"Efficacy of Memantine compared to sodium Valproate as prophylactic treatment for Episodic Migraine" A controlled randomized pilot clinical trial

A controlled randomized clinical trial

NCT04698525

ID 74-19

Study Protocol document date: February 15, 2019.

Statistical Analysis Plan document date: November 20, 2020.

Informed Consent Form document date: February 15, 2019.

Objetive

HOSPITAL CENTRAL
"DR. IGNACIO
MORONES PRIETO"

The aim of this study was to assess the efficacy of memantine and compared sodium valproate in the prophylactic treatment of migraine.

Methods

Study design

A single center, doble-blinded, controlled, randomized pilot clinical trial.

The present study was designed as a randomized, double-blind, controlled pilot trial. It was authorized by the Research and Ethic Committee in February 2019, with the ID 74-19 and register in Clinical Trials from INH with the NCT04698525.

The study was conducted from July 2019 to November 2020 at Neurology service at Hospital Central Dr. Ignacio Morones Prieto, San Luis Potosí, México.

Inclusion Criteria:

HOSPITAL CENTRAL
"DR. IGNACIO
MORONES PRIETO"

1. Men and women from 18 to 65 years old.
2. Diagnosis of migraine according to the ICHD-III of the IHS at least one year before the study.
3. You must have at least 4-14 migraine attacks per month.
4. Not receiving prophylactic treatment for migraine
5. Sign informed consent

Exclusion Criteria:

HOSPITAL CENTRAL
"DR. IGNACIO
MORONES PRIETO"

1. Pregnant or lactating patients.
2. Patients with another type 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 (myocardial, coronary, or valvular disease) prevents their participation in the study.

Outcomes

A.Primary outcomes

1. The primary outcome was the difference in change from baseline in the monthly attack frequency at week 12 between the two groups (using migraine diary).

B.Secondary outcomes

1. Evaluate the response rate to treatment.
2. Evaluate migraine disability using MIDAS (Migraine Disability Assessment) before and after treatment.
3. Identify adverse effects to sodium valproate and memantine.

Statical analysis.

- Descriptive statistical analysis of the variables of interest will be carried out.
- For continuous variables, their research will be analyzed using the t-student test.
- First, the number of participants (n) and the final analysis were calculated using R (56).
- Alpha, the probability of a type 1 error was set to 0.05.
- The power was set to 0.8, resulting in a type 2 error of 0.2.
- Since we were limited to 20 participants per treatment, the delta was estimated with this restriction.

RESULTS

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Memantine	Sodium Valproate	*p*
Female sex – no (%) *Male sex – no (%)*	13(81.25%) 3 (18.75%)	13 (76.47%) 4 (23.52%)	0.54*
Age	31.18 ±10.94§	31.58 ± 7.51§	0.91*
A family history of migraine (%)	10 (62.5%)	9 (52.94%)	0.82*
Clinical characteristics			
Photophobia - no (%)	14 (87.50%)	16 (94.12%)	0.48*
Phonophobia - no (%)	16 (100%)	10 (58.82%)	0.60*
Nausea - no (%)	14 (87.5%)	17 (100%)	0.23*
Disability activities of daily living	15 (93.75%)	16 (94.12%)	0.74*
Migraine without aura	13 (81.25%)	13 (76.47%)	0.54*
Migraine with aura	3 (18.75%)	4 (23.52%)	

* Fisher's exact test

§ Plus–minus values are means ±SD

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Baseline Characteristics Template — *Age* (use at least one)* — *ClinicalTrials.gov*

* Arm/Group Title		Memantine		Valproate				Total	
*§ Arm/Group Description ①									
* Overall Number of Baseline Participants ②								③	
[*] Baseline Analysis Population Description									
Age, Categorical									
<=18 years								③	
Between 18 and 65 years		16		17				③	
>=65 years								③	
* Unit of Measure	Participants								
Age, Continuous									
* Measure Type	* Measure of Dispersion								
(Select One) Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM	(Select One) Standard Deviation Inter-quartile Range Full Range	31.18	+/-10.94	31.58	+/- 7.51				
* Unit of Measure	years old								
Age, Customized									
* Measure Type	* Measure of Dispersion								
(Select One) Count of Participants ④ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ④	(Select One) Not Applicable ⑤ Standard Deviation Inter-Quartile Range Full Range								
[*] Row/Category Title ⑥	Min	18	④⑤	53	④⑤		④⑤	③	④⑤
[*] Row/Category Title ⑥	Max	50	④⑤	20	④⑤		④⑤	③	④⑤
* Unit of Measure	Years old								

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ Total values are automatically calculated for Overall Number of Baseline Participants and for data reported with a Measure Type of Number, Count of Participants, or Count of Units.
④ If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Baseline Participants/Units Analyzed. The percentage can be hidden (display is optional).
⑤ Not Applicable should be used only if Measure Type is Number, Count of Participants, or Count of Units. No dispersion value is needed if Measure of Dispersion is Not Applicable.
⑥ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Baseline Measure Data are required for each row.

