"Efficacy of memantine compared with sodium valproate in the prophylactic treatment of migraine" Randomized controlled clinical trial.

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SAN LUIS POTOSÍ AUTONOMOUS UNIVERSITY

MEDICAL SCHOOL

CENTRAL HOSPITAL "DR. IGNACIO MORONES PRIETO" CENTRAL HOSPITAL

Thesis to obtain the diploma in the specialty of Neurology.

"Efficacy of memantine compared with sodium valproate in the prophylactic treatment of migraine" Randomized controlled clinical trial.

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SUMMARY

Objectives
To compare the efficacy of Memantine versus sodium Valproate as a prophylactic treatment of episodic migraine for three months. Evaluating efficacy (measured in reduction in the number of migraine attacks per month) and safety (measured in frequency and severity of adverse events), as well as response rate.

Subjects and methods
The prospective, randomized, double-blind, controlled clinical trial was conducted with patients who attended the outpatient clinic, either by referral or by the Emergency Department of the Neurology Service of the Central Hospital. Participants were randomized into two groups, the Memantine group received doses of 10 mg twice a day and the Sodium Valproate group received 500 mg twice a day, both groups for 3 months.

Results
A total of 33 patients were included in the study, 27 of them concluded the study; 14 in the Memantine group and 13 in the Sodium Valproate group. The Memantine group with mean number of migraine attacks per month prior to treatment of 5.31 (SD $\pm$ 1.54) and after three months of treatment, mean number of migraine attacks per month 0.93 (SD $\pm$ 1.49) with a decrease of 4.21 (SD+1.76) migraine attacks p <<0.001. In the VPA group the mean number of migraine attacks before treatment was 5.35 (SD $\pm$ 1.11) migraine attacks per month and after three months of treatment the mean number of migraine attacks per month was 0.77 (SD $\pm$ 1.16), with a decrease of 4.5 (SD $\pm$ 1.39) migraine attacks p <<0.001. All 27 patients had a good response rate. Adverse effects were infrequent in both groups and of minimal severity.

Conclusions
Memantine could be a new prophylactic treatment option in migraine, the study showed that there was no inferiority of Memantine compared to sodium Valproate as a prophylactic treatment for episodic migraine.

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LIST OF ABBREVIATIONS AND SYMBOLS

- **IHS:** International Headache Society
- **NMDA:** (N-methyl-D-aspartate)
- **5-HT 1D**: Serotonin I Receptors$_D$
- **CGRP**: Calcitonin gene
- **PACAP-38:** Pituitary adenylate cyclase activating polypeptide.
- **ICHD-III:** III edition of the International Classification of Headaches
- **AAN**: American Academy of Neurology
- **VPA**: Sodium Valproate
- **GABA** - γ-aminobutyric acid
- **MIDAS**: Migraine Disability Assessment
- **VAS**: visual analog scale

LIST OF DEFINITIONS

- **Episodic migraine:** the presence of migraine ≤ 14 days per month.

- **Prophylactic treatment of migraine**: preventive treatment of migraine attacks with the purpose of reducing the frequency, intensity and duration of migraine attacks.

- **Frequency of migraine attacks:** the number of migraine attacks during the month.

- **Treatment response rate:** a decrease equal to or greater than 50% in the frequency of days with migraine compared to baseline.

- **Migraine disability:** defined numerically according to the MIDAS (Migraine Disability Assessment) survey, (where 0-5=no disability, 6-10 points mild disability, 11-20 points moderate disability, and >21=severe disability).

DEDICATION

BACKGROUND

Migraine is a primary headache, currently one of the three most disabling diseases worldwide. [1] It has an annual and lifetime prevalence of 18% and 33% in women, and 6 to 13% in men respectively, with a predominance in women (3:1). [2] The age of onset with the highest prevalence is 25 to 55 years [3]

Migraine is described by the International Headache Society (IHS) as recurrent episodes of headache lasting from 4 to 72 hours, characterized by: unilateral localization, pulsating character, moderate or severe intensity, worsening with physical activity and association with nausea or photophobia and/or phonophobia. The IHS also classifies migraine according to the frequency of attacks: episodic migraine when the headache occurs less than 15 days a month, and chronic migraine, when the headache occurs 15 or more days a month for three months, and for at least 8 days a month with migraine headache characteristics. [4]

The subtypes of migraine with respect to its clinical presentation are: migraine with aura and without aura.[4] Up to one third of migraine patients present with aura, with visual symptoms being the most frequent.[5]

Four phases have been identified during migraine: prodromal phase, aura, headache, and postdrome. The prodromal phase is characterized by premonitory symptoms hours before the headache, including difficulty concentrating, irritability, fatigue, repetitive yawning, neck stiffness and photophobia. [6]

Aura is characterized by recurrent episodes, lasting from 5 minutes to 60 minutes, with unilateral transient visual, sensory or other central nervous system symptoms, which develop progressively, usually preceding headache and migraine-associated symptoms.[4] The genesis of aura is NMDA (N-methyl-D-aspartate) receptor activation and disseminated cortical depression. Disseminated cortical depression is an extreme depolarization of the cell membranes of glia and neurons that produces alteration of the ionic gradient, an increase in extracellular potassium concentrations, glutamate release, and a transient increase followed by a decrease in cerebral blood flow.[6]

The pain phase of migraine is due to activation and sensitization of the trigeminovascular pain pathway which innervates intracranial structures, including the eye, dura mater, large brain cases and venous sinuses. It has been shown that it involves neuronal presynaptic activation by serotonin I receptors$_D$ (5-HT 1D) results in the release of calcitonin gene (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP-38), which are neuroinflammatory peptides. The post synaptic effect on the meninges includes the activation of the arachidonic acid cascade which conditions inflammation and vasodilatation, stimulates nociceptive pain afferent to the first branch of the trigeminal nerve. [7]

The diagnosis of migraine is clinical and must meet the criteria of the III edition of the International Classification of Headache Disorders (ICHD-III), which are for migraine without aura:
At least five crises that meet criteria B-D.

A. Headache episodes lasting 4 to 72 hours (untreated or unsuccessfully treated).
B. The headache has at least two of the following four characteristics:
    1. Unilateral localization.
    2. Pulsatile character.
    3. Pain of moderate or severe intensity.
    4. Worsened by or conditioned by the abandonment of habitual physical activity
       (e.g., walking or climbing stairs).
C. At least one of the following during headache:
    1. Nausea and/or vomiting.
    2. Photophobia and phonophobia.
D. Without better explanation by another diagnosis of ICHD-III.

Non-pharmacological treatment of migraine goes hand in hand with pharmacological treatment, one of which is to avoid the factors that trigger migraine attacks, and to make the respective lifestyle modifications. Pharmacological treatment is divided into abortive (that which is administered at the time of the headache) and prophylactic (that which is administered daily to reduce the probability of migraine episodes). [8]

The aim of prophylactic treatment is to reduce the frequency, duration and intensity of migraine attacks, improve response to acute treatment, improve functionality and reduce disability.[9]

The American Academy of Neurology (AAN) recommends initiating prophylactic treatment in migraine patients with one or more of the following characteristics[9]

1. Recurrent migraine, which interferes with the patient's activities of daily living and quality of life.
2. Frequent headaches.
3. Who have an inadequate response or contraindication to abortive treatment.
4. Adverse events to abortive treatment.
5. Infrequent migraine conditions: Ophthalmoplegic migraine, basilar migraine, hemiplegic, prolonged aura, migraine infarction.

