32	10.14±1.98	10.09±2.10	0.938
Duration of headache (h): Mean±SD	24.37±7.65	22.13±6.68	23.1±6.95	0.892
Headache severity: Mean±SD	4.15±0.87	4.41± 0.79	4.21±0.91	0.988
24 h migraine Qol questionnaire (5 domains): Mean±SD				
Symptoms	8.21±2.28	11.28±3.39	9.98±2.25	0.015*
Feelings	8.16±2.91	9.45±3.52	9.01±3.01	0.331
Work	10.57±3.54	10.98±3.27	10.65±3.39	0.441
Social	9.78±2.99	10.01±3.11	9.98±3.01	0.489
Vitality	9.78±3.35	10.11± 2.09	9.84±3.02	0.238

*Significant differences

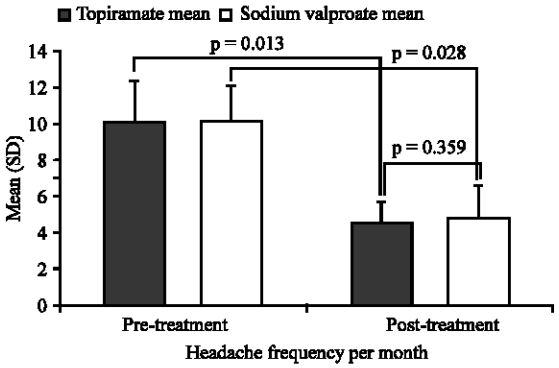

Fig. 1: Comparison of the both drugs effect on the headache frequency per month

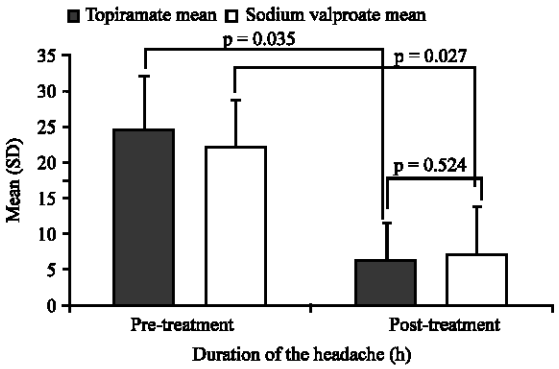

Fig. 2: Comparison of the both drugs effect on the duration of the headache

in topiramate groups and sodium valproate group were 10.07±2.32 and 10.14±1.98, respectively (Table 1). The average duration of headache before treatment in topiramate group was 24.37±7.65 h and in the sodium valproate group was 22.13±6.68 h (Table 1). The MIDAS score in topiramate group rated as 53.23±6.52% and in group receiving valproate sodium was 46.76±4.29% that indicates changes was statistically significant in both groups before treatment ($p<0.05$). Comparison between two groups indicated significant differences in reduction rate of the MIDAS score in the group topiramate to valproate group (Table 1).

The headache frequency per month in topiramate receiving group before and after starting the treatment (10.07±2.32 vs. 4.58±1.1, $p = 0.013$) and in the group receiving sodium valproate (10.14±1.98 vs. 4.81±1.7, $p = 0.028$) show the significant reduction (Fig. 1). Although, the reduction in both group were statistically significant, but the difference between groups was not statistically significant ($p = 0.359$). Compare the mean duration of the headache per episode during headache attack showed that medium-term average reduced in topiramate group from 24.37±7.65 hours to 6.23±5.22 h ($p = 0.035$) and in sodium valproate group from 22.13±6.68 h to 7.27±6.47 h ($p = 0.027$) (Fig. 2). Although, the headache duration seems to be tangible in group receiving topiramate but more statistical analysis and comparison between groups indicated no statistically significant differences ($p = 0.524$). After 12 weeks follow-up period the severity, duration and frequency of headache in both groups of patients was studied. Headache intensity in topiramate group was declined from 9.3±1.45 to 4.70±1.24 ($p = 0.024$) and in the group receiving sodium valproate of 9.20±1.36 to 4.15±0.864 ($p = 0.018$). In this case despite the significant decrease in both headache intensities and severity of headache, but the two groups showed no significant differences ($p = 0.259$) (Fig. 3).

