Journal of Family Medicine

Open Access

Austin Publishing Group

Research Article

Comparison of the Combination of Butterbur, Riboflavin and Magnesium Versus Topiramate in Migraine Prophylaxis

Chedid T, Jaafar N, Makki A and Sawaya R*

1Department of Neurology, American University of Beirut Medical Center, Beirut, Lebanon

***Corresponding author:** Sawaya R, Department of Neurology, American University of Beirut Medical Center, POB: 113 – 6044 / C-27, Beirut, Lebanon

Received: April 28, 2020; **Accepted:** June 23, 2020; **Published:** June 30, 2020

Abstract

Objective: To compare the efficacy in migraine prophylaxis of topiramate versus the combination of butterbur, riboflavin and magnesium.

Materials and Methods: 124 adults with episodic migraine requiring prophylaxis were enrolled prospectively. 61% received topiramate (TPM) 50 mg/d and 39% received the triple combination therapy (TCT) that consisted of butterbur 150 mg/d, riboflavin 200 mg/d and magnesium 750-1000 mg/d. The subjects were asked to chart the frequency, severity and duration of their headaches over 3 months after initiating their prophylactic treatment.

Results: 29 patients in the TPM arm and 25 in the TCT arm were followed-up over 3 months. TPM and TCT decreased the number of headache days per month by 67% and 65% respectively. There was also a decrease in the attack duration by 48% and 52% and in its severity by 3 and 2.6 points on the visual analog scale in the TPM and TCT groups respectively. 13 patients (29%) discontinued their medication due to side effects in the TPM group.

Conclusion: Low dose topiramate was as efficacious in migraine prophylaxis as the combination of butterbur, riboflavin and magnesium. However, TPM has more side effects and the TCT is more expensive.

Keywords: Migraine; Migraine prophylaxis; Topiramate; Nutraceuticals; Butterbur; Magnesium; Riboflavin

Abbreviations

TPM: Topiramate; TCT: Triple Combination Therapy; VAS: Visual Analog Scale; D/C: Discontinued

Background

Migraine is the third leading disabling neurological disorder [1]. Prophylactic treatment is given when migraine headaches are frequent and disabling. Antiepileptic drugs, beta-blockers and calcium channel blockers are effective in migraine prophylaxis [2]. Multiple nutraceutical drugs were also studied like butterbur, magnesium and riboflavin [3]. Treatment is based on efficacy, adverse events and the patient's preference and coexistent comorbidities. A treatment that reduces attack frequency by 50% is considered successful [2]. In this study, we present a comparison between a combination of butterbur, magnesium and riboflavin versus topiramate in migraine prophylaxis.

Materials and Methods

We performed a prospective open-label study at a hospital-based neurology clinic in Lebanon. 124 subjects were enrolled. The inclusion criteria are age 18-65 years old and a diagnosis of episodic migraine with or without aura, as defined by the ICDH-3 criteria, with a frequency of more than 6 headache days per month. Excluded were the patients on prophylactic treatment for migraine, antidepressants in the past 3 months and those with co-morbid primary headaches, pregnancy or lactation, renal or hepatic failure, hypertension, kidney stones, angle-closure glaucoma, myasthenia gravis, suicidal ideation, anorexia nervosa and psychosis.

Patients assigned to receive prophylaxis were started on either topiramate (TPM) or the triple combination therapy (TCT). The former was prescribed as 50mg daily. The combination consisted of a co-administration of butterbur (PrevaMig®) 75mg twice daily, riboflavin 100mg twice daily and magnesium 375-500 mg twice daily. To note that the butterbur extract used is 100% free of the hepatotoxic pyrrolizidine alkaloids [4]. The subjects were asked to keep a headache diary for 90 days to record the frequency, severity and duration of their attacks. The severity of the headache was rated from 0 to 10 based on the visual analog scale. Data collection at baseline included age, gender, smoking status, alcohol use, water intake >1L per day and physical activity (>2 times weekly). The presence of aura and specific triggers were also recorded. Patients were instructed to report back to the primary physician if they needed to increase their abortive treatment use during the period of study.

Patients enrolled were interviewed by the first author on follow-up visits or on the phone 3 months after initiating treatment. The evolution of the severity, frequency and duration of their headaches was recorded. Side effects were noted. If the patient or the physician stopped the medication, the reason for the discontinuation was identified.

The primary outcome measure was the decrease in the headache

Citation: Chedid T, Jaafar N, Makki A and Sawaya R. Comparison of the Combination of Butterbur, Riboflavin and Magnesium Versus Topiramate in Migraine Prophylaxis. J Fam Med. 2020; 7(5): 1212.

Table 1: Demographic characteristics of the patients in each treatment arm.

