ORIGINAL ARTICLE

Comparison of efficacy and safety of topiramate with gabapentin in migraine prophylaxis: randomized open label control trial

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Abstract

Objective: To compare the efficacy and safety of topiramate with gabapentin in the prophylaxis of migraine patients.

Methods: A 12-week randomised open label control trial was conducted at the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre (JPMC), Karachi from January to March 2011 involving 80 outpatients who had a history of migraine. The sample was divided into two equal groups. Primary efficacy measure was changed into mean monthly migraine frequency. Secondary efficacy measure included reduction in severity and average duration of an attack. Chi square test and paired t-test were used to analyse the data through SPSS 15.

Result: Reduction in mean monthly migraine frequency (10.67±4.25 to 1.82±2.02) in the topiramate group was significantly greater compared with (11.97±4.452 to 2.73±2.59) that in the gabapentin group ($p<0.001$). Reduction in severity from 6.60±2.122 to 1.03±0.92 in the topiramate group was also significantly greater compared with 6.93±1.90 to 1.18±1.01 in the gabapentin group ($p<0.001$). Reduction in the average duration of attacks from 25.77±22.32 hours to 1.05±1.06 hours in the topiramate group was significantly greater compared with 22.20±20.72 to 1.08±1.40 hours in the gabapentin group ($p<0.001$). Weight loss and numbness were common adverse effects in the topiramate group. Dizziness, weight gain and somnolence were reported in the gabapentin group.

Conclusion: Gabapentin appeared well tolerated in 30(75%) patients compared to topiramate in 23(57.5%) patients. Both drugs were equally effective in migraine prophylaxis.

Keywords: Topiramate, Gabapentin, Migraine, Prophylaxis. (JPMA 63: 3; 2013)

Introduction

Migraine is a chronic incapacitating neurovascular disorder, characterised by attacks of severe headache, autonomic nervous system dysfunction and in some patients, an aura involving neurologic symptoms.[1]

The headache of migraine is often throbbing and frequently unilateral. When untreated, these attacks typically last 4 to 72 hours which are usually associated with nausea, vomiting, sensitivity to light, sound, movement, vertigo[2] and aggravated by routine physical activity.[3] Migraine is the 19th leading cause of years lived with disability[4] and WHO estimates that 324 million persons worldwide have migraine.[5] The prevalence has been estimated to 6-29% in women and 3-12% in men.[6] About 25% of migraine patients have a high frequency of migraine attacks, with upto 6 per month, leading to considerable disability and consequences for professional life or social function,[7] academic, leisure, family life and responsibilities.[4]

Migraine with aura affects about 20-30% of patients. Symptoms of aura include spots of light, zigzag lines or region of visual loss (Scotoma). Non-visual symptoms include somatosensory features like tingling, positive symptoms and numbness, a negative symptom and language or motor effects like weakness.[8,9]

Preventive treatment of migraine should be mandatory for patients with frequent headaches.[10] In the United States alone, 40% of patients with migraine, nearly 12 million people are candidates for preventive therapy, but only 1 in 5 (19.6%) currently receives migraine-specific preventive care.[11]

Topiramate, an anti-convulsant, is approved in more than 50 countries, including the United States, for the prevention of migraine headache in adults.[11] It is a derivative of the naturally occurring monosaccharide D-fructose, it has antiepileptic effects through modulation of voltage-gated sodium ion channels and voltage-gated calcium ion channels, blockade of excitatory glutamate transmission, potentiation of gamma-aminobutyric acid (GABA) inhibition and by inhibition of carbonic

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anhydrase.[12,13]

Gabapentin (1-aminomethyl cyclohexane acetic acid) is a novel anti-epileptic agent, a structural analogue of GABA, has no direct GABAergic action and does not block GABA uptake or metabolism. It increased extracellular GABA concentration in the same region of the brain caused by an increase in activity of glutamic acid decarboxylase that produces GABA and a decreased breakdown by GABA decarboxylase.[14]

Patients and Methods

The study was a randomized open label control trial conducted at the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute, JPMC in collaboration with the Department of Neurology, JPMC, Karachi from January to March 2011. The study was approved by the ethical committee of the JPMC. After explaining the procedure, consent was obtained from the participants. The study period lasted 12 weeks with monthly follow-up visits.

The sample size was caluculated using the formula:

$n = [A+B]^2 \times 2 \times S.D^2 + DIFF^2$ [15]

Where n = sample size required in each group for comparing two means; double this for total sample size; A = significance level 5% (1.96); B = power 80% (0.84); SD = standard deviation (8); DIFF = size of difference (5); n= 40.14. The actual sample size is twice the calculated result.