The IHS defines response to treatment as a decrease equal to or greater than 50% in the frequency of migraine days compared to baseline.[10]

The American Academy of Neurology guideline for the prophylactic pharmacological treatment of episodic migraine classifies divalproate sodium, valproate sodium (VPA), topiramate, metoprolol and propranolol in level A (Drugs with established efficacy). [11]

Valproic acid (2-propylpentanoic acid) was first synthesized in 1882 as an analog of valeric acid, which is naturally found in valerian. Valproic acid, sodium valproate or a mixture of the two (sodium divalproate), with mechanism of action characterized by increasing or enhancing γ-aminobutyric acid (GABA) neurotransmission, blockade of voltage-dependent sodium channels and T-type calcium channels.[12] In 2013 Cochrane conducted the review: Valproate for episodic migraine prophylaxis (Lindae et al)[12] where they evaluated 10 clinical trials. Two crossover clinical trials for sodium Valproate demonstrated a significant reduction in headache frequency compared to placebo (MD -4.31 95% CI -8.32 to -0.30) which shows us in clinical terms an approximate reduction of four headaches per 28 days. The Jensen 1994 study[13] showed that sodium valproate is superior to placebo (OR 4.67; 95% CI 1.54 - 14.14), suggesting that patients are three times more likely to have a reduction equal to or greater than 50% in the frequency of headaches compared to placebo.[13] The recommended dose for migraine is 500 to 1000 mg per day.[11] The most frequent adverse effects are: asthenia, fatigue, dizziness/vertigo, nausea, tremor and weight gain. [12]

In recent years, there has been an increased interest in the use of glutamate receptor antagonists for migraine prophylaxis, such as Memantine. Within the pathophysiology of migraine, glutamate is involved in disseminated cortical depression, trigeminal-vascular activation.[14] Other studies corroborate its role, reporting elevated glutamate levels in cerebrospinal fluid in patients with chronic migraine in the ictal period and elevated serum levels in patients with migraine. In addition, elevated levels of glutamate in the trigeminal-cervical complex have been evidenced after experimental stimulation in the structures of the dura mater and in the ventro-posteriomedial thalamic nucleus. [15]

In 2006 Charles and colleagues reported a case series with a total of 71 patients diagnosed with migraine refractory to prophylactic treatment. The headache frequency per month ranged from 4 to 30 (median =12.5) after treatment with Memantine for two months with a headache frequency per month of 0 to 22 (median =3.5). Only 54 patients answered the mailed survey of which 67% (n=37) presented a greater than 50% reduction in headache frequency. However, this study had limitations such as being retrospective, without a control group and without blinding. Therefore, it only suggested Memantine as a possible treatment for migraine.[16]

In 2008 Bigal and colleagues conducted the first open clinical trial, a pilot study to evaluate the efficacy and safety of memantine as a prophylactic treatment in patients diagnosed with refractory migraine. With a sample of 28 participants who presented a baseline frequency of headache days of 21.8 days per month, they received Memantine from 10 mg to 20 mg per day for three months. A decrease in the frequency of headache days was obtained to 16.1 ($P<0.01$). Whereby the authors concluded that Memantine as a prophylactic treatment is safe and effective in patients with refractory migraine.[17] In 2015 Noruzzadeh and colleagues conducted the first randomized double-blind placebo-controlled clinical trial to evaluate the efficacy of Memantine as a prophylactic treatment of migraine without aura. The

Memantine group had a greater reduction in migraine attack frequency compared to placebo, which was a difference of 2.3 attacks per month with a $P<0.001$. [14]

Based on two of the three clinical trials of prophylactic treatment with Memantine that have been conducted, memantine could be an effective new treatment alternative.

JUSTIFICATION

The frequency of migraine attacks is a risk factor for progression from episodic migraine to chronic migraine, the recommendation is to initiate prophylactic treatment.[13] The rate of adherence to prophylactic migraine treatment is low; adherence has been reported to range from 26% at 6 months to 17% at 12 months. [18] The main causes of low adherence to prophylactic treatment are side effects and low efficacy of the treatment. [8]

In the review conducted in PubMed, Scopus and Web Science there is no clinical trial from 2000 - 2018 comparing the efficacy of memantine against sodium valproate, the latter being a first-line drug in prophylactic treatment.

The study was presented and approved by the Research and Ethics Committees of the Central Hospital and was registered in Clinical Trials of the National Institutes of Health of the United States, being accepted and approved by all of them for its performance, with registration 74-19 in the HC and NCT04698525 for Clinical Trials.

The Neurology service of the Central Hospital "Dr. Ignacio Morones Prieto" has a high prevalence of patients with migraine in the outpatient clinic, in 2018 there were about 600 consultations for primary headaches. In addition, we have the support of the pharmacological company who will donate the corresponding treatment of memantine and sodium Valproate for 3 months.

For this reason we propose this clinical trial to compare the efficacy of Memantine against sodium Valproate in the prophylactic treatment of migraine, and to consider it as a new drug for the prophylactic treatment of migraine.

Unfortunately, due to the pandemic that we faced during the year 2020 when the patients were to be recruited for the study, we were unable to reach the goal set for patient inclusion. However, although the number of participants was lower, we were able to determine with them the difference between pre- and post-treatment for both drugs. In two population groups totally comparable in their demographic characteristics.

WORKING HYPOTHESIS

The frequency of migraine attacks under prophylactic treatment with Memantine is equal to or less than that observed with sodium valproate for three months in adult patients with episodic migraine.

OBJECTIVES

A. General Objective

1. To compare the efficacy in reducing the frequency of migraine attacks under prophylactic treatment with Memantine at a rate of 20 mg divided into two doses per day against sodium Valproate at a rate of 1000 mg divided into two doses per day for three months in adult patients with migraine.

B. Specific objectives

1. To evaluate the baseline frequency of migraine attacks in adult patients with migraine 28 days prior to the study.
2. To evaluate the frequency of migraine attacks of the group - treatment with sodium Valproate for three months, in adult patients with migraine.
3. To evaluate the frequency of migraine attacks of the group - treatment with Memantine for three months, in adult patients with migraine.

C. Secondary **objectives**

1. Evaluate the response rate to treatment.
2. Assess migraine disability using MIDAS (Migraine Disability Assessment) before and after treatment.
3. To assess pain intensity in migraine attacks with the visual analog scale (VAS) before and after treatment.
4. Identify adverse effects to sodium Valproate and Memantine.

SUBJECTS AND METHODS

Site
The study was conducted at the outpatient clinic of the Hospital Central Dr. Ignacio Morones Prieto, San Luis Potosí.

Design
Prospective, randomized, double-blind, controlled clinical trial.

Inclusion criteria
1. Men and women from 18 to 65 years old.
2. Diagnosis of episodic migraine according to the ICHD-III of the IHS at least one year prior to the study.
3. Must present at ≥ 4 - ≤ 8 migraine attacks per month.
4. Not receiving prophylactic treatment for migraine headache.
5. Sign informed consent

Exclusion Criteria
1. Pregnant or breastfeeding patients.
2. Patients with other types of non-migraine headache.
3. Allergy to Sodium Valproate and/or Memantine
4. Being a carrier of systemic disease (infectious, immunological or metabolic processes) or cardiovascular disease (myocardial, coronary or valvular heart disease) that prevents participation in the study.