Frequency of headache attacks in topiramate group, in the first month was 12.5%, the second month was 23.5% and in the third month was 18.5%, whereas in the group receiving sodium valproate it was 14.5% in the first month, in the second month was 20.5 and 17.5% in the third month. These results showed decreased in headache frequency following use of both drugs in the third month (Fig. 4). Although, both drugs have been successful in reducing headache frequency more than 50% within the study, the comparison between the two groups had no statistically significant difference.

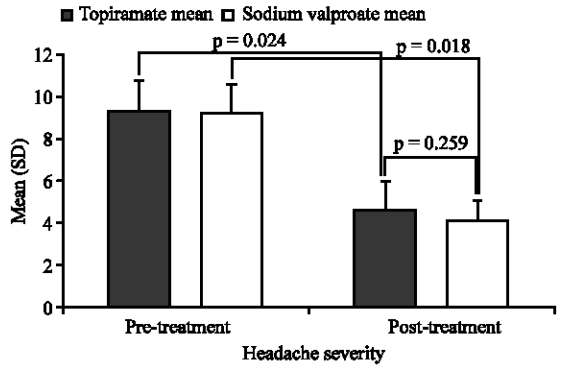

Fig. 3: Comparison of the both drugs effect on the headache severity

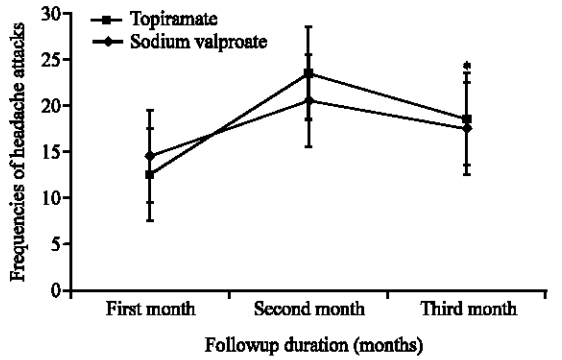

Fig. 4: Duration based comparison of the headache frequencies: In spite of the reduction in both drugs the difference between those was not significant (*p = 0.479)

Out of 19 patients in the young age group receiving topiramate, 21.1% at the end of first month showed more than 50% reduction in headache intensity. Hence, in sodium valproate receiving group out of 23 cases in young age group, 26.1% showed over 50% reduction in the intensity of their headaches. This result showed no statistically significant difference ($p>0.05$). In case of middle age group the results showed that out of total of 21 patients in topiramate group, 4.8 over 50% reduction in the intensity of their headaches over the first month. Also the valproate sodium receiving middle age group, between 17 cases, 11.8% showed reduction over 50% reductions in the intensity of their headaches. Results of analysis indicated that in the middle age group also significant differences between the two groups do not exist ($p>0.05$).

The most common medical complications recorded in the study group receiving topiramate were: paresthesia (8, 11.42%), weight loss (2, 2.85%), drowsiness (8, 11.42%) and dizziness (3, 4.28%), but the severity of these symptoms was not as enough as stop taking the medicine. In the sodium valproate group the complications include: drowsiness (3, 4.28%), weight gain (2, 2.85%), hair loss (2, 2.85%), nausea (4, 5.71%) and Tremor (3, 4.28%).

DISCUSSION

What obtained in this study suggests is that the topiramate average dosage (50-75 mg) is able to reduce intensity, duration and frequency of migraine-induced headaches as similar as sodium valproate with middle dosage (400-600 mg). Considering the MIDAS score the topiramate receiving group had noticeably improvement of performance than patients receiving sodium valproate.