Eighty outpatients were selected with history of migraine for at least 1 year of either sex with age more than 18 years, who had 1 to 8 migraine attacks per month with or without aura that typically lasted 4-72 hours untreated, in the preceding two months. Patients were excluded from the study if they had non-migraine headache, hepatic or renal impairment, uncontrolled hypertension, renal stones, osteoporosis, angle closure glaucoma, psychosis, pregnant or lactating women, inadequate contraception, patients taking anti-depressant, monoamine oxidase inhibitor, carbonic anhydrase inhibitor, b-blocker or calcium channel blocker or any other migraine prophylactic therapy.

Patients were divided into two groups. Group A was given topiramate randomly with dosage ranging from 50-200mg/day. Group B was given gabapentin randomly with dosage 300-1200mg/day. Complete history, general physical examination, neurological examination baseline vitals, weight, height, Body Mass Index (BMI), fundoscopic examination, X-ray PNS view, Computed tomography scan and Magnetic Resonance Imaging were done. Baseline serum urea and creatinine was performed for safety profile. Height, weight and BMI were repeated at the end of the study period. The data of the patients were recorded in tabulated forms and analysed statistically at the end of the study by using SPSS 15. Three grades visual analog scale (VAS) was used to assess the severity of pain: score 0-3 represented mild; 4-6 moderate; 7-10 severe pain. Mean monthly migraine frequency and average duration of hours were calculated. Change in height, weight and BMI was evaluated from day 0 to days 90. Chi square test and paired t-test were used to evaluate results.

Result

Group A had 38(95%) females and 2 (5%) males. The mean age of the topiramate treated patients was 28±6.73 years. Group B had 32(80%) females and 8(20%) males. The mean age in the group was 32±10.15 years. All patients were monitored from Day 0 to Day 90 for their response to the respective treatment (Table).

Thirteen (32.5%) patients in topiramate group and 9(22.5%) patients in gabapentin group had migraine aura with following symptoms: Out of 40 patients, 12(30%) had unilateral headache, 7(42.5%) had bilateral headache, 11(27.5%) had both sided headache, in 18(45%) patients

Table: Changes in mean and percentage following with treatment in Group A and B.

VAS (Severity)	Day-0		Day-30		Day-60		Day-90	
	Topiramate (n=40)	Gabapentin (n=40)	Topiramate (n=40)	Gabapentin (n=40)	Topiramate (n=40)	Gabapentin (n=40)	Topiramate (n=40)	Gabapentin (n=40)
Mild	5(12.5%)	2(5%)	25(62.5%)	9(22.5%)	32(80%)	34(85%)	40(100%)	40(100%)
Moderate	17(42.5%)	19(47.5%)	12(30%)	22(55%)	8(20%)	6(15%)	0	0
Severe	18(45%)	19(47.5%)	3(7.5%)	9(22.5%)	0	0	0	0
Mean(SD)	6.60 2.12	6.93 1.90	3.83 2.08	4.80 1.77	2.40 1.44	2.48 1.35	1.03 0.92	1.18 1.01
Average duration of attack (Hours) Mean(SD)	25.77 22.32	22.20 20.72	9.20 7.76	8.90 7.16	2.68 2.94	3.13 3.36	1.05 1.06	1.08 1.40
Frequency(Days) Mean(SD)	10.67 4.25	11.97 4.45	7.35 3.69	8.50 3.94	4.63 2.71	5.87 3.23	1.82 2.02	2.73 2.59

SD: Standard Deviation.

pain was pulsating in nature, 24(60%) had nausea, 20(50%) had vomiting, 26(65%) had vertigo, 18(45%) had photophobia, 26(65%) had phonophobia, in 18(45%) patients pain aggravating by routine physical activity in topiramate treated group. In gabapentin treated group, 9(22.5%) patients had unilateral headache, 27(67.5%) had bilateral headache, 4(10%) had both sided headache, in 24(60%) patients pain was pulsating, 25(62.5%) had nausea, 7(17.5%) had vomiting, 25(62.5%) had vertigo, 26(65%) had photophobia, 24(60%) had phonophobia and in 5(12.5%) patients pain was aggravated by routine physical activity.

Reduction in mean monthly migraine frequency from 10.67±4.25 to 1.82±2.02 in the topiramate group was significantly greater compared with 11.97±4.45 to 2.73±2.59 in the gabapentin group. The total mean migraine frequency reduction was 8.85±4.11 in topiramate group and 9.25±3.62 in gabapentin treated group which were highly significant (p<0.001) (Figure-1).