Elimination Criteria
1. Patients who do not tolerate the study drug during titration.
2. Patients who voluntarily leave the study.
3. Patients lost to follow-up.

Variables

Dependent´s
1. Frequency of migraine attacks: Defined as the number of migraine attacks presented during the month. It is a continuous variable.
2. Treatment response rate: Defined as a decrease equal to or greater than 50% in the frequency of days with migraine compared to the baseline situation. It is a continuous variable.
3. Migraine disability: Numerically defined according to the MIDAS (Migraine Disability Assessment) survey, (where 0-5=no disability, 6-10 points mild disability, 11-20 points moderate disability, and >21=severe disability). It is an ordinal variable.

4. Pain intensity: Numerically defined according to the visual analog scale (VAS) the pain intensity of the migraine attack before and after prophylactic treatment where 0=no pain and 10=very severe pain). It is a continuous variable.
5. Adverse treatment effects: Any response to a drug that is noxious, unintended and occurs at doses usual in our case for prophylactic treatment. The ICH Harminised Tripartite guideline classifies any of the following: non-severe and severe, severe being any that results in death, is life threatening, requires hospitalization, results in disability.

Independent

1. Treatment
   Group A: Memantine at a dose of 20 mg per day divided into two doses per day (morning and evening) for three months.
   Group B: Sodium valproate at a dose of 1000 mg per day divided into two doses per day (morning and evening) for three months.

Confusers

1. Age: years completed by the patient. Migraine is most prevalent from 25 to 55 years of age, so it was expected that our patients would be young, and it was hoped that simple randomization would eliminate this bias.
2. Gender: is the organic condition that distinguishes men from women. It is a qualitative, nominal variable. The prevalence in women is higher with a 3:1 ratio between women and men, respectively. Therefore, a greater participation of women in the study was expected, 3 men in the Sodium Valproate group and 3 in the Memantine group participated and concluded the study.

Randomization method

By computer until the sample size is reached. Randomization will be performed by computer. Computer generated numbers will be used for the creation of a randomization sequence.

Method of follow-up.

Double blind, the blindness is for the investigator who does not know the assigned medication (blindness 1) and for the patient (blindness 2) who does not know the assigned medication. At the end of the visit, a third person, who is part of the research team, will give the medication (tablets for 4 weeks) and will be the only one who could open the blindness security code if necessary.

Work Plan

Recruitment was carried out from July 2019 to August 2020 in the outpatient service of Neurology, Referral and Emergency of the Central Hospital. Patients who met the inclusion criteria and signed the informed consent form participated in the study. At the time of recruitment, they will be randomized by computer by an external collaborator of wide experience, assigning them a number and an external collaborator will distribute them in one of the two groups. Double-blinding will be performed, both for the researcher and for the participant, the only one who knew which group they were assigned to was the one who performed the randomization.

A total of 4 visits were made, with a time interval of one month for each visit.

Visit 1 (Week 0): a clinical history was taken, a physical examination was performed, the informed consent form was signed (Annex 1), and the inclusion and exclusion criteria form (Annex 2) was filled out by the researcher. A "Migraine diary" (Annex 3) was provided to the patient where the migraine attacks were recorded to identify the baseline characteristics such as frequency, intensity, duration.

Visit 2 (Week 4): the patient was given the medication assigned by the corresponding randomization. Memantine or VPA was prescribed as an oral tablet at night for one week and then increased in the second week to one tablet in the morning and at night. The baseline MIDAS survey was performed to identify migraine disability. The baseline "Migraine Diary" was collected and a new "Migraine Diary" was provided.

Visit 3 (Week 8): Frequency of migraine attacks, adverse effects and tolerability of treatment were assessed by the investigator. The "Migraine Diary" was collected and a new "Migraine Diary" was provided. The corresponding medication was given for four weeks.

Visit 4 (Week 12): Visit 3 (Week 8): Migraine attack frequency, adverse effects and tolerability of treatment were assessed by the investigator. The "Migraine Diary" was collected and a new "Migraine Diary" was provided. The corresponding medication was given for four weeks.

Visit 5 (Week 16): Frequency of migraine attacks, adverse effects and tolerability of treatment were evaluated by the investigator. The "Migraine Diary" was collected. The MIDAS survey was performed again to assess post-treatment disability.

Financing

A donation of the pharmacological treatment Memantine and sodium Valproate was received from the Torrent Pharma Laboratory (Annex 5).

STATISTICAL ANALYSIS

Sample size calculation

Normal distribution model: $x=Z(^{c}/_{100})^{2} r(100\text{-}r)$. $n=^{N x}/_{((N\text{-}1)E^{2}+x)}$ $E=Sqrt[^{(N-n)x}/_{n(N\text{-}1)}]$. With a margin of error of 5%, a confidence level of 95%, with a prevalence of migraine in the general population of the State of San Luis Potosi of 271800 with a distribution response of 15%.[19] The recommended sample size is 196 participants. Due to the fact that a pilot study will be conducted, 10% of the sample size will be taken to make it representative, a sample size of 20 participants for each group is decided.[20]

Descriptive statistical analysis of the variables of interest will be performed. For continuous variables, analysis will be performed using the Student's t-test. The number of participants (n) and the final analysis was calculated using R (56). Alpha, the probability of type 1 error was set to 0.05 and the power was set to 0.8 which resulted in the probability of a type 2 error of 0.2, given that we limited to 20 participants per treatment, delta was estimated with this restriction.

ETHICS

Risk category: Risk greater than minimal.
Authorization will be requested from the Research Ethics Committee of the Hospital Central "Dr. Ignacio Morones Prieto". The study will be performed according to the Mexican Official Standard for the conduct of clinical studies in humans NOM-012-SSA3-2012[21] , and international standards (Declaration of Helsinki[22] and International Harmonized Guide (ICH) of Good Clinical Practices[23]) The diagnostic maneuvers that will be used are considered of higher than minimal risk because it is an interventional study according to article 17 of the regulations of the General Law of Health[23] on Health Research.

In addition, it is a priority to safeguard the physical and mental integrity of the patient, and privacy is respected by maintaining the confidentiality of the data at all times during the research, as well as the data obtained at the end of it. The consent of the legal subjects will be obtained through a document specifying the objective of the study, the duration, as well as the methods and medications that they will receive randomly.

RESULTS

Eighty-seven patients were evaluated, of which only 33 patients were included in the study. In the Memantine group with 16 patients and 17 in the Sodium Valproate (VPA) group; only 27 patients concluded the study.