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Baseline Characteristics Template — *Study-Specific Measure**§ — *ClinicalTrials.gov*

* Arm/Group Title		Memantine		Valproate				Total	
*§ Arm/Group Description ①		16		17					
* Overall Number of Baseline Participants ②		16		17				*p*= 0.7 ③	
[*] Baseline Analysis Population Description									
[*] Study-Specific Baseline Measure Title		Pain distribution							
Baseline Measure Description									
* Measure Type	* Measure of Dispersion								
(Select One) Count of Participants ④ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ④	(Select One) Not Applicable ⑤ Standard Deviation Inter-Quartile Range Full Range								
[*] Row/Category Title ⑥	Hemicranial	14	④⑤	13	④⑤		④⑤	③	④⑤
[*] Row/Category Title ⑥	Holocranial	2	④⑤	4	④⑤		④⑤	③	④⑤
* Unit of Measure									

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② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ Total values are automatically calculated for Overall Number of Baseline Participants and for data reported with a Measure Type of Number, Count of Participants, or Count of Units.
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⑥ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Baseline Measure Data are required for each row. Row/Category Titles are only required if more than one row.

Study Protocol document date: February 15, 2019;
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Baseline Characteristics Template — *Sex/Gender* (use at least one)* — *ClinicalTrials.gov*

* Arm/Group Title		Memantine		Valproate				Total	
*§ Arm/Group Description ①									
* Overall Number of Baseline Participants ②								87	③
[*] Baseline Analysis Population Description									
Sex: Female, Male									
Female		13		13				26	③
Male		3		4				7	③
* Unit of Measure	Participants								
Sex/Gender, Customized									
* Measure Type	* Measure of Dispersion								
(Select One) Count of Participants ④ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ④	(Select One) Not Applicable ⑤ Standard Deviation Inter-Quartile Range Full Range								
[*] Row/Category Title ⑥	Pulsatile headache	13	81.2 % ④ ⑤	13	76.4 % ④ ⑤		④ ⑤	③	④ ⑤
[*] Row/Category Title ⑥	Opresive headache	3	18.7 % ④ ⑤	4	23.5 % ④ ⑤		④ ⑤	③	④ ⑤
[*] Row/Category Title ⑥			④ ⑤		④ ⑤		④ ⑤	③	④ ⑤
* Unit of Measure									

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① Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ Total values are automatically calculated for Overall Number of Baseline Participants and for data reported with a Measure Type of Number, Count of Participants, or Count of Units.
④ If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Baseline Participants/Units Analyzed. The percentage can be hidden (display is optional).
⑤ Not Applicable should be used only if Measure Type is Number, Count of Participants, or Count of Units. No dispersion value is needed if Measure of Dispersion is Not Applicable.
⑥ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Baseline Measure Data are required for each row.

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Baseline Characteristics Template — *Race**§, Ethnicity**§, and Region* — *ClinicalTrials.gov*

* Arm/Group Title	Memantine	Valproate		Total
*§ Arm/Group Description ①				
* Overall Number of Baseline Participants ②	16	17		33 ③
[*] Baseline Analysis Population Description				
Race (NIH/OMB) ④				
American Indian or Alaska Native				③
Asian				③
Native Hawaiian or Pacific Islander				③
Black or African American				③
White				③
More than one race	Mexicasn Mestizos	Mexican Mestizos		③
Unknown or Not Reported				③
* Unit of Measure: Participants				
Ethnicity (NIH/OMB) ④				
Hispanic or Latino				③
Not Hispanic or Latino				③
Unknown or Not Reported				③
* Unit of Measure: Participants				
Region of Enrollment				
United States				③
Region/Country Name ⑤: San Luis Potosi				③
Region/Country Name ⑤: SLP				③
Region/Country Name ⑤: Mexico				③
* Unit of Measure: Participants				

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ Total values are automatically calculated for Overall Number of Baseline Participants and for each Baseline Measure.
④ If not using NIH/OMB categories, use Race/Ethnicity, Customized (not shown); if not collected, use Race and Ethnicity Not Collected (not shown).
⑤ [Optional] Region of Enrollment Baseline Measure is optional, but at least one Region/Country is required if reporting Region of Enrollment. Add as many Regions/Countries as needed.

