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

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BACKGROUND

Migraine is one of the three diseases most disability worldwide. [1] The 1-year prevalence of Migraine is approximately 15–18% in women and 6% in men; thus, it can create a sizeable socio-economic problem. [2]

The goal of prophylactic treatment is decreased frequency, duration, and severity of migraine attacks. [3] The drugs recommended evidence-based with established efficacy as a first-line are sodium valproate, topiramate, propranolol, and metoprolol. [4] Although, oral preventive medications found adherence rates of 26% to 29% at six months, which diminished to 17% to 20% at 12 months. [5]

Interestingly, there has been increased interest in studying receptor glutamate antagonist drugs with the potential form of migraine treatment because glutamate has a potential role in migraine pathophysiology. One of the first evidence points was the role in cortical spreading depression, an extreme depolarization neuronal membrane that results in the released glutamate, and a transient increase followed by a decrease in cerebral blood flow. [6] Levels of glutamate are increased in the trigeminocervical complex after stimulation of dural structures. Other studies found high levels of glutamate in the blood of migraine patients and cerebrospinal fluid of patients with Chronic Migraine. [7]

Memantine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor, one of the ionotropic glutamate receptors. [7,8]. Charles et al. reported a case series of 71 patients with refractory Migraine who received Memantine as a prophylactic treatment for two months, 54 of them reported reductions of 50% in frequency of headaches. and security of Memantine as a preventative treatment in refractory Migraine. [9]

Noruzzadeh et al. conducted the first randomized, double-blind placebo-controlled clinical trial. The aim objective was to evaluate the efficacy of Memantine as a prophylactic treatment in Migraine with aura. Patients in the memantine group showed a more significant reduction in monthly attack frequency than the placebo group. [10]

This study aimed to assess the efficacy of Memantine and compared sodium valproate in the prophylactic treatment of Migraine.

METHODS

Study design

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 will be conducted in Neurology clinic at Hospital Central "Dr. Ignacio Morones Prieto" at San Luis Potosí, México from July 2019, to October 2020.

Participants

Eligible patients were adults aged between 18 and 65 with a history of Migraine for at least 12 months, that met the criteria specified in the *International Classification of Headache Disorders, 3rd edition* (*beta version*), for Migraine with or without aura. In addition, patients were required to have four or more Migraine attacks the last three months before the study; patients were not under prophylactic treatment and were considered with a signed letter of informed consent.

Patients were excluded from the study if they were pregnant or lactation, patients with 15 or more headache days per month during the last three months before the study, other types of headaches, allergy to Memantine or Valproate.

Procedures and Interventions

Computer-generated numbers performed random assignment will be used to create a random assignment sequence. Patients were randomized in the group of Memantine or the group of Valproate. All the investigators and patients were blinded to the random allocation during the study, except for the study technician who undertook the randomization.

There were five clinic visits, a screening visit, 4-week run-in period, and participants underwent randomization in visit 2; each visit was every 4-week for 12-weeks double-blind treatment period.
The group of Memantine started with a tablet of 10mg per night for one week, followed by an increase to one tablet of 10mg per day and per night with maximum doses of 20mg and divided into two doses. The group of Valproate started with a pill of 500mg per night for one week, followed by an increase to one tablet of 500mg per day and per night with maximum doses of 500mg.

Efficacy was assessed based on data recorded by the participant on a migraine diary provided where they recorded frequency, duration, triggers, and clinical characteristics. In addition, MIDAS (Migraine Disability Assessment) test was performed in visit two and visit 5.

Endpoints

The primary outcome was the change from baseline in the monthly attack frequency at week 12 between the two groups (using migraine diary). The secondary results were to evaluate the response rate to treatment in each group defined as a reduction of 50% or more in days with Migraine, evaluate migraine disability using MIDAS before and after treatment, the intensity of Migraine was assessed with the Visual Analogue Scale (VAS) pretreatment and post-treatment and, 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. Next, 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.

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