Demographic data: In the Memantine group there were 13 women and three men, in the VPA group 13 women and four men. The average age of the patients in the Memantine group was 31.18 ± 10.94 years and those in the VPA group 31.58 ± 7.51 years (*Table 1).*

Migraine characteristics: In the Memantine group 62.5% (n=10) had a family history of migraine and in the VPA group 52% (n=9). The age of migraine onset in both groups was 18 years on average. Headache pain characteristics in the memantine group were pulsatile in 81.25% (n=13), hemicranial 87.5%% (n=14), disabling activities of daily living 93.75% (n=15), with photophobia in 87.50% (n=14), sonophobia 100% (n=16), disabling activities of daily living 93.75% (n=15), nausea and vomiting in 87.5% (n=14) in the VPA group was pulsatile in 76.47% (n=13), hemicranial 76.47% (n=13), disabling activities of daily living in 94.12% (n=16) with photophobia in 94.12% (n=16), sonophobia 58.82% (n=10), nausea and vomiting in 100% (17). With respect to aura only present in three patients in the memantine group and in four in the VPA group. (*Table 1: Migraine characteristics.)*

Primary objective: In the Memantine group with average migraine attacks before treatment of 5.31 (SD+1.54) per month in the three months before and after three months of treatment 0.93 (SD+1.49) per month, with a decrease of 4.21 (SD+1.76) migraine attacks *p* <<0.001 *(Figure 1).Figure 1).* In the VPA group with pretreatment mean migraine attacks of 5.35 (SD+1.11) and after three months of treatment of 0.77 (SD+1.16) (*Figure 2*) with a decrease of 4.5 (SD+1.39) migraine attacks *p* <<0.001 *(Figure 3)*.

Figure 1. Frequency of migraine attacks in the Memantine group.

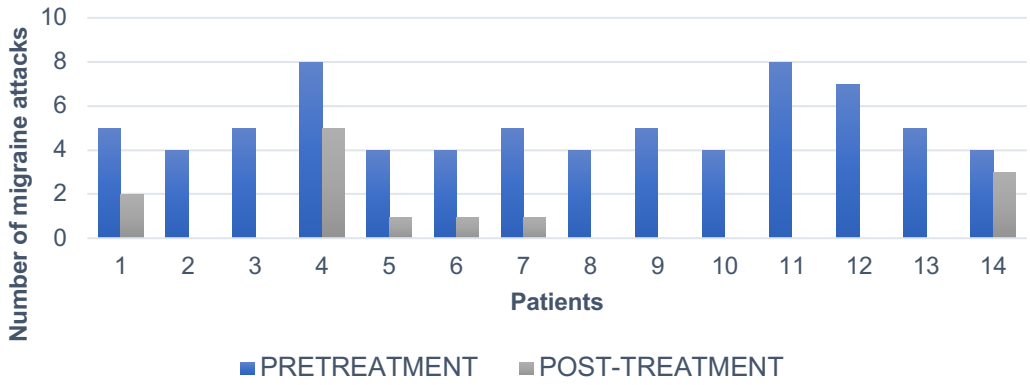
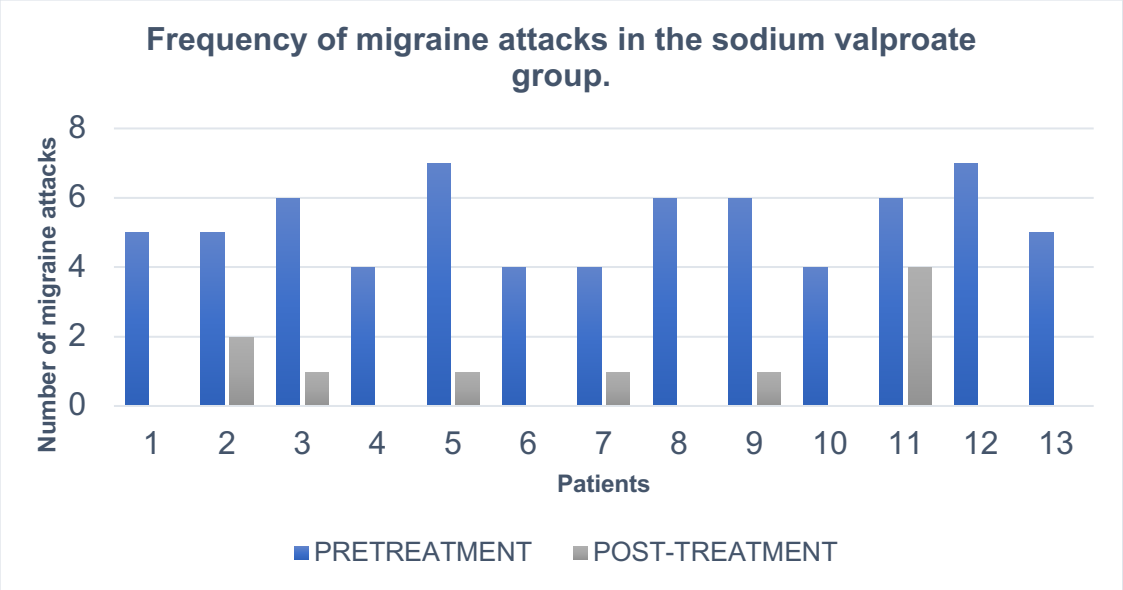
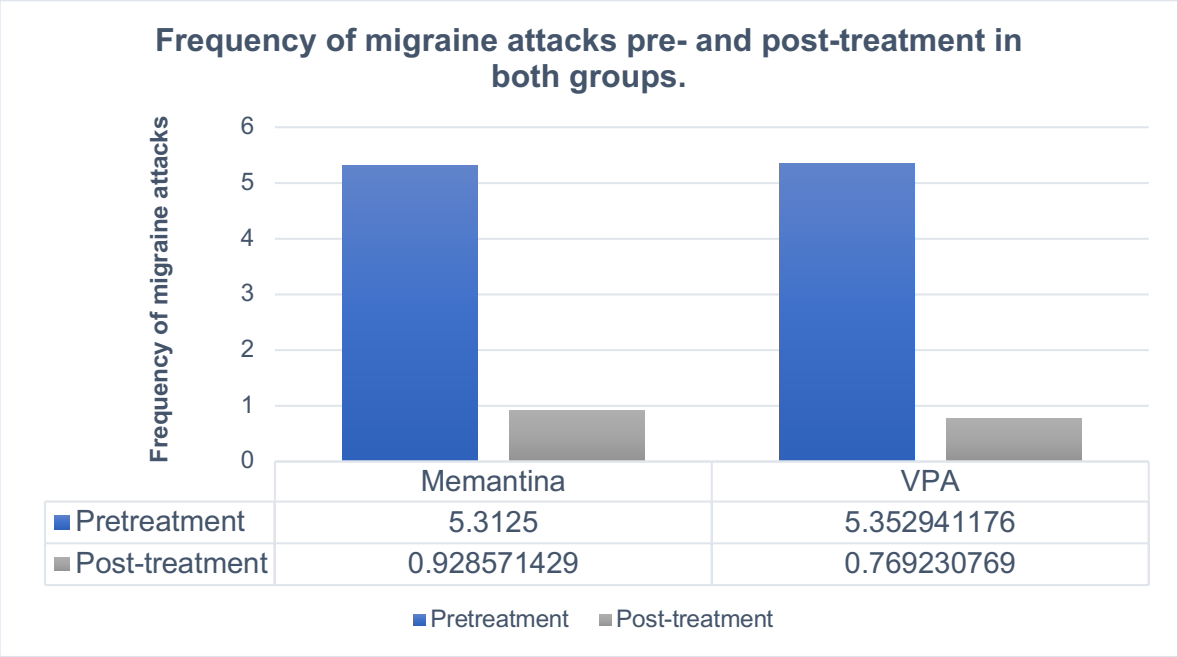


Table 1 . Baseline characteristics of both groups.