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Baseline Characteristics Template — *Study-Specific Measure**§ — *ClinicalTrials.gov*

* Arm/Group Title		Memantine		Valproate				Total	
*§ Arm/Group Description ①		17.8 +/- 7.68		17.6 +/- 4.64					
* Overall Number of Baseline Participants ②		16		17				33 ③	
[*] Baseline Analysis Population Description									
[*] Study-Specific Baseline Measure Title		Age of migraine onset							
Baseline Measure Description									
* Measure Type	* Measure of Dispersion								
(Select One) Count of Participants ④ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ④	(Select One) Not Applicable ⑤ Standard Deviation Inter-Quartile Range Full Range								
[*] Row/Category Title ⑥	Min	9	④⑤	4	④⑤		④⑤	③	④⑤
[*] Row/Category Title ⑥	Max	35	④⑤	35	④⑤		④⑤	③	④⑤
* Unit of Measure	years of old								

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Baseline Characteristics Template — *Study-Specific Measure**§ — *ClinicalTrials.gov*

* Arm/Group Title		Memantine		Valproate				Total	
*§ Arm/Group Description ①									
* Overall Number of Baseline Participants ②		16		17				③	
[*] Baseline Analysis Population Description									
[*] Study-Specific Baseline Measure Title		Average migraine days per month in the last three months							
Baseline Measure Description									
* Measure Type	* Measure of Dispersion								
(Select One) Count of Participants ④ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ④	(Select One) Not Applicable ⑤ Standard Deviation Inter-Quartile Range Full Range								
[*] Row/Category Title ⑥	Pre-treatment	10	④⑤	8.9	④⑤		④⑤	③	④⑤
[*] Row/Category Title ⑥	Post-treatment	1.7	④⑤	0.76	④⑤		④⑤	③	④⑤
* Unit of Measure	Days number								

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② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ Total values are automatically calculated for Overall Number of Baseline Participants and for data reported with a Measure Type of Number, Count of Participants, or Count of Units.
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⑥ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Baseline Measure Data are required for each row. Row/Category Titles are only required if more than one row.

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Baseline Characteristics Template — *Study-Specific Measure**§ — *ClinicalTrials.gov*

* Arm/Group Title		Memantine		Valproate				Total
*§ Arm/Group Description ①		16		17				
* Overall Number of Baseline Participants ②		35.4 (SD24.81)		36.8 (SD20.30)				③
[*] Baseline Analysis Population Description								
[*] Study-Specific Baseline Measure Title		Average migraine duration in hours						
Baseline Measure Description								
* Measure Type	* Measure of Dispersion							
(Select One) Count of Participants ④ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ④	(Select One) Not Applicable ⑤ Standard Deviation Inter-Quartile Range Full Range							
[*] Row/Category Title ⑥	Minimun	6	④⑤	12	④⑤		④⑤	③ ④⑤
[*] Row/Category Title ⑥	Maximun	72	④⑤	72	④⑤		④⑤	③ ④⑤
* Unit of Measure								

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ Total values are automatically calculated for Overall Number of Baseline Participants and for data reported with a Measure Type of Number, Count of Participants, or Count of Units.
④ If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Baseline Participants/Units Analyzed. The percentage can be hidden (display is optional).
⑤ Not Applicable should be used only if Measure Type is Number, Count of Participants, or Count of Units. No dispersion value is needed if Measure of Dispersion is Not Applicable.
⑥ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Baseline Measure Data are required for each row. Row/Category Titles are only required if more than one row.

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Baseline Characteristics Template — *Study-Specific Measure**§ — *ClinicalTrials.gov*

* Arm/Group Title		Memantine		Valproate				Total	
*§ Arm/Group Description ①									
* Overall Number of Baseline Participants ②		16		17				③	
[*] Baseline Analysis Population Description		How the patient rated the headache before and after treatment by the visual analog scale							
[*] Study-Specific Baseline Measure Title		Visual analogue scale							
Baseline Measure Description		The patient is asked to rate his or her pain on a scale of 1 to 10. A rating of "1" represents mild discomfort from time to time, and a "10" is so severe that an emergency room visit is required for care.							
* Measure Type	* Measure of Dispersion								
(Select One) Count of Participants ④ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ④	(Select One) Not Applicable ⑤ Standard Deviation Inter-Quartile Range Full Range								
[*] Row/Category Title ⑥	Pre-treatment	8.5 (SD 1.3)	④⑤	8.9 (SD0.8)	④⑤		④⑤	③	④⑤
[*] Row/Category Title ⑥	Post-treatment	4.28 (SD 3.6)	④⑤	2.5 (SD 0.8)	④⑤		④⑤	③	④⑤
* Unit of Measure	Rating: 0-10 VAS								

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② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ Total values are automatically calculated for Overall Number of Baseline Participants and for data reported with a Measure Type of Number, Count of Participants, or Count of Units.
④ If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Baseline Participants/Units Analyzed. The percentage can be hidden (display is optional).
⑤ Not Applicable should be used only if Measure Type is Number, Count of Participants, or Count of Units. No dispersion value is needed if Measure of Dispersion is Not Applicable.
⑥ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Baseline Measure Data are required for each row. Row/Category Titles are only required if more than one row.