Rapoport *et al.* (2006) design a study on 567 patients with an established history of migraine with or without aura were enrolled in preventive therapy when used for up to 14 months. They claimed that patients receiving topiramate experienced a sustained reduction in migraine frequency for up to 14 months. Jensen *et al.* (1994) conducted crossover study of the prophylactic effect of slow-release sodium on 43 patients with migraine. Fifty percent of the patients were responders, which mean their initial migraine frequency was reduced to 50% or less during sodium valproate as compared with 18% during placebo. The number of responders increased during the trial to 65% in the last 4 weeks of the active treatment period. There were no serious side effects requiring withdrawal of patients from the study.

In agreement with the present many studies have been conducted to show the effect of toprimate in headache treatment. Silberstein *et al.* (2006) evaluated the efficacy and safety data from a pilot study of topiramate 200 mg day^{-1} as preventive therapy in adult subjects with a history of migraine with or without aura. In this pilot study, mean monthly migraine frequency did not differ significantly between topiramate and placebo. Huppertz *et al.* (2001) investigated 37 epilepsy patients in an open study with regard to cognitive impairments in anticonvulsant add-on therapy with topiramate that was started and increased by 25 mg $week^{-1}$. The study showed a higher frequency of cognitive side effects under topiramate. Silberstein *et al.* (2008) in a review presents comparative data from these 2 clinical trials, which suggest that topiramate at a dose of 100 mg daily is effective and generally well tolerated in chronic migraine. Silberstein *et al.* (2007) evaluate the efficacy and safety of topiramate (100 mg day^{-1}) compared with placebo for the treatment of chronic migraine. The study was consisting of 16 weeks of double-blind treatment in subjects aged 18 to 65 years with 15 or more headache days per month. The study showed that topiramate treatment at daily

doses of approximately 100 mg resulted in significant improvements compared with placebo in mean monthly migraine headache. In another study Gupta *et al.* (2007) investigated low-dose topiramate versus lamotrigine on 60 patients with frequent migraine. They concluded that Low-dose topiramate is efficacious in migraine prophylaxis as compared to lamotrigine, as well as lamotrigine in low doses might be beneficial for headache frequency. In general, the efficacy and complications been proved to be dose dependent. In the present study, because topiramate and sodium valproate dosage were less than consumed dosage in earlier studies so the complications were less frequent.

Silberstein *et al.* (2008) reported paresthesia as the most common complication in topiramate group followed by upper respiratory tract infection, fatigue. In spite of the different used dosage, in the present study the most common complications recorded in the group receiving topiramate were, paresthesia followed by weight loss, drowsiness and dizziness in topiramate group. This mean that the most common adverse-event of topiramate observed in this trial was similar to that observed in the topiramate migraine trials done by Silberstein *et al.* (2008) and Blumenfeld *et al.* (2008) reported nausea as the most common complication in sodium valproate group followed by fatigue, hair loss, sleepiness and tremors. In the present study the most common complications recorded in the group receiving sodium valproate were, drowsiness, weight gain, hair loss, nausea and Tremor. The most common adverse-event profile of topiramate observed in this trial was similar to that observed in the sodium valproate migraine trials done by Blumenfeld *et al.* (2008).

CONCLUSION

Unlike other studies, this study introduced the positive effects of treatment are topiramate low dosage. The second point it seems, according to results obtained in both groups of patients most therapeutic response was reducing headache frequency in the second month of treatment. This comment is always important for patients to continue treatment during the second and third months and more helpful to encourage them for better treatment and complete response. While today in sight of the availability of the new generation of anti-migraine drugs, in patients who have not the ability or capacity of taking other drugs, including beta ß-blockers, simply new generation of anti-convolution drugs including low dosage of topiramate with fewer complications can be used. The adverse effects of sodium valproate including weight gain and hair loss particularly in female patients is a very important point and selection criteria for a drug with tolerable side effects. This trial demonstrates that topiramate 50-75 mg day^{-1} significantly reduced mean monthly migraine and was a safe and well-tolerated preventive therapy in this group of subjects with migraine, a therapeutic area in which profound clinical needs exist. These results add to the existing evidence supporting the consistent therapeutic efficacy of topiramate in subjects with migraine.

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