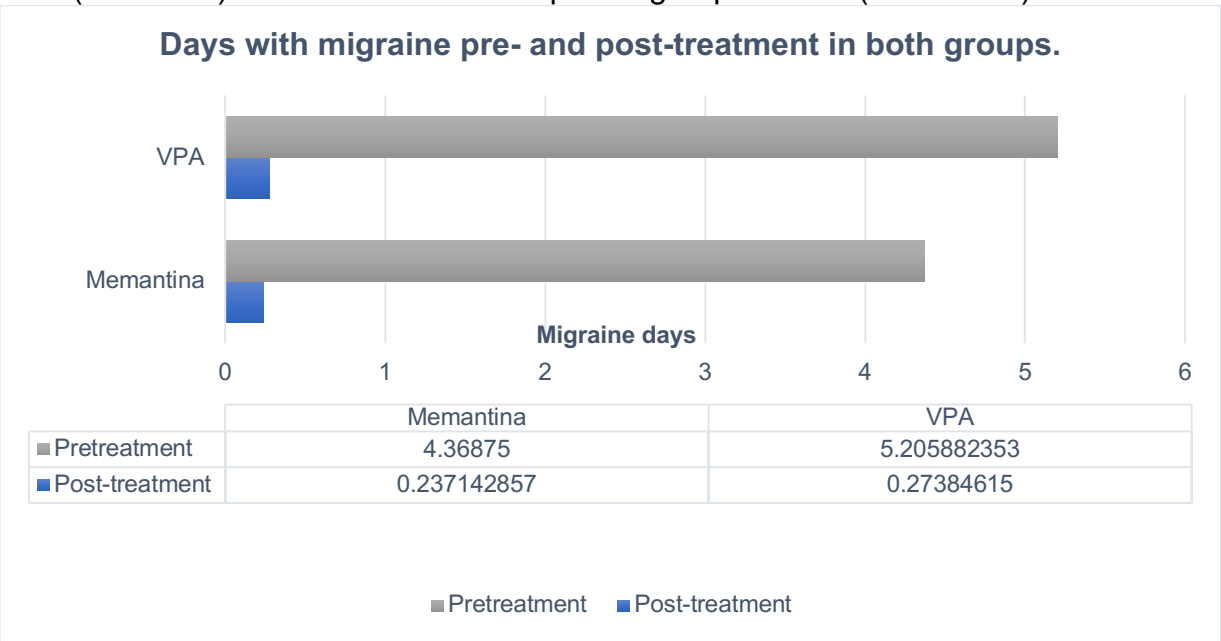
Variable	**Memantine**	**Sodium Valproate**
Sex (%)		
Woman	13 (81.25%)	13 (76.47%)
Man	3 (18.75%)	4 (23.52%)
Average age	31.18 ± 10.94	31.58 ± 7.51
Family history of migraine (%)	10 (62.5%)	9 (52.94%)
Characteristics of migraine		
Type of pain (%)		
Pulsating	13 (81.25%)	13 (76.47%)
Oppressive	3 (18.75%)	4 (23.52%)
Pain location (%)		
Hemicranial	14 (87.5%)	13 (76.47%)
Holocranean	2 (12.5%)	4 (23.52%)
Photophobia No. (%)	14 (87.50%)	16 (94.12%)
Sonophobia No. (%)	16 (100%)	10 (58.82%)
Nausea and vomiting No. (%)	14 (87.5%)	17 (100%)
Incapacitates activities of daily living	15 (93.75%)	16 (94.12%)
Migraine without aura	13 (81.25%)	13 (76.47%)
Migraine with aura	3 (18.75%)	4 (23.52%)





Secondary objectives. - Treatment response rate which is referred to as the decrease of equal or more than 50% of migraine days. In the Memantine group with pretreatment migraine days 4.3 (SD+ 1.93) and post treatment 0.23 (SD+ 0.44) with a mean decrease in migraine days of 3.9 (SD+ 1.89) *p* <<0.001. In the Sodium Valproate group with pretreatment migraine days 5.5 (SD+ 1.25) and post treatment 0.27 with mean decrease of migraine days 4.88 with (SD+ 1.29) *p* <<0.001 *(Figure*

4). In both groups the 27 patients presented a successful treatment response rate, in the Memantine group with a decrease in percentage of migraine days average 94% (SD+ 9.95) and in the Sodium Valproate group 93.18% (SD+ 14.50).

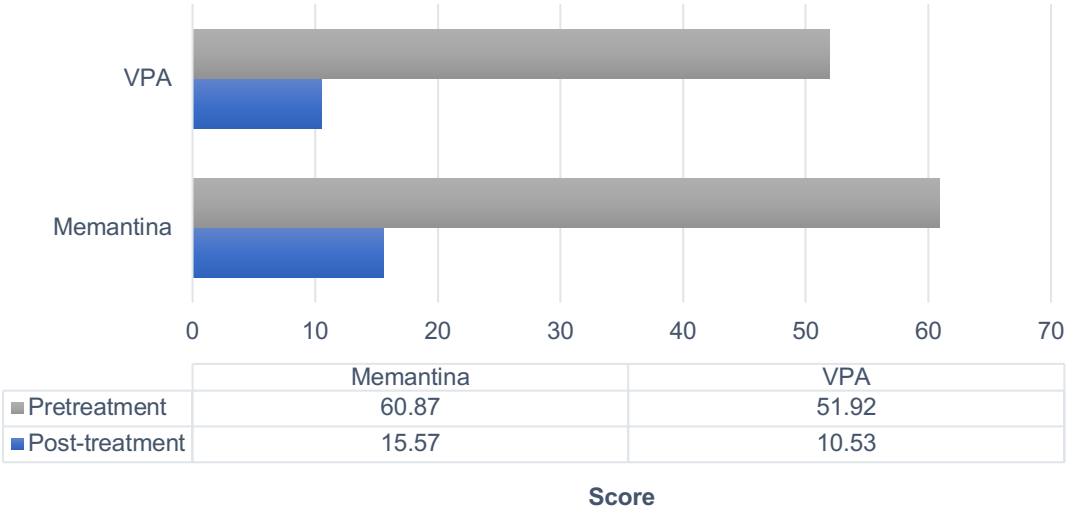


	Memantina	VPA
Pretreatment	4.36875	5.205882353
Post-treatment	0.237142857	0.27384615

The intensity of migraine was evaluated with the Visual Analog Scale (VAS) pre and post treatment. In the Memantine group pre-treatment VAS 8.5 (SD+ 1.36) and post-treatment 4.28 (3.65) p<0.00014. In the VPA group with pretreatment VAS 8.94(SD+ 0.87) and post treatment 2.5 (SD+ 0.87) *p* <0.0000012.

Migraine disability assessed with MIDAS in the Memantine group with MIDAS mean pretreatment 60.87 (SD+ 25.22) and post-treatment 15.57 (SD+ 14.32) *p* < 0.000004. In the Sodium Valproate group with MIDAS pretreatment of 51.92 (SD+ 22.67) and post treatment 10.53 (SD+ 19.97) *p* < 0.00002 *(Figure 5).*

Figure 5. MIDAS pre- and post-treatment in both groups.