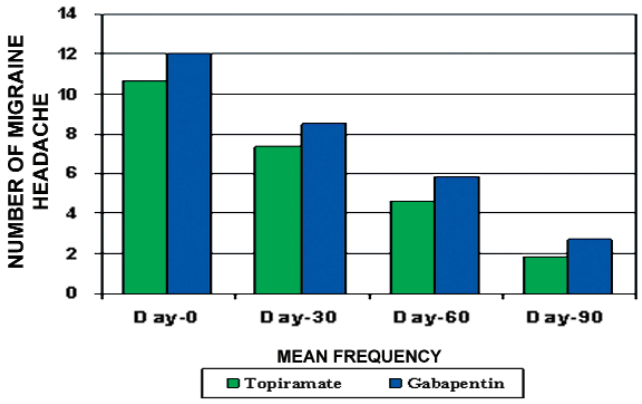

Figure-1: Mean change in frequency from baseline to day 90.

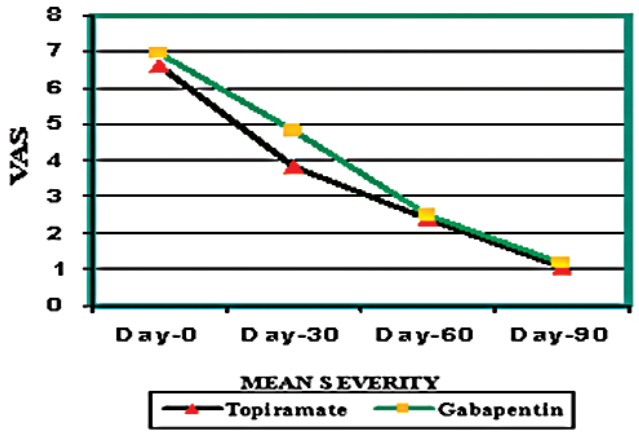

Figure-2: Mean change in visual analog score as from baseline to day 90.

Reduction in mean severity (VAS) from 6.60±2.12 to 1.03±0.92 in Group A was significantly greater compared with 6.93±1.90 to 1.18±1.01 in Group B. The total mean VAS reduction was 5.57±1.67 in Group A and 5.75±1.51 in Group B which were highly significant (p=<0.001) (Figure-2).

All the patients in both the groups (100%) showed mild severity of pain at the end of the study. Reduction in mean average duration of attacks from 25.77±22.32 hours to 1.05±1.06 in the topiramate group was significantly greater compared with 22.20±20.72 to 1.08±1.40 in the gabapentin group. The total mean reduction was 24.72±22.36 in topiramate and 21.12±20.45 in gabapentin groups, which were highly significant (p<0.001).

Weight loss seen in 9(22.5%) patients and numbness in 2(5%) patients were common adverse effects in topiramate group. Dizziness was seen in 3(7.5%) patients, weight gain in 3(7.5%) patients and somnolence in 2(5%) patients in gabapentin group. Most of the side effects were mild to moderate in intensity and were not significant enough to withdraw from the study.

Paired difference in mean BMI was 0.01 ± 0.43 (p=0.05) in Group A due to change in weight from day 0 to day 90 i.e. 0.37±0.97 mean reduction in weight (p=0.20) was observed. The paired difference in mean BMI was -0.77±0.34 (p=0.16) in Group B due to change in weight from day 0 to day 90 i.e. -0.22±0.83 gain in mean weight (p=0.09). This was evaluated through paired t- test.

Discussion

Migraine attacks can significantly impair social functioning, family life, and workplace productivity. An effective migraine preventive therapy should decrease migraine frequency and improve patient function.

Freitag et al. elaborated pooled analysis of the data from the two trials in which topiramate at dosages of 100 mg per day and 200 mg per day significantly reduced mean monthly migraine frequency throughout the double-blind phase, compared with placebo (p 0.002).[11] These results are in line with the present study.

Topiramate has been shown to be effective for migraine preventive treatment by Bussone et al. in three large placebo controlled dose ranging trials, in which 46.3% patient achieved 50% reduction in monthly migraine frequency compared with 22.8% with placebo (p <0.001).[16-18]

A 26-week, double blind, randomised placebo controlled study showed the significant reduction in mean monthly migraine frequency for patients receiving topiramate at 100mg (p<0.008) and 200mg (p<0.001) versus placebo

(p<0.005) within the first month. Proportion of patients with 50% reduction in monthly headache was significantly greater with topiramate at 50mg/d (39%; p<0.001), 100mg/d (49%; p<0.001), 200mg/d (47%; p<0.001) and placebo (23%). Statistically significant difference in mean migraine severity with topiramate at 100mg/d (p<0.04) versus placebo but not with topiramate at 50mg/d (p<0.61) vs placebo or 200mg/d (p<0.46).[17]

In another analysis conducted by Brandes, patients receiving topiramate 100 and 200mg/d had significantly reduced mean monthly migraine frequency (p<0.008 and p<0.001, respectively) compared with placebo but not patients receiving topiramate 50mg/day (p<0.48).[18] The results of these studies are in line with the present study.