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Baseline Characteristics Template — *Study-Specific Measure**§ — *ClinicalTrials.gov*

* Arm/Group Title		Memantine		Valproate				Total	
*§ Arm/Group Description ①									
* Overall Number of Baseline Participants ②		16		17				③	
[*] Baseline Analysis Population Description									
[*] Study-Specific Baseline Measure Title		MIDAS (Migraine disability questionaryMigraine Disability Assessment (MIDAS) questionnaire)							
Baseline Measure Description		Measure pre and post average							
* Measure Type	* Measure of Dispersion								
(Select One) Count of Participants ④ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ④	(Select One) Not Applicable ⑤ Standard Deviation Inter-Quartile Range Full Range								
[*] Row/Category Title ⑥	Pre-treatment	60.87	SD 25.2④⑤	51.92	SD 10.5④⑤		④⑤	③	④⑤
[*] Row/Category Title ⑥	post-treatment	15.57	SD 14.3④⑤	22.67	SD 19.9④⑤		④⑤	③	④⑤
* Unit of Measure									

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① Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ Total values are automatically calculated for Overall Number of Baseline Participants and for data reported with a Measure Type of Number, Count of Participants, or Count of Units.
④ If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Baseline Participants/Units Analyzed. The percentage can be hidden (display is optional).
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⑥ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Baseline Measure Data are required for each row. Row/Category Titles are only required if more than one row.

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Baseline Characteristics Template — *Study-Specific Measure**§ — *ClinicalTrials.gov*

* Arm/Group Title		Memantine		Valproate				Total	
*§ Arm/Group Description ①									
* Overall Number of Baseline Participants ②		16		17				③	
[*] Baseline Analysis Population Description		NUMBER OF MIGRAINE ATTACKS IN THREE MONTHS AFTER PROPHYLAXIS							
[*] Study-Specific Baseline Measure Title									
Baseline Measure Description									
* Measure Type	* Measure of Dispersion								
(Select One) Count of Participants ④ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ④	**(Select One)** Not Applicable ⑤ Standard Deviation Inter-Quartile Range Full Range								
[*] Row/Category Title ⑥	Minimun	0	④⑤	0	④⑤		④⑤	③	④⑤
[*] Row/Category Title ⑥	Maximun	3	④⑤	4	④⑤		④⑤	③	④⑤
* Unit of Measure									

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
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③ Total values are automatically calculated for Overall Number of Baseline Participants and for data reported with a Measure Type of Number, Count of Participants, or Count of Units.
④ If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Baseline Participants/Units Analyzed. The percentage can be hidden (display is optional).
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⑥ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Baseline Measure Data are required for each row. Row/Category Titles are only required if more than one row.

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Baseline Characteristics Template — *Study-Specific Measure**§ — *ClinicalTrials.gov*

* Arm/Group Title		Memantine		Valproate				Total	
*§ Arm/Group Description ①									
* Overall Number of Baseline Participants ②								*p = 0.8* ③	
[*] Baseline Analysis Population Description		Family history of migraine							
[*] Study-Specific Baseline Measure Title									
Baseline Measure Description									
* Measure Type	* Measure of Dispersion								
(Select One) Count of Participants ④ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ④	(Select One) Not Applicable ⑤ Standard Deviation Inter-Quartile Range Full Range								
[*] Row/Category Title ⑥	Positive	10	④⑤	9	④⑤		④⑤	③	④⑤
[*] Row/Category Title ⑥	Negative	6	④⑤	8	④⑤		④⑤	③	④⑤
* Unit of Measure									