Side effects: The side effects presented by the patients were not severe in their totality, eight patients in the Memantine group presented non-severe side effects and seven patients in the sodium valproate group *(Table 2)*, the most frequent in both groups being somnolence.

Table 2 . Side effects

	Memantine	**Sodium Valproate**
None		
Drowsiness		
Lack of concentration		0
Parasomnia	0	1
Dizziness		0
Total		

DISCUSSION

This is the first randomized double-blind pilot clinical trial comparing the efficacy and safety of memantine with a first-line treatment, sodium valproate.

With the objective of recruiting 40 patients as a pilot study, the Neurology outpatient clinic was suspended due to the COVID-19 pandemic, we finally managed to recruit 33 patients, 3 lost follow-up and 3 dropped out of the study due to COVID-19 and only 27 patients were included.

Both groups were very homogeneous in terms of gender distribution, age, number of migraine attacks, duration of migraine attacks and clinical characteristics (pain location, type of pain, among others).

In comparison with the Noruzzadeh and colleagues study, where the Memantine group had a baseline migraine frequency per month (pre-treatment) 5.4+ 2.5 and after 3 months of treatment the baseline migraine frequency was 1.9. In our study we found a similar response in the Memantine group with average migraine attacks before treatment of 5.31 and after 3 months of treatment 0.92 with a difference of 4.39 migraine attacks p <<0.001. As in previous studies and reaffirming the reason why sodium Valproate is a drug of recommendation A, a decrease of 4.5 migraine attacks was obtained with p <<0.001.

The migraine disability assessed by MIDAS initially showed severe disability (> 20 points) in both groups, the patients presented scores higher than 50; after treatment, the Valproate group presented mild disability and the memantine group presented moderate disability.

With respect to migraine intensity, a post-treatment decrease of > 50% was observed on the VAS scale. In view of the decrease in frequency, days and intensity, the impact of both treatments on the MIDAS scale that assesses migraine disability was demonstrated. Initially, severe disability (> 20 points) was observed in both groups, the patients presented scores higher than 50; after treatment, the Valproate group presented mild disability and the memantine group presented moderate disability.

As in the only two clinical trials of memantine as a prophylactic treatment for migraine, side effects were not severe. In the study by Noruzzadeh and colleagues, three patients had sedation, mild vertigo and nausea, the placebo group had one patient with nausea and a second patient had vertigo. In the study by Bigal and colleagues the most frequent side effects were in seven patients reported drowsiness, three patients with anxiety and asthenia. In our study four patients reported somnolence, two reported lack of concentration and two reported dizziness.

LIMITATIONS

One of the limitations is the failure to include the required number of participants in the sample size. Since this clinical trial is a pilot study, new randomized double-blind clinical trials with a larger number of participants should be conducted.

CONCLUSIONS

In this double-blind randomized clinical trial, so far (to our knowledge) the only pilot study comparing Memantine against sodium valproate, a first-line drug in the prophylactic treatment of migraine.

The response in both groups was evident and significant ($p<0.05$) according to the treatment they received, with a clear decrease in the number of migraine attacks, days with migraine, disability and intensity.

Memantine could be a new prophylactic treatment option in migraine, the study showed that there was no inferiority of Memantine compared to sodium Valproate as a prophylactic treatment for episodic migraine.

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ANNEX 1

PATIENT INFORMED CONSENT DOCUMENT
CENTRAL HOSPITAL "DR. IGNACIO MORONES PRIETO" CENTRAL HOSPITAL
NEUROLOGY DEPARTMENT

ADULT PATIENT

TITLE OF THE RESEARCH PROTOCOL	
"Efficacy of memantine compared with sodium valproate in the prophylactic treatment of migraine". Randomized controlled clinical trial.	
REGISTRATION NUMBER OF THE PROTOCOL AUTHORIZED BY THE RESEARCH ETHICS COMMITTEE	**PERIOD OF EXECUTION OF THE AUTHORIZED PROTOCOL**
_____	___/___/____ - ___/___/____
PRINCIPAL INVESTIGATOR AND RESPONSIBLE AT THE HOSPITAL	**PRINCIPAL INVESTIGATOR'S AFFILIATION**
Dr. Ildefonso Rodríguez Leyva	Department of Neurology Division of Internal Medicine Central Hospital "Dr. Ignacio Morones Prieto". Autonomous University of San Luis Potosi Professional license 763163
CO-INVESTIGATOR	**CO-INVESTIGATOR'S AFFILIATION**
Dr. Damaris Daniela Vazquez Guevara	Department of Neurology Division of Internal Medicine Central Hospital "Dr. Ignacio Morones Prieto". Autonomous University of San Luis Potosi Professional license 10045226

DATE OF SUBMISSION OF INFORMED CONSENT	
PATIENT IDENTIFICATION NUMBER	

The Neurology Department of the Central Hospital Dr. Ignacio Morones Prieto is conducting a research study with the objective of comparing the efficacy of memantine versus sodium valproate in the prophylactic treatment of migraine. This study will include 40 patients for 3 months each participant, from July 08 to October

30, 2019 and will be conducted in the Outpatient Referral Service, Emergency Outpatient and Neurology of the Central Hospital "Dr. Ignacio Morones Prieto".

Patient information

Migraine is a neurological disease characterized by headaches of variable duration, usually located in the middle of the head, although it can be located in the forehead or in the whole head. Most patients report that the pain is throbbing (like a heartbeat) and often accompanied by nausea, vomiting, discomfort, intolerance to light and noise. Some patients are warned of migraine prior to the headache with special symptoms such as blurred vision, flashes of light or stars, tunnel vision, which is known as aura.

To know if your headache is migraine you should be evaluated by a doctor, because migraine headaches are very intense, migraine becomes incapacitating causing missing work, school or not being able to perform activities of daily living, is one of the reasons why you should go to a neurologist who will make the diagnosis and assess whether you are a candidate for treatment. The treatment of migraine is divided into two types: acute, which is given at the time of the migraine attack, and prophylactic, which is given to prevent new migraine attacks and reduce their intensity. The complications of migraine is that it becomes a chronic disease, which implies migraine attacks more than 15 days a month.

You have been invited to participate in this study because you have been diagnosed with migraine and are a candidate for prophylactic treatment. In this research study we will compare the efficacy of two types of treatment, one known as sodium valproate already known as a treatment for migraine and another that could be a new treatment for migraine which is Memantine.

To perform this study, patients will be included in two groups at random, each group will have 20 participants. One group will receive sodium Valproate and the other will receive Memantine, however, it is important that neither you nor the physician will know which drug treatment you will be receiving for 3 months.

Procedures to be undergone by the patient

Your participation in this research study is completely voluntary and if you agree to participate, we will ask you to carefully read this informed consent document and to ask all the necessary questions to the responsible research physician, **Dr. Ildefonso Rodriguez Leyva,** so that he can resolve your doubts. When you no longer have any doubts regarding what will be done in this study, we will ask you to sign your acceptance to participate at the end of this document, and we will ask you to provide us with general information such as your name, age, weight, height; your medical history; in an interview of approximately 45 minutes, which will be conducted by **Dr. Damaris Daniela Vazquez Guevara** in the outpatient area of this hospital, so it will not be necessary to review your clinical record. At the end of this first medical assessment, you will be given a migraine diary where you can record your migraine attacks and their characteristics. To keep your data anonymous, you will be assigned a code with which only the research physicians participating in this study

will be able to know your identity.

Medical evaluations will be performed every 4 weeks on 5 occasions in total at the Neurology outpatient clinic of the Central Hospital by **Dr. Damaris Daniela Vazquez Guevara**. From the second visit on, she will be asked again about the frequency of migraine attacks, if she tolerates the medication and possible adverse effects. In addition, at visits 2, 3, and 4 the research team will provide you with the medication at no cost randomly assigned for 4 weeks, and at each visit you will be given a new migraine diary which will be collected at the next visit. At all visits you will be given a survey to assess the intensity of your migraine attack pain. While you are receiving the drugs you will have medical attention by the team for possible adverse effects.

Your doctor has explained to you in detail what your disease consists of and the importance of having a prophylactic treatment in order to reduce the frequency of your migraine attacks.

Patient benefits:
You may benefit from having a favorable response to the treatment and decrease the frequency of migraine attacks. However, you will be collaborating with the research area of the Neurology Department of the Central Hospital "Dr. Ignacio Morones Prieto" and we will not know which drug you will be receiving. This study is intended to evaluate a new prophylactic treatment for migraine that seems to be well tolerated by patients.

Benefits for society:
This research study will help to evaluate a new drug for the prophylactic treatment of migraine, although there are already drugs indicated for migraine, sometimes patients do not tolerate it or have no response, which is why this new drug is proposed.

Potential risks for the patient:
The potential risks involved in your participation are greater than minimal as it is an interventional study. You may experience side effects from the medications such as: nausea, vomiting, weight gain, tremor, hair loss.

However, in the remote case that you feel any other discomfort generated by the research drug, it is necessary to immediately notify **Dr. Damaris Daniela Vazquez Guevara** who will provide you with the necessary attention, which will not generate any cost for you.

You should be aware that in the event of a side effect or adverse drug reaction requiring hospitalization or treatment, expenses will be covered by the principal investigator.

It is important to note that you will not receive any payment for participating in the study and you will be given a copy of this informed consent document signed by the responsible investigators.

Confidentiality:
The personal and medical information obtained from you in this study is confidential and will be used only by the research team of this project to analyze and complement the results obtained and will not be available for any other purpose. This information will be combined with that of other participants to carry out the present study. In order to maintain anonymity, you will be assigned a code for the use of your data.

If you so choose, the investigators responsible for this study may inform your treating physician that you have agreed to participate in this study, so that the information obtained may be included in your clinical record. For this purpose, we will ask you to indicate at the end of this document whether or not you agree to the above.

The results of this study may be published for scientific purposes in special journals directed to medical personnel, nurses, chemists and researchers related to the health area in order to make them aware of the possibility of a new prophylactic treatment for migraine. The results of this study may also be presented at scientific meetings where new findings obtained from this and other studies related to the health and treatment of patients with the same diagnosis are discussed. The clinical data of all participants will be presented anonymously and in such a way that you or any of the patients participating in this study cannot be identified.

In accordance with the General Law for the Protection of Personal Data in Possession of Obligated Subjects and the Law for the Protection of Personal Data of the State of San Luis Potosi, your personal data may not be processed, transferred or used for purposes not expressly described in this document, unless it is strictly necessary for the exercise and fulfillment of the powers and obligations expressly provided for in the rules governing the actions of the researchers responsible for the study; it is in compliance with a legal mandate; it is necessary for reasons of public safety, public order, public health or safeguarding the rights of third parties.

Any other use required for the use of your data or analysis or handling of your samples and/or results of the analyses described in this document, must be informed and requested with due justification to the Research Ethics Committee of this Hospital, who will determine the relevance of the request and, if applicable, will authorize a different use for your data, samples and/or products derived from your samples and/or results. Always in compliance with national and international legislative guidelines and norms and for the benefit and protection of the integrity of the participating actors.

There are Mexican institutions or organizations such as the Ministry of Health, the Federal Commission for Protection against Health Risks (COFEPRIS), the National Bioethics Commission (CONBIOETICA) or even the Research Ethics Committee (CEI) of this hospital, which are responsible for monitoring the proper handling of personal and medical data that you and other patients have authorized to be used in the conduct of research studies such as this one. These institutions or

organizations may request at any time to the researchers of this study, the review of the procedures that are performed with your information and measurements, in order to verify that a correct and ethical use is made of them; so they may have access to this information that has been previously assigned with an identification code, when required.

Participation or withdrawal:
Your participation in this study is absolutely voluntary and you have been invited to participate because of the characteristics of your disease, and you are a candidate to receive prophylactic treatment for migraine.

You are free to refuse to participate in this research study; but if you decide to participate, at any time and without explanation, you may revoke or cancel the consent you are now signing. Your decision whether or not to participate will in no way affect the medical treatment you receive at the institution for your illness. If you decide to terminate your participation in this study, you must communicate it to **Dr. (a) Dr. Damaris Daniela Vazquez Guevara** who will provide you with a very simple document (format) in which you will put some of your data and indicate that you no longer wish to participate in the study. Your decision to participate or not, will not affect in any way the medical treatment you receive in the institution for your disease.

You will be given a copy of this informed consent form, which includes the contact information of the person in charge of this study and of the hospital's Research Ethics Committee, in order to clarify any doubts that may arise.

Ethical Considerations:
This study is considered to be of greater than minimal risk as it is an intervention study and will be randomized between 2 interventions, because the investigators responsible for this study will make decisions regarding treatment for 3 months.

We will not ask for your authorization to review your medical record, we will only ask you a few questions, as we have already explained.

You will be given a copy of this informed consent, signed by the responsible investigator, which includes his or her contact information and the contact information of the Research Ethics Committee of this hospital to clarify any doubts that may arise.

Commitment to answer questions and doubts:
For any questions, doubts or clarifications about this double-blind Randomized Clinical Trial study to compare the efficacy of Memantine versus Sodium Valproate in the prophylactic treatment of Migraine, or about any adverse reaction related to the medication that you are taking as treatment and that has been prescribed by your treating physician, you may contact:

Dr. Ildefonso Rodríguez Leyva
Department of Neurology
Central Hospital "Dr. Ignacio Morones Prieto".

Av. Venustiano Carranza 2395, Col. Zona Universitaria, San Luis Potosí, S.L.P., C.P. 78290, Tel. 6643759438

Dr. Damaris Daniela Vazquez Guevara
Department of Neurology
Central Hospital "Dr. Ignacio Morones Prieto".
Av. Venustiano Carranza 2395, Col. Zona Universitaria, San Luis Potosí, S.L.P., C.P. 78290, Tel. 6643759438

If you have any questions regarding your rights as a participant in the research study, you may also contact a person not involved with the research team for this study:

Dr. Emmanuel Rivera López
Chairman of the Research Ethics Committee
Central Hospital "Dr. Ignacio Morones Prieto".
Venustiano Carranza Av. 2395,
Col. Zona Universitaria, San Luis Potosi, S.L.P., C.P. 78290,
Tel. (52-444) 8 34 27 01, Ext. 1710

Acceptance of the Informed Consent Document

If you wish to voluntarily participate in this research, please provide your name, signature and date this document in the spaces provided below. Your signature signifies your agreement to the following:

1. I have been given complete and adequate information verbally and in writing about the purpose of the study, explained that the risks are greater than minimal because it is an interventional study, and the benefits of participating in clear language.
I have been informed that I may withdraw my consent and terminate my participation in this study at any time without affecting my right to receive medical care.
3. It is my responsibility to ask questions to clarify any points I do not understand regarding my participation in this study. I have asked all questions of the person conducting the consent process and have received satisfactory answers.
4. I have not concealed or misrepresented any current medical condition or any medical history related to my health. I have answered all questions regarding my health accurately and truthfully.
5. I am of legal age and legally capable of giving this consent.
6. I agree to participate in this study on a voluntary basis without duress or coercion. I understand that my refusal to participate or discontinuation of participation at any time will not result in penalty or loss of benefits to which I am otherwise entitled.
7. I understand and agree that the information obtained from the present study may be used for publication of these results for academic purposes as part of scientific dissemination and in support of clinical practice, but that at all times an assigned code will be used to maintain my anonymity and the confidentiality of my data.
8. I have had it explained to me that the personal and clinical information I have consented to provide will retain my privacy and will be used only for purposes arising from this study.

