Comparative Study of Magnesium, Sodium Valproate, and Concurrent Magnesium- Sodium Valproate Therapy in the Prevention of Migraine: A Randomized Controlled Double-Blind Trial.

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Abstract

Objective

This study aimed to assess the efficacy of concurrent magnesium-sodium valproate therapy and compare it with either magnesium or sodium valproate alone in the prevention of migraine prophylaxis.

Materials and Methods

This randomized single-center double-blind parallel-group controlled clinical trial study was conducted on migraine patients within the age range of 18-65 years. The subjects with at least four monthly attacks were randomly assigned to group A (n=82), group B (n=70), and group C (n=70) with the administration of sodium valproate, magnesium-sodium valproate, and magnesium, respectively. The patients passed a one-month baseline without prophylactic therapy and then received a 3-month treatment. The characteristics of migraine, including frequency, severity, duration of the attacks, and the number of painkillers taken per month, were monthly recorded in each visit. The Migraine Disability Assessment (MIDAS) and Headache Impact Test-6 (HIT-6) scores were recorded at the baseline and after 3 months of treatment in each group. Within- and between-group analyses were performed in this study.

Results

The obtained results revealed a significant reduction in all migraine characteristics in all groups compared with baseline ($P<0.001$). Intragroup data analysis indicated that there was no statistically significant difference in headache frequency between groups A and B in the third month ($P= 0.529$); nevertheless, three other parameters showed a significant reduction in group B, compared to those reported in group A in the third month ($P<0.05$). On the other hand, group C could not effectively reduce measured parameters in the patients, compared to groups A and B after three months ($P<0.001$). Furthermore, the MIDAS and HIT-6 scores diminished significantly in groups A, B, and C compared with baseline ($P<0.001$), and also these changes were more significant in groups A and B than group C ($P<0.001$).

Conclusion

The obtained results of this study revealed that magnesium could enhance the antimigraine properties of sodium valproate in combination therapy and reduce the required valproate dose for migraine prophylaxis.

Introduction

Migraine as a primary headache disorder with substantial pain is included in the 20 most disabling diseases according to the World Health Organization (Steiner, Birbeck et al. 2011). Epidemiologic studies have indicated that the prevalence of migraine is about 14% in Iran similar to or even higher than that reported worldwide (Farhadi, Alidoost et al. 2016) . Lifestyle management, acute treatment, and preventive treatment are three approaches in order to treat migraine (Weatherall 2015). Prophylactic therapy for migraine is recommended in patients with four or more attacks per month, eight or more headache days a month, debilitating headaches, and medication-overuse headaches (Ha and Gonzalez 2019).

Reduction in the frequency of headaches about 50% or more, reduced intensity, and improved response to symptomatic medication can be three outcomes of preventive therapy (Pringsheim, Davenport et al. 2012). However, lack of effectiveness, adverse effects, and poor compliance are also common in these patients (Hesami, Shams et al. 2018, Skljarevski, Matharu et al. 2018). Beta-blockers, calcium-channel blockers, anticonvulsants, selective serotonin reuptake inhibitors, tricyclic antidepressants, and angiotensin blockers are some of the medications used for migraine prophylaxis. Furthermore, botulinum toxin, flunarizine, vitamins, minerals, and herbal agents were also suggested in many studies (Weatherall 2015, Giorgio Dalla, Zavarize et al. 2017).

Sodium valproate is one of FDA-approved antiepileptic drugs (AEDs) for the prevention of migraine (Parikh and Silberstein 2019). Several functions have been proposed for the antimigraine action of this drug in such patients; nevertheless, the exact mechanism is not completely understood due to its various biochemical effects and multifactorial nature of migraine pathophysiology (Cutrer, Limmroth et al. 1997) (Spasić, Živković et al. 2003) (Sprenger, Viana et al. 2018). Despite the proven efficacy of valproate in the prevention of migraine, poor compliance with therapy has been observed due to its side effects, such as fatigue, dizziness, nausea, tremor, and weight gain (Assarzadegan, Tabesh et al. 2016, Romoli, Costa et al. 2018).

Magnesium is a cofactor in more than 300 biochemical reactions and helps to maintain normal nerve and muscle functions (Faryadi 2012). In recent years, studies have focused on the clinical use of magnesium as a prophylactic regimen for migraine due to good efficacy and tolerability in patients (Dolati, Rikhtegar et al. 2019). Oral magnesium supplementation has been reported with level B evidence for its efficacy in the prophylactic therapy of episodic migraine based on the American Academy of Neurology Guidelines (Daniel and Mauskop 2016).

Although there have been existing evidence on the effectiveness of magnesium for migraine prophylaxis, no study has evaluated magnesium potency in increasing sodium valproate efficacy in combination therapy of migraine. The current study was the first attempt to compare the efficacy of combination therapy of magnesium and sodium valproate with each treatment alone in the prophylaxis of migraine.

Methods

Study design

This single-center placebo-controlled double-blind randomized trial study (registered in Iranian Registry of Clinical Trials with registry no. IRCT2015081923685N1) was conducted on migraine patients on October 11 in 2015. This study was conducted at the neurological special clinic of *Shahid-Beheshti* Hospital in Qom. Research assistant evaluated eligibility obtained informed consent and enrolled the participants

A total of 260 patients entered into the study from December 2015 to October 2019 with signed consent about the inclusion and exclusion criteria. Patients were recruited from those referred to an outpatient neurological clinic and also through advertisement on social networks (Telegram and WhatsApp). Approval for this trial was granted from the Ethics Committee of Qom University of Medical Sciences in Qom, Iran (IR.MUQ.REC.1394.73). The patients were randomly assigned into three groups, including the intervention groups A, B, and C. The intervention group A received a 200 mg sodium valproate tablet twice a day orally for 12 weeks and a placebo tablet twice a day orally for 12 weeks. The intervention group B was administered with a 200 mg sodium valproate tablet twice a day orally for 12 weeks and a 250 mg magnesium oxide tablet twice a day orally for 12 weeks. The intervention group C received a 250 mg magnesium oxide tablet twice a day orally for 12 weeks and a placebo tablet twice a day orally for 12 weeks.

All the patients underwent a one-month baseline period (without prophylactic medication) to assess the frequency of attacks, severity of attacks, and amount of collaboration with the physician. The study duration from the onset of drug prescription would be 3 months, and the patients were monthly followed. The concurrent administration of acute abortive treatment was not prohibited during this study; however, the patient should record the dose of pain killer in diaries. Headache diaries and headache questionