Topiramate *vs.* Amitriptyline in prophylactic treatment of migraine: A controlled clinical trial

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INTRODUCTION

Migraine-related headache is a frequent problem in medical practice. Its prevalence is between 15 and 25% in the female population and between 6 and 10% in the male population.[1-3] Identifying and avoiding the triggering agents is the first treatment step. The second step is acute headache management with non steroid anti inflammatory drugs (NSAID), Ergotamine, or a Triptane. The third step is prophylactic treatment. Beta-blockers, calcium channel blockers, serotonin antagonists, antidepressants, antiepileptic drugs, and NSAID can be used for this.[4] Prophylaxis is used when the patient's headaches:

- Occur with a frequency of 3 or more each month.
- Interrupt his daily activities and quality of life.
- Has poor response to acute treatment.
- Under special conditions such as ophthalmoplegic migraine, basilar migraine, familiar hemiplegic migraine, prolonged aura, or migraine related stroke.[5]

The objective of the prophylactic treatment is to reduce the frequency and intensity of the migraine events, improve acute treatment response, and to restore the patient´s functional ability.[6,7] Amitriptyline has discrete collateral effects and is inexpensive. Theoretically, Topiramate has fewer

ABSTRACT

Background: Migraine-related headache is a frequent problem in medical practice. Its treatment begins by identifying and avoiding triggering agents. The next step is acute headache management and the third step is choosing the best prophylactic treatment for each patient. **Objective:** To compare the efficacy and cost of Topiramate vs. Amytriptiline as prophylactic treatment for migraine. **Materials and Methods:** Randomized clinical trial comparing the frequency and severity of migranous headache between Topirmate vs. Amitryptiline as measured by the Migraine Disability Assessment (MIDAS). These measurements were taken before and after the prophylactic treatment in both groups for 4 months. Their adverse effects were also compared as well as each group response to Ketorolac for acute headache management. **Results:** Thirty six patients were included in the study, eighteen patients in each group. We found a statistically significant reduction of the frequency and intensity of the migranous pain in both groups ($p<0.007$), without any significant difference between them. The number of side effects was greater for the Topiramate group (69) than for the Amitriptyline

Topiramato* vs. *Amitriptilina* *en el tratamientoprofiláctico de la migraña: Ensayo clínico controlado

RESUMEN

Antecedentes: *La cefalea relacionada con la migraña es un problema frecuente en la práctica médica, el tratamiento comienza por la identificación de agentes desencadenantes para evitarlos. La siguiente etapa es el manejo de la cefalea aguda y la tercera, consiste en la elección del mejor tratamiento profiláctico para cada paciente.* ***Objetivo:*** *Comparar la eficacia y costo de la amitriptilina vs. el topiramato como tratamiento profiláctico para la migraña.* ***Pacientes y métodos:*** *Ensayo clínico controlado que compara la frecuencia e intensidad de la cefalea migrañosa entre pacientes que recibieron topiramato vs. amitriptilina (18 en cada grupo), utilizando como medición la Evaluación de Discapacidad de la Migraña (MIDAS, por sus siglas en inglés). Estas mediciones fueron realizadas antes y después del tratamiento profiláctico por cuatro meses en ambos grupos. También se compararon los efectos adversos así como la respuesta al ketorolaco en*

group (43) (p <0.001). The Amtriptilyne group showed weight gain while the Topiramate group showed weight loss being this their main side effect. **Conclusion:** Topiramate and Amitriptyline are both effective prophylactic treatments for migraine. Drug election must be made according to the patient´s characteristics and economic possibilities.

Key words: Amitriptyline, migraine, prophylaxis, Topiramate.

cada grupo para el manejo agudo de la migraña. ***Resultados:*** *Se encontró reducción estadísticamente significativa en la frecuencia e intensidad del dolor migrañoso en ambos grupos (p<0.007), sin diferencias entre ambos grupos. La frecuencia de efectos colaterales fue mayor para el grupo de topiramato (n=69) que para el grupo de amitriptilina (n=43)(p<0.001). El aumento de peso fue el efecto indeseable más frecuente en el grupo que recibió amitriptilina mientras que la pérdida de peso lo fue para el topiramato.* ***Conclusión:*** *El topiramato y la amitriptilina son tratamientos profilácticos efectivos en el tratamiento profiláctico para la migraña. La elección del fármaco debe hacer de acuerdo a las características del paciente y posibilidades económicas.*

Palabras clave: *Amitriptilina, migraña, profilaxis, topiramato.*

collateral effects but it is expensive and therefore inaccessible to some patients.

Our objective was to compare the efficacy of Amitriptilyne and Topiramate administrated every 12 hours during 4 months and measure each group response to Ketorolac for acute headache management. The frequency and severity of their adverse effects were also measured.[8-10]

PATIENTS AND METHODS

We designed a randomized, double blinded, controlled clinical trial following the Guidelines for controlled trials of drugs in migraine.[11] Placebo was not considered as the guidelines state that it should only be used when the scientific question cannot be solved without its use. Placebo-controlled clinical trials for Amitriptyline and Topiramate were considered as references for this study. The study was performed at the first author private practice with the approval of the ethics committee of the Hospital Central Dr. Ignacio Morones Prieto in San Luis Potosi, S.L.P., Mexico.

The inclusion criteria were male and female subjects between the age of 18 and 60, with a previous diagnosis meeting the International Headache Society (IHS) criteria. This diagnosis made at least 6 months prior to the clinical trial and before the age of 40. Only patients with 3 or more migraine events per month during the last four months and with a signed letter of informed consent were considered. Exclusion criteria were pregnancy or lactation, patients presenting other types of headache, allergy to Topiramate or Amitriptyline, history of renal lithiasis, glaucoma, schizophrenia, bipolar disorder history, and infectious, immunologic, cardiovascular, prostatic or metabolic disease.

The patients were randomized to receive the same dose of Topiramate or Amitriptyline: 1mg/kg/day (0.8 - 1.2 mg/kg/day according to the weight of each participant) for four months. Because of the 25 mg presentation of both drugs, doses were adjusted to an average of 1 mg/kg/day. Topiramate and Amitriptyline were prepared in identical presentations by the Janssen-Cilag Company. Both the frequency and severity of the migraine events were measured using MIDAS before and after the prophylactic treatment.[12-20]

The response to Ketorolac, used as treatment for acute migraine headache presentation in 30 mg sublingual doses, was evaluated by obtaining a pain score two hours after taking the drug. The scale used was the following: 0 = No pain, 1 = Minimal pain, 2 = Moderate pain, 3 = Intense pain. Ketorolac was provided by the Syntex-Roche Company.

We also measured Body Mass Index (BMI) variations in both groups. Where BMI = weight/height^2.

Sample Size

Sample size was estimated based on a hypothetical 30% delta of improvement both in intensity and frequency of the migraine. We also considered the criteria suggested by Browne[21] for sample size calculation of a pilot study. The number of subjects needed per group was 18.

Randomization

Prior to the study, a list of randomized sequential numbers was generated with R.2.0.1. This was maintained

by a blinded collaborator unrelated to the hospital and trial. The same collaborator prepared the drugs according to the list provided. Medications were administered only by the infirmary staff that was also blinded from the study groups. Recruitment was sequential and done by the main researcher (also blinded).

Statistical analysis

The analysis was performed using statistical software R version 2.0.1 with a 95% confidence level.[22] Descriptive statistics were calculated. Normality was tested with the Shapiro-Wilk procedure. Variance homogeneity was tested with Levene's procedure. T-student was used to compare the MIDAS scores and the rest of the studied variables in both groups.

RESULTS

Thirty six patients were included in the study, eighteen patients in each group. There were 15 women in the Topiramate group and 16 in the Amitriptyline group.

The basal values of the anthropometric variables were similar in both groups (Table 1). The initial MIDAS scores did not show significant differences between groups. The mean basal MIDAS score for the Topiramate group was 63 (SD = 6.6) and for the Amitriptyline group it was 63.39 (SD = 5.0) (Figure 1). Four patients in the Topiramate group did not conclude the study. Three of them presented intolerance (somnolence, clumsiness and paresthesia) to the drug. The other patient was dropped from the study after presenting headaches associated with left hemiparesis. A magnetic resonance was performed and cortical frontal parietal hiperintensity was observed. Positive antinuclear antibodies were also found. The investigator decided to exclude the patient from the study considering that a serious adverse event, which was not necessarily drug related, had occurred. In the Amitriptyline group, 3 patients did not complete the study because they presented intolerance to the treatment (somnolence and appetite changes) and 2 didn't return for their programmed consultations. However all patients were considered on an intension-to-treat basis with an initial score of 70 and a final score of 40 on the MIDAS scale.

The number of total events (migraine-related headaches) presented during the four months preceding the study were 284 and 116 post-treatment for the whole Topiramate group ($p < 0.001$) and 272 pre-treatment and 87 post-treatments for the Amitriptyline group ($p < 0.001$). No significant differences between groups were found ($p = 0.88$) (Figure 1).

We also analyzed the response to Ketorolac when patients had intense migraine-related headaches during the trial. The Topiramate group total initial pain score was of 230 points and two hours after the administration of the medication it was of 103. The total initial pain score for the Amitriptyline group was of 126 and two hours after de administration of the medication it was of 57 ($p < 0.05$) (Figure 2). It appears that the Amitriptyline group had a less intense headache ($p < 0.27$). Both groups had a similar frequency of the events and showed a similar improvement with Ketorolac.

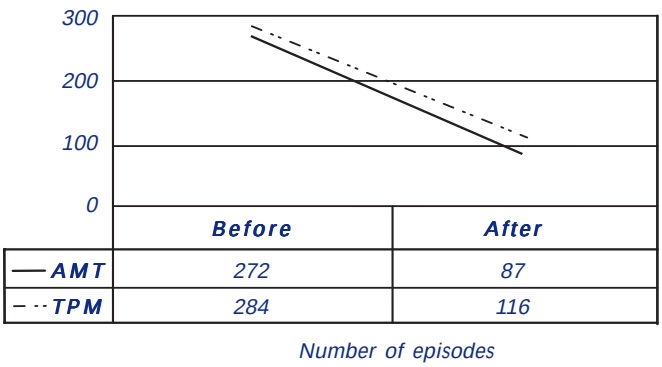

Figure 1. *Number of Migraine episodes before and after the treatment.* ***AMT:*** *Amitriptiline.* ***TPM:*** *Topiramate.*

Table 1
Basal anthropometric variables per study group in patients receiving Migraine prophylaxis

Variable	*Topiramate Mean ± SD*	*Amitriptiline Mean ± SD*	*P*
Age (years)	*36.3± 10.5*	*31.6± 9.6*	*0.16*
Height (cm)	*159.8± 8.1*	*158.2± 8.9*	*0.57*
Weight (kg)	*68.4± 14.6*	*61.7± 10.5*	*0.21*
Initial MIDAS	*63.0± 6.6*	*63.4± 5.0*	*0.84*
Initial BMI	*26.8± 5.1*	*24.6± 3.3*	*0.14*

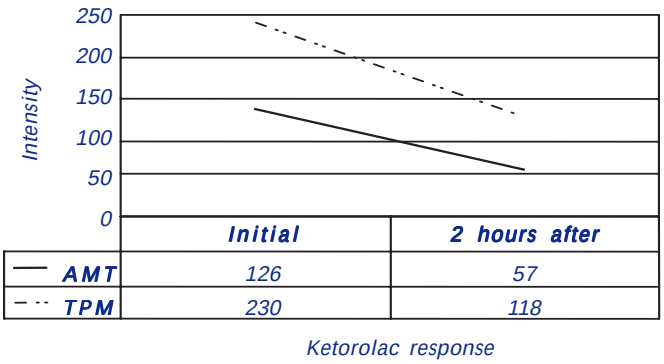

Figure 2. *Migraine intensity score. Addition of all pain intensity given by each patient was measured.* ***AMT:*** *Amitriptiline.* ***TPM:*** *Topiramate.*

Finally, the patient´s satisfaction was compared in both groups; 55% of the patients from Topiramate group graded the response as "excellent" or "very good", while 72% of the Amitriptyline group answered the same. The difference was not statistically significant ($p = 0.65$).

In the Topiramate group 9 patients lost weight and 7 gained weight. In the Amitriptyline group 2 lost weight and 12 patients gained weight ($p = 0.023$). The mean weight loss for Topiramate was of 0.1633 kg and the mean weight gain was of 1.0222 kg for Amitriptyline. There was no statistically significant difference in BMI between both groups at the beginning of the treatment ($p > 0.141$).

Other adverse effects: Constipation and appetite alterations were more frequent in the Amitriptyline group. Patients in both groups reported dry mouth with the same frequency. Vertigo, depression, irritability, somnolence, abdominal distension and paresthesia were reported in the Topiramate group.

The number of side effects was greater for the Topiramate group (69) than for the Amitriptyline group (43) ($p < 0.001$).

DISCUSSION

Headache is the main cause of patient consultation at the first level of medical attention. The most common diagnosis for these patients are Migraine and Tensional Headache.[23-25] In the USA migraine causes a loss of 150 million work days and 329,000 school days each year. This shows the importance of finding an effective, low-cost, and accessible safe treatment to improve the patient´s quality of life.[26,27]

This is the first study that compares both drugs in the Mexican population. Amitriptyline has been sold for more than 50 years. It was first reported as a prophylactic treatment for migraine in 1973.[4] Topiramate is the most studied antimigraine drug and both are included in the Guides for Treatment of the American Academy of Neurology[10] as a Group 1 drug (high efficacy and minimal to moderate collateral effects) and in the Group A drugs (well designed drug with consistent results in randomized clinical trials).

This trial demonstrates that Topiramate is as effective as Amitriptyline for migraine control. We suggest that future studies should be done to evaluate the pain response in the patients diagnosed with migraine.

The frequency of the collateral effects could be used to decide which drug to prescribe. The most important of these is weight variations.[28-32] We found an average weight gain of 1 kg in the Amitriptyline group and an average loss of 160 g in the Topiramate group at the end of the study. Topiramate has an anorexic effect and Amitriptyline causes weight gain both effects have been described in the literature.[29-32]

While not necessarily true in the United States, in Mexico Topiramate is much more expensive than Amitriptyline. Even with the difference in prices, treatment with both medications proves to be cost-effective. This is because of the great amount of work and school days lost without it and the overall improvement on the patient's quality of life.[33,34] The price for Ketorolac is in average USD $0.50 per pill.[34]

Topiramate has been shown to be more efficient (50%) than placebo in migraine prophylaxis in two large controlled trials.[35] Amitriptyline has also shown more efficacy than placebo as a migraine prophylactic drug.[36] The drug election for each patient should take into account his particular characteristics. More studies should be performed to verify these results as the sample size was small.

ABBREVIATIONS

NSAID: Non steroid anti inflammatory drugs.
IHS: International Headache Society.
MIDAS: Migraine Disability Assessment.
BMI: Body Mass Index.
TPM: Topiramate.
AMT: Amitriptyline.

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