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

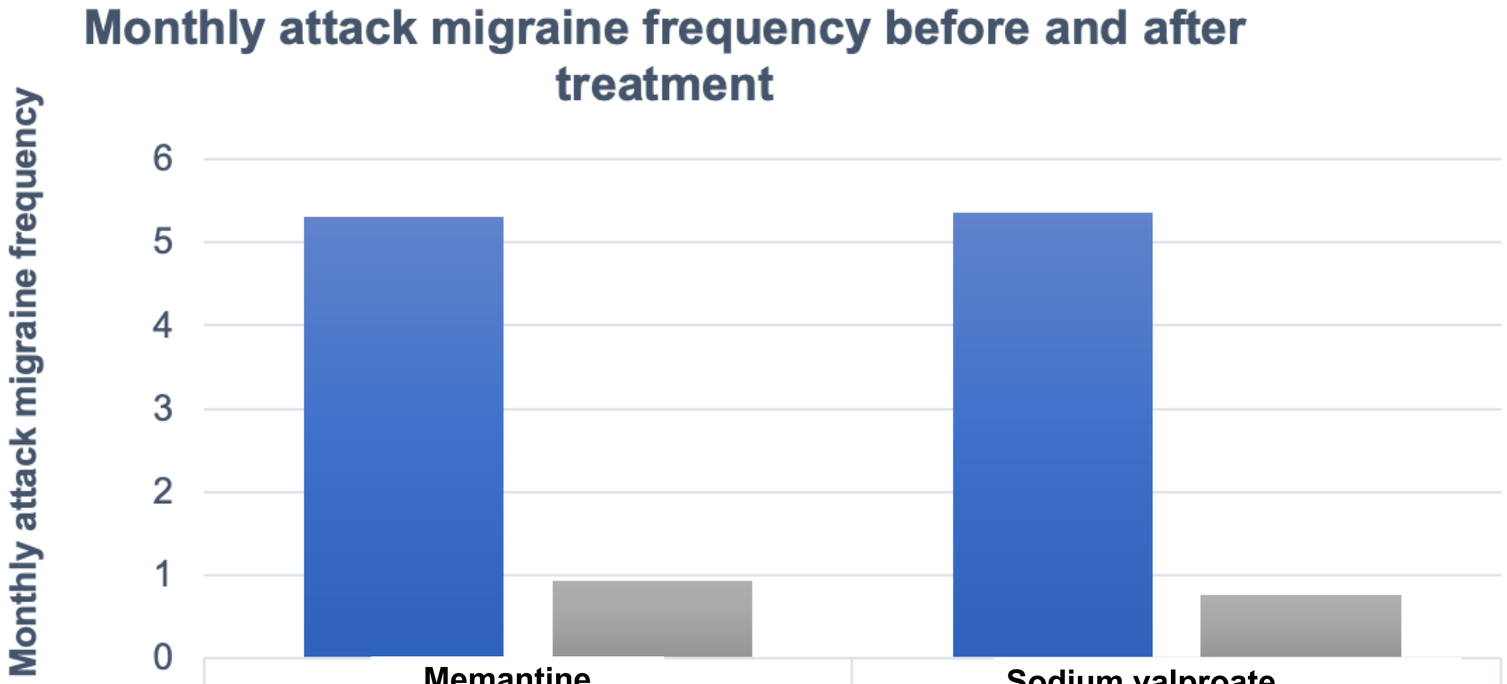
① Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ Total values are automatically calculated for Overall Number of Baseline Participants and for data reported with a Measure Type of Number, Count of Participants, or Count of Units.
④ If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Baseline Participants/Units Analyzed. The percentage can be hidden (display is optional).
⑤ Not Applicable should be used only if Measure Type is Number, Count of Participants, or Count of Units. No dispersion value is needed if Measure of Dispersion is Not Applicable.
⑥ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Baseline Measure Data are required for each row. Row/Category Titles are only required if more than one row.

Results

HOSPITAL CENTRAL
"DR. IGNACIO
MORONES PRIETO"

NCT04698525

Primary outcome



	Memantine	Sodium valproate
Pretreatment	5.3125	5.352941176
Post-treatment	0.928571429	0.769230769
	p <<0.001	p <<0.001

Study Protocol document date: February 15, 2019;
Statistical Analysis Plan document date: November 20, 2020;
Informed Consent Form document date: February 15, 2019.

Outcome Measure Template *ClinicalTrials.gov*

* Outcome Measure Type	(Select One) Primary Secondary Other Pre-specified Post-Hoc
* Outcome Measure Title	The primary outcome was the difference in change from baseline in the attack frequency at week 12 between the two groups (using migraine diary).
[*] Outcome Measure Description	Change in the frequency and intensity of migraine attacks by moonth, comparing 12 weeks pre-treatment Vs. 12 weeks post-treatment
* Outcome Measure Time Frame	12 weeks pre and 12 weeks post-treatment, using to active drugs in a double blind method

* Arm/Group Title		Memantine		Valproate			
*§ Arm/Group Description ①							
* Overall Number of Participants Analyzed ②							
[*] Analysis Population Description							
* Measure Type	* Measure of Dispersion/Precision						
(Select One) Count of Participants ③ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ③	(Select One) Not Applicable ④ Standard Deviation Standard Error Inter-Quartile Range Full Range _____ % Confidence Interval Geometric Coefficient of Variation						
[*] Row/Category Title ⑤	Average of attacks of migraine, pre	5.31	SD 1.5) ③④	5.35	SD1.11 ③④		③④
[*] Row/Category Title ⑤	Average of attacks of migraine, post	0.93	SD 1.4) ③④	0.77	SD 1.16 ③④		③④
* Unit of Measure	Number of attacks of migraine						

*** Required** ***§ Required if Primary Completion Date is on or after January 18, 2017** **[*] Conditionally required**

① **Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.**
② **Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.**
③ **If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Participants/Units Analyzed. The percentage can be hidden (display is optional).**
④ **Not Applicable should be used only if Measure Type is Number, Count of Participants, or Count of Units. No dispersion/precision value is needed if Measure of Dispersion is Not Applicable.**
⑤ **[Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Outcome Measure Data are required for each row. Row/Category Titles are only required if more than one row.**