According to Denier et al. topiramate treatment resulted in a robust reduction in the number of monthly migraine days in the medication overuse sub-population.[19] Topiramate has also been found to be associated with weight loss of up to 15% to 18% of the baseline weight. The mechanism underlying this side effect is still uncertain, but seems to be related to neuropeptide Y, a neuropeptide widely distributed in the mammalian central nervous system. Centrally administered neuropeptide Y markedly reduces pharmacologically-induced seizures and induces antidepressant-like activity as well as feeding behaviour. Two other peptides, galanin and corticotropin-releasing hormone, have also been proposed to play a modulatory role in mood, appetite and seizure regulation, and may be involved in topiramate's effect of promoting weight-loss.[20] Our study is closely related to this in showing 22.5% loss in weight in a predominant female population.

Topiramate has no established therapeutic range, dosing is based upon clinical judgment of the balance between therapeutic response and adverse event profile. In renal tubules, carbonic anhydrase isoenzyme inhibition decrease hydrogen ion secretion and increases secretion of Na+, K+, HCO3- and water. They enhance the likelihood of acidosis and renal stone formation.[21]

A study evaluated that low-dose topiramate is efficacious in migraine prophylaxis as compared to both placebo and lamotrigine. Topiramate showed statistically significant benefits (p<0.017) in reduction in the mean monthly frequency, intensity and duration of attacks.[22] Our study showed better result of topiramate than this study.

A double-blind randomised placebo controlled study on the prophylactic effect of gabapentin 1200mg/day in 63 migraine patients over 3 months was conducted. The study demonstrated, statistically significant reduction in the frequency of attacks (5.08±3.13 in patients without aura, 5.14±2.47 in patients with aura) and intensity of migraine (2.33±1.59 in patients with aura, 2.38±1.16 without aura) in patients receiving gabapentin.[23,14] The results of this study are similar with the present study.

Gabapentin is well tolerated with few serious adverse effects. Reviewing data from a controlled clinical trial conducted prior to 1995, a study reported that somnolence (20%), dizziness (18%), ataxia (13%) and fatigue (11%) were the most common side effects.[14] These results are closely related to the present study.

A Cochrane review has shown that anti-epileptics can reduce the frequency of migraine by 1.4 attacks per 28 days. Patients are 2.4 times more likely to experience a 50% or greater reduction in migraine frequency when using anti-epileptic compared with placebo. The NNT (number needed to treat) to achieve a 50% or greater reduction in migraine frequency for each are: all anti-epileptic: 3.9 (95% CI 3.4 to 4.7); topiramate, 3.9 (95% CI 3.4 to 5.1); sodium valporate, 3.1 (95% CI 1.9 to 8.9); and gabapentin, 3.3 (95% CI 2.1 to 8.4).[24]

Topiramate significantly reduces the number of acute migraine episodes from 5.26 to 2.60 per 28 days (p<0.001) as well as causing a greater mean reduction in migraine frequency than placebo (1.55 vs. 0.47, p=0.001). The mean monthly frequency decreased significantly for patients receiving 100mg/day of topiramate from (5.4 to 3.3, p<0.001) or 200mg/day of topiramate (from 5.6 to 2.6, p<0.001) as compared to placebo.[24]

A multi-centre randomised placebo controlled crossover study showed efficacy of gabapentin 2400mg/day over placebo in chronic daily headache with 9.1% difference in headache-free rates (p<0.005), headache-free days/month (p<0.005), severity (p<0.03), and VAS (p<0.0006).[25]

The efficacy of topiramate for migraine prevention is believed to be a result of its neuro-stabilizing properties, which may act to reduce neuronal hyper-excitability and cortical spreading depression. Topiramate appears to fulfil Group 1 criteria for a first-line migraine prevention medication, as described by Freitag et al.[11]

Preventive therapy may reduce the risk of medication-overuse (i.e. rebound) headache resulting from frequent usage. Studies have also shown that effective migraine prevention therapy is associated with improvements in health-related quality of life.[11] An observational open label study among migraine patients with gabapentin, 900-1800mg/day showed 15.8±8.6 mean reduction in

headache frequency (45.3%) and 50% reduction in intensity in 61.5% patients.[6] While 25% reduction of headache intensity was observed with sodium valporate i.e. from 7.7 to 5.8 and 46% with topiramate i.e. from 6.9 to 3.7 by VAS in a randomized, double blind crossover study conducted by Shaygannejad et al.[26] Our results showed 82% reduction in intensity in gabapentin and 84% reduction in intensity in topiramate treated patients.

Small sample size was a limitation in our study. Due to limited resources, it was not possible to collect a large sample. To avoid bias in terms of follow-up, further large double blind, placebo-controlled studies are needed to establish the results in a large population.

Conclusion

Topiramate showed significant efficacy in migraine prevention within the first month of treatment compared to gabapentin. Both drugs, however, were equally effective in migraine prophylaxis.

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