	Topiramate	Triple combination	P-value
Female Gender	86.20%	92%	0.5
Age in years	36.1 ± 8.5	33.8 ± 10.3	0.36
Presence of Aura	31%	20%	0.36
Smoking	34.50%	32%	0.29
Alcohol use	6.90%	16%	0.85
Water intake	62.10%	72%	0.44
Physical activity	27.60%	20%	0.52

frequency at 3 months. Secondary outcome measures were the reduction in headache severity and duration at 3 months and the tolerability of the side effects.

The study was approved by the IRB committee at the American University of Beirut Medical Center and all patients signed a written consent form.

Statistical analysis

SPSS was used for data cleaning, management and analysis. The descriptive statistics for the continuous variables was reported by mean and standard deviation, and by the numbers and percentages for the categorical variables.

The comparison between the 2 groups and categorical variables was assessed by using χ^2. The t-test was used for the continuous ones.

Results and Discussion

Patient enrollment

124 patients were enrolled. 76 patients received TPM, 48 received TCT. In the TPM group, 25 patients were lost to follow-up and 7 were non-compliant. Out of the remaining 44 patients, 13 discontinued TPM due to side effects, 2 due to lack of efficacy and 29 were followed-up for 3 months. In the TCT group, 13 were lost to follow-up and 6 were non-compliant. Out of the remaining 29 patients, 4 discontinued due to lack of efficacy, none due to side effects, and 25 were followed-up for 3 months.

Baseline characteristics

The mean age was 36.1 ± 8.5 years for the TPM group and 33.8 ±10.3 years for the TCT group. Both groups had a female preponderance (TPM 86.2%, TCT 92%). There was no significant difference in demographic characteristics of the 2 groups regarding the presence of aura, smoking, alcohol use, water intake and physical activity (Table 1).

TPM and the TCT decreased the number of headache days per month from 13.1 days at baseline to 3.9 days (9.2 days; 67%) and from 15.3 days at baseline to 5.2 days (10.1 days; 65%) respectively after 3 months (p = 0.62). 26 patients (90%) in the TPM achieved more than 50% reduction in headache days compared to 20 patients (80%) in the TCT group (p = 0.99). There was also a decrease in the attack duration by 48% and 52% (p = 0.53) and in its severity by 3 and 2.6 points on the visual analog scale in the TPM and TCT groups respectively (p=0.38). The differences in frequency, duration and severity in both groups were not statistically significant (Table 2).

Table 2: Response to treatment by changes in frequency, duration and severity of headaches and reasons and frequency of drug discontinuation.

		Topiramate	Triple Combination	P-value
		N=29	N=25	
Frequency (days/ month)	Day 0	13.1 ± 6.7	15.3 ± 7.9	0.28
	Day 90	3.93 ± 2.7	5.2 ± 6	0.32
	Interval decrease	9.2 ± 5.6	10 ± 7.25	0.62
	Decrease in %	67%	65%	0.76
Duration (hour/ attack)	Day 0	37.2 ± 25.8	42 ± 25.9	0.5
	Day 90	15.8 ± 19	18 ± 21	0.68
	Interval decrease	21.4 ± 23.4	23.9 ± 23	0.532
	Decrease in %	48%	52%	0.7
Severity (on VAS)	Day 0	8.5 ± 1	9 ± 0.8	0.09
	Day 90	5.5 ± 1.7	6.4 ± 1.6	0.07
	Interval decrease	3 ± 2	2.6 ± 1.7	0.42
	Decrease in %	35%	29%	0.3
Reason for discontinuation	Lack of efficacy	4.50%	13.79%	0.07
	Side effects	29.50%	0%	0.0007

*VAS: Visual Analog Scale.

13 patients (29%) discontinued TPM due to side effects, mainly acral paresthesia, word finding difficulty, depression, somnolence and fatigue. Less common side effects included flank pain, cramps, irritability, alopecia, dry skin and nausea. To note that weight loss was a desirable effect for all the patients. In the TCT group, the only side effect was diarrhea in 1 patient out of 29 (3.44%)

None of the patients in both arms reported an increase in the use of abortive medication during the study period.

The combination of butterbur, magnesium and riboflavin as prophylaxis for migraine was not assessed before. Butterbur decreases migraine headaches by a maximum of 60% [5]. This butterbur extract activates the transient receptor potential ankyrin 1 channels which result in excitation of neuropeptide-containing nociceptors, followed by marked heterologous neuronal desensitization leading thus to the attenuation of pain and neurogenic inflammation which may explain how it improves migraine [6]. Riboflavin is also recommended in migraine prophylaxis. A systematic review done in 2017 found 5 out of 7 clinical trials showing a consistent positive therapeutic effect in adults [7]. Its beneficial effect may be the improvement of mitochondrial brain energy metabolism that reduces the susceptibility to migraine when brain energy demand increases due to both physiological and biopsychological factors [8]. Magnesium has been shown to improve migraine headaches in an abortive and a preventive manner, likely by acting on NMDA receptors, voltage-gated calcium channels inhibition, connexin channels, and other ion channels [9]. It is reasonable to expect a synergistic effect when combining these drugs of different mechanisms of action.