Outcome Measure Template — *ClinicalTrials.gov*

* Outcome Measure Type	(Select One) Primary Secondary Other Pre-specified Post-Hoc
* Outcome Measure Title	The primary outcome was the difference in change from baseline in the days with migraine frequency at week 12 between the two groups (using migraine diary).
[*] Outcome Measure Description	Change in the frequency and intensity of migraine attacks by moonth, comparing 12 weeks pre-treatment Vs. 12 weeks post-treatment
* Outcome Measure Time Frame	12 weeks pre and 12 weeks post-treatment, using to active drugs in a double blind method

* Arm/Group Title		Memantine		Valproate			
*§ Arm/Group Description ①							
* Overall Number of Participants Analyzed ②							
[*] Analysis Population Description							
* Measure Type	* Measure of Dispersion/Precision						
(Select One) Count of Participants ③ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ③	(Select One) Not Applicable ④ Standard Deviation Standard Error Inter-Quartile Range Full Range _____ % Confidence Interval Geometric Coefficient of Variation						
[*] Row/Category Title ⑤	Average of days with migraine, pre	4.31	SD 1.9) ③④	5.5	SD 1.25 ③④		③④
[*] Row/Category Title ⑤	Average of days with migraine, post	0.23	SD0.4) ③④	0.27	SD 1.16 ③④		③④
* Unit of Measure	Days of migraine						

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Participants/Units Analyzed. The percentage can be hidden (display is optional).
④ Not Applicable should be used only if Measure Type is Number, Count of Participants, or Count of Units. No dispersion/precision value is needed if Measure of Dispersion is Not Applicable.
⑤ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Outcome Measure Data are required for each row. Row/Category Titles are only required if more than one row.

Study Protocol document date: February 15, 2019;
Statistical Analysis Plan document date: November 20, 2020;
Informed Consent Form document date: February 15, 2019.

Outcome Measure Template *ClinicalTrials.gov*

* Outcome Measure Type	**(Select One)** Primary Secondary Other Pre-specified Post-Hoc
* Outcome Measure Title	The intensity of migraine was evaluated with the Visual Analogue Scale (VAS) pre-treatment and post-treatment.
[*] Outcome Measure Description	0 to 10 points
* Outcome Measure Time Frame	Average pre and post-treatment

* Arm/Group Title		Memantine		Valproate			
*§ Arm/Group Description ①							
* Overall Number of Participants Analyzed ②							
[*] Analysis Population Description							
* Measure Type	* Measure of Dispersion/Precision						
(Select One) Count of Participants ③ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ③	**(Select One)** Not Applicable ④ Standard Deviation Standard Error Inter-Quartile Range Full Range _____ % Confidence Interval Geometric Coefficient of Variation						
[*] Row/Category Title ⑤	Pre-treatment	8.5	SD1.36 ③④	8.94	SD 0.87 ③④		③④
[*] Row/Category Title ⑤	Post-treatment	4.28	SD3.65 ③④	2.5	SD 0.87 ③④		③④
* Unit of Measure	0-10 points						

*** Required** ***§ Required if Primary Completion Date is on or after January 18, 2017** **[*] Conditionally required**

① Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Participants/Units Analyzed. The percentage can be hidden (display is optional).
④ Not Applicable should be used only if Measure Type is Number, Count of Participants, or Count of Units. No dispersion/precision value is needed if Measure of Dispersion is Not Applicable.
⑤ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Outcome Measure Data are required for each row. Row/Category Titles are only required if more than one row.