9. The investigators participating in this project have agreed to provide me with updated information obtained during the study at the time I request it and will provide me with a copy of this informed consent document.

By means of this informed consent document I agree to participate in the medical study entitled **"Efficacy of memantine compared to sodium valproate in the prophylactic treatment of migraine". Randomized controlled clinical trial**, free and voluntary.

Authorization for use of clinical data

You are asked to indicate your agreement or disagreement that the investigators responsible for this project may use the clinical data, anonymously for the conduct of this research protocol, whose objectives and procedures have been explained to you and that you have freely and voluntarily provided them, Mark your answer with an X:

____ I give my permission to the investigators participating in this project to use the clinical data that I have provided to them in the research that they have explained to me.

____ I do not give my permission to the investigators participating in this project to use the clinical data I have provided in the research they have explained to me.

Authorization to inform my treating physician of my participation in this research study and to have my results included in my medical record.

You are requested to indicate your agreement or disagreement for the investigators responsible for this research study to inform your treating physician, Dr. (a) _____, that you have agreed to participate in this study with the registration number _____ before the IRB of this hospital and for the results obtained from the measurements of blood flow in the arteries of your brain, which you have consented to be performed, to be included in your clinical record so that they can be used as a reference for your treatment by your treating physician. Please mark your answer with an X:

____ I give my authorization to the investigators to inform my treating physician of my participation in this research study and to include my results in my file, in accordance with the above and as explained to me.

____I do not give my authorization to the investigators to inform my treating physician of my participation in this research study and to include my results in my file, in accordance with the above and as explained to me.

By means of this informed consent document I agree to participate in the research study entitled **"Efficacy of memantine compared to sodium valproate in the prophylactic treatment of migraine". Randomized controlled clinical trial, on a** free and voluntary basis.

PATIENT'S NAME	PATIENT'S SIGNATURE OF ACCEPTANCE
DATE INFORMED CONSENT OBTAINED	

NAME OF LEGAL REPRESENTATIVE (if necessary)	ACCEPTANCE SIGNATURE OF THE LEGAL REPRESENTATIVE
DATE INFORMED CONSENT OBTAINED	**RELATIONSHIP**
ADDRESS / CONTACT PHONE NUMBER	

NAME OF WITNESS 1	SIGNATURE OF WITNESS 1
DATE	**RELATIONSHIP**
ADDRESS / CONTACT TELEPHONE NUMBER OF WITNESS 1	

NAME OF WITNESS 2	SIGNATURE OF WITNESS 2
DATE	**RELATIONSHIP**
ADDRESS / CONTACT TELEPHONE NUMBER OF WITNESS 2	

Dr. Damaris Daniela Vazquez Guevara (name and signature of the person obtaining informed consent) **RESEARCHER PARTICIPATING IN THE PROTOCOL**

Dr. Ildefonso Rodríguez Leyva	**Dr. Damaris Daniela Vazquez Guevara**
PRINCIPAL INVESTIGATOR AND RESPONSIBLE OF THE RESEARCH PROTOCOL **Department of Neurology** Autonomous University of San Luis Potosi PROFESSIONAL LICENSE 763163	**CO-INVESTIGATOR** **Department of Neurology** Autonomous University of San Luis Potosi PROFESSIONAL LICENSE 10045226

REVOCATION OF INFORMED CONSENT

I declare to the Principal Investigator, Dr. (a) _____ that it is my will to revoke the informed consent that I have accepted on _____, to participate in the research protocol entitled **"Efficacy of memantine compared to sodium valproate in the prophylactic treatment of migraine". Randomized controlled clinical trial.** It is my right to request that my clinical and personal data, as well as the results of the tests that have been performed on me so far, be removed from this research and no longer be included in the final results and reports or publications that will be generated from this research study.

PATIENT'S NAME	PATIENT SIGNATURE
DATE OF REVOCATION OF INFORMED CONSENT	

NAME OF WITNESS 1	SIGNATURE OF WITNESS 1
DATE OF REVOCATION OF INFORMED CONSENT	

NAME OF WITNESS 2	SIGNATURE OF WITNESS 2

DATE OF REVOCATION OF INFORMED CONSENT	

Dr. Ildefonso Rodríguez Leyva **PRINCIPAL INVESTIGATOR AND RESPONSIBLE OF THE RESEARCH PROTOCOL** **Department of Neurology** Autonomous University of San Luis Potosi PROFESSIONAL LICENSE 763163		**Dr. Damaris Daniela Vazquez Guevara** **CO-INVESTIGATOR** **Department of Neurology** Autonomous University of San Luis Potosi PROFESSIONAL LICENSE 10045226

MIDAS SURVEY

Answer the following questions about all the headaches you have had in the last 3 months.

1. How many days did you miss work or school in the last 3 months due to your headache (if not going to school or work indicate 0)? ☐

2. How many days did your productivity at work or school decrease by half or less in the last 3 months because of your headache? (Do not include the days you checked in question 1 for missed work. If you do not go to school or work, mark 0) _____

3. How many days did you not do your household chores in the last 3 months because of your headache?

4. How many days did your productivity in household chores decrease by half or less in the last 3 months because of your headache? (Do not include the days you already counted in question 3 for not having done your chores).

5. How many days were you unable to participate in family, social and fun activities in the last 3 months because of your headache?

A. How many days did you have a headache in the last 3 months (if an attack lasted more than one day, count each day)?

B. On a scale of 0 to 10, how intense were those headaches on average (0: no pain, 10: worst pain imaginable)?

Score	Degree of Disability MIDAS
0-5 points	No or minimal disability
6-10 points	Mild disability
11-20 points	Moderate disability
>21 points	Severe disability

Stewart W F, et al. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. Pain 2000;88(1):41-52.

ANNEX 5

To whom it may concern:

We hereby inform you that the drug used in the clinical trial: "Efficacy of memantine compared to sodium valproate in the prophylactic treatment of migraine", a randomized controlled clinical trial, conducted by Dr. Ildefonso Rodriguez Leyva, was donated by Laboratorios Torrent to support clinical research.

Under no circumstances did Torrent Pharma participate in the study, nor do we have access to any information about the patients, doses, or results.

SINCERELY

Laboratorios Torrent S. A. de C. V.