Our study included 73 patients with migraine headaches requiring prophylaxis. We compared TPM to TCT in this population and found that both of these treatments similarly decrease headache frequency by around 65-67%. The response to treatment is also evident by a decrease in the duration of the headaches around 50%

and in their severity around 30% in both arms. The control of the headache frequency, duration and severity is similar in both groups.

On the other hand, the side effect profile is much worse in the TPM group with a 30% discontinuation rate due to side effects compared to 3.5% in the TCT group (p= 0.007). Furthermore, around 14% of patients in the TPM group discontinued their treatment due to a lack of efficacy in comparison to 4.5 % in the TPM group (p = 0.07). This indicates that the TPM is as effective as TCT in headache control but has more side effects.

In this study, we prescribed TPM at 50mg/d and this resulted in 90% of the patients achieving more than 50% reduction in their headache days per month. The literature did not find such a good response at this dose and describes this improvement of headache only at 100 and 200 mg per day [10–12].

Gaul et al performed a study comparing the combination of riboflavin, magnesium and coenzyme Q10 to placebo and found a slight improvement in their patient population [13]. Our study has the advantage of comparing nutraceuticals to an already approved treatment for migraine.

The fact that the frequency of headache decreased in both treatment groups confirmed the efficacy of both treatments as prophylaxis for migraine headaches. The improvement in the severity and duration of the headaches in both groups could be secondary to the prophylactic treatment itself, but also to the lifestyle modifications recommended by the physician in the first visit. The patients who completed the study confirm no increase in the number of abortive therapies needed.

The reservation in using the TCT as a prophylaxis for migraine headaches in comparison to TPM is that it is three times more expensive. Thus, patients may sometimes accept the side effects of TPM in favor for the price of TCT.

The limitations of this study are the small number of patients and that it was open-label. Nevertheless, it proved the efficacy of both prophylactic treatments.

Conclusion

In conclusion, low dose TPM has an equipotent benefit in treating migraine headaches compared to the triple combination of butterbur, riboflavin and magnesium but has a higher frequency of side effects. Patients who do not tolerate the side effects of TPM will benefit from the TCT but this combination is more expensive.

References

1. Steiner TJ, Stovner LJ, Birbeck GL. Migraine: the seventh disabler. J Headache Pain. 2013; 14: 1.
2. Silberstein SD. Preventive Migraine Treatment. Continuum (Minneap Minn). 2015; 21: 973–989.
3. Tepper SJ. Nutraceutical and Other Modalities for the Treatment of Headache. Continuum (Minneap Minn). 2015; 21: 1018–1031.
4. Green Made PrevaMig. Pharmaholic. 2020.
5. Grossmann M, Schmidramsl H. An extract of Petasites hybridus is effective in the prophylaxis of migraine. Int J Clin Pharmacol Ther. 2000; 38: 430–435.
6. Benemei S, De Logu F, Li Puma S, Marone IM, Coppi E, Ugolini F, et al. The anti-migraine component of butterbur extracts, isopetasin, desensitizes peptidergic nociceptors by acting on TRPA1 cation channel. Br J Pharmacol. 2017; 174: 2897–2911.
7. Thompson DF, Saluja HS. Prophylaxis of migraine headaches with riboflavin: A systematic review. J Clin Pharm Ther. 2017; 42: 394–403.
8. Colombo B, Saraceno L, Comi G. Riboflavin and migraine: the bridge over troubled mitochondria. Neurol Sci. 2014; 35: 141–144..
9. Dolati S, Rikhtegar R, Mehdizadeh A, Yousefi M. The Role of Magnesium in Pathophysiology and Migraine Treatment. Biol Trace Elem Res. 2019.
10. Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schmitt J, et al. Topiramate for Migraine Prevention: A Randomized Controlled Trial. JAMA. 2004; 291: 965–973.
11. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews. 2013; 6.
12. Silberstein SD, Neto W, Schmitt J, Jacobs D. Topiramate in Migraine Prevention: Results of a Large Controlled Trial. Arch Neurol. 2004; 61: 490–495.
13. Gaul C, Diener H-C, Danesch U. Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: a randomized, placebo-controlled, double-blind, multicenter trial. J Headache Pain. 2015: 16.