Results

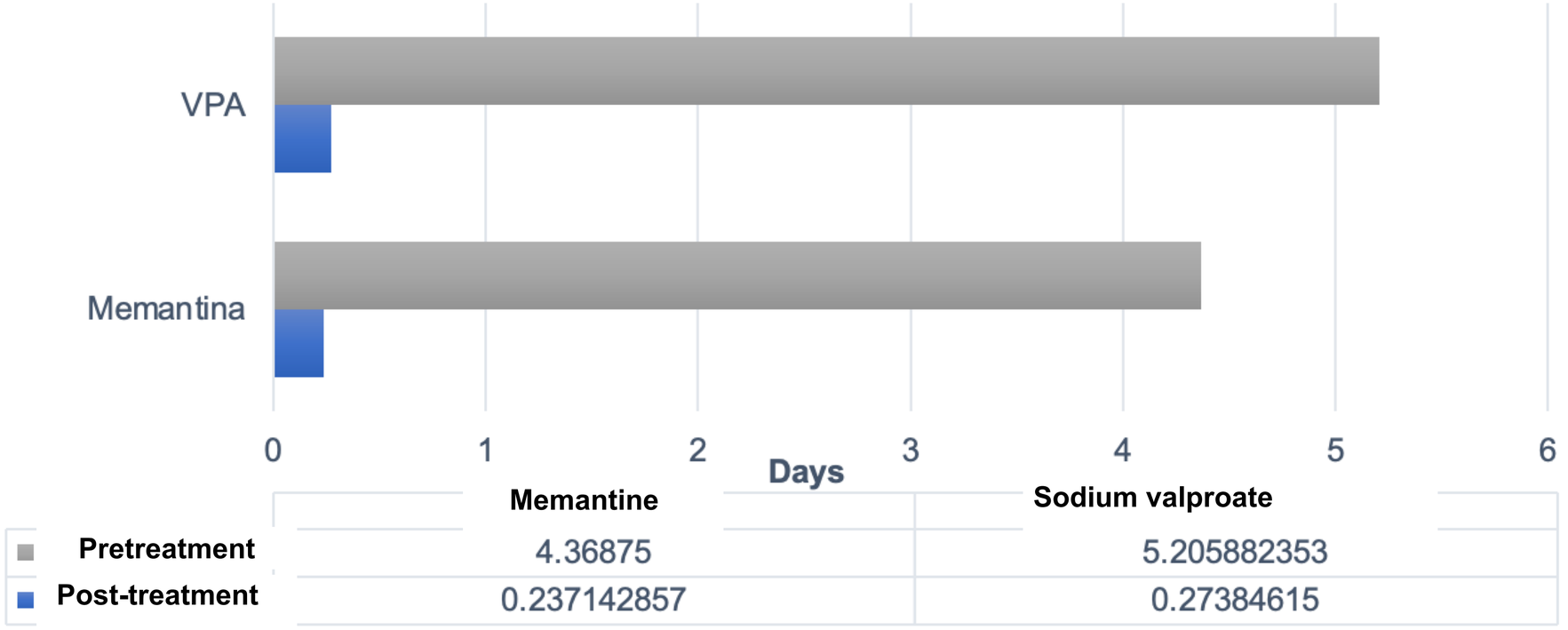
HOSPITAL CENTRAL "DR. IGNACIO MORONES PRIETO"

NCT04698525

Secondary outcome

Evaluate the response rate to treatment

Figure 2. Days with migraine before and after treatment



	Memantine	Sodium valproate
Pretreatment	4.36875	5.205882353
Post-treatment	0.237142857	0.27384615

p <<0.001

p <<0.001

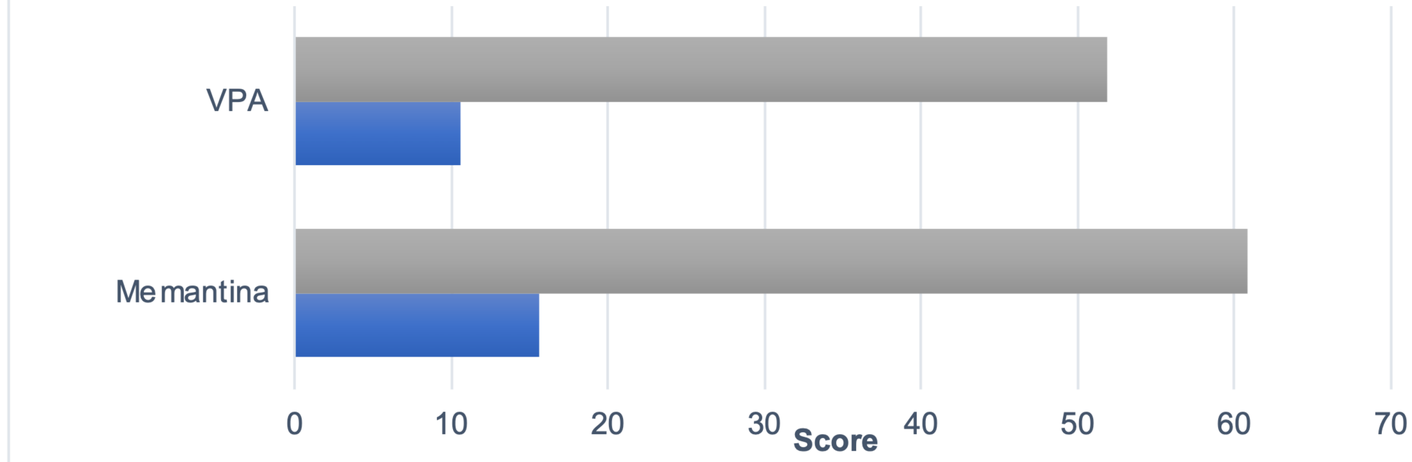
Results

NCT04698525

Secondary outcome

Evaluate migraine disability using MIDAS (Migraine Disability Assessment) before and after treatment

Figura 5. MIDAS pretreatment and postreatment



	Memantina	VPA
Pretratamiento	60.87	51.92
Postratamiento	15.57	10.53

$p < 0.000004$ $p < 0.00002$

Results

HOSPITAL CENTRAL
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MORONES PRIETO"

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Table 2. Adverse Events According to Group

	Memantine (n=17)	Sodium Valproate (n=16)	Clinical severity CTCAE*
Any adverse event	8	7	
Somnolence	4	6	Grado 1 Leve
poor concentration	2	0	Grado 1 Leve
Parasomnia	0	1	Grado 1 Leve
Dizziness	2	0	Grado 1 Leve

CTCAE v5.0 Common Terminology Criteria for Adverse Events

Study Protocol document date: February 15, 2019;
Statistical Analysis Plan document date: November 20, 2020;
Informed Consent Form document date: February 15, 2019.

Participant Flow Template *ClinicalTrials.gov*

Recruitment Details	Eligible patients were adults aged between 18 and 65 years with a history a migraine for at least 12 months, with a without aura, that met the criteria specified in International Classification of Headache Disorders, 3rd edition (beta version)
[*] Pre-assignment Details	Patients were required to have 4 or more migraine attacks the last three months before the study, patients were not under prophylactic treatment and with a signed letter of informed consent were considered.

Period ①

*** Period Title**	Overall Study ①		
*** Arm/Group Title**	Memantine	Valproate	
***§ Arm/Group Description** ②			
	Number of Participants ④	**Number of Participants** ④	**Number of Participants** ④
*** Started**	87	33 were randomized	33
[*] Milestone Title ③ Male/female	3/13	4/13	
[*] Milestone Title ③ without aura	13	13	
[*] Milestone Title ③ with aura	3	4	
*** Completed**			
Not Completed	*(automatically calculated)*		
Reason Not Completed Type ③			
[*] Adverse Event	8	7	
[*] Death	0	0	
[*] Lack of Efficacy	2	1	
[*] Lost to Follow-up	2	1	
[*] Physician Decision	0	0	
[*] Pregnancy	0	0	
[*] Protocol Violation	0	0	
[*] Withdrawal by Subject	2	1	
[*] Other Reason			
[*] Other Reason			
[*] Other Reason			

*** Required** ***§ Required if Primary Completion Date is on or after January 18, 2017** **[*] Conditionally required**

① Complete a Period table for each stage of the study. If only one Period, the Title is "Overall Study". For multiple Periods, include descriptive Titles for each Period.
② Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
③ [Optional] Add as many Milestone Title or Other Reason Not Completed rows as needed. A descriptive title for each row is required.
④ Number and Type of Units Assigned may also be specified.

Study Protocol document date: February 15, 2019;
Statistical Analysis Plan document date: November 20, 2020;
Informed Consent Form document date: February 15, 2019.

Other (Not Including Serious) Adverse Events Template — *ClinicalTrials.gov*

*§ Time Frame	Adverse Events According to Group
[*] Adverse Event Reporting Description	Memantine group eight patients presented non-severe side effects and seven patients in the sodium valproate group
Source Vocabulary Name for Table Default ①	
*§ Collection Approach for Table Default ①	(Select One) Systematic Non-Systematic Non-systematic

* Arm/Group Title	Memantine	Valproate	
*§ Arm/Group Description ②	8	7	Total of any adverse event, all Grade 1 (Mild)

*** Other (Not Including Serious) Adverse Events**

* Frequency Threshold for Reporting Other Adverse Events (0–5%) _____%		* Number Participants Affected	* Number Participants at Risk	Number Events	* Number Participants Affected	* Number Participants at Risk	Number Events	* Number Participants Affected	* Number Participants at Risk	Number Events
* Total										
* Adverse Event Term	* Organ System									
Somnolence	CNS ③	4	④[*]		6	④[*]		10	33 ④[*]	10
Poor concentration	CNS ③	2	④[*]		0	④[*]		2	33 ④[*]	2
Parasomnia	CNS ③	0	④[*]		1	④[*]		1	33 ④[*]	1
Dizziness	CNS ③	2	④[*]		0	④[*]		2	33 ④[*]	2
	③		④[*]			④[*]			④[*]	
	③		④[*]			④[*]			④[*]	
	③		④[*]			④[*]			④[*]	
	③		④[*]			④[*]			④[*]	

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① If entered, the table default values apply to all Adverse Event Terms. The values may be changed for any single Adverse Event, if different from the table default.
② Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
③ Organ System must be selected from a pick-list of high-level categories. See the Results Data Element Definitions for details.
④ Number of Participants at Risk for an Adverse Event Term is only required when the value differs from the Total Number of Participants at Risk.

Conclusion

HOSPITAL CENTRAL "DR. IGNACIO MORONES PRIETO"

NCT04698525

This double blind randomized clinical trial, is the only pilot study where Memantine is compared to Sodium Valproate as prophylactic treatment for migraine.

The response of both groups was dramatic and significant ($p < 0.05$)to the management they received, with a clear difference in the number of attacks, duration of four, intensity (EVA), and disability caused by the attack (MIDAS)

Memantine could be considerer as a prophylactic treatment option in migraine.

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""Efficacy of memantine compared to sodium valproate as prophylactic treatment for Episodic Migraine" A controlled randomized pilot clinical trial

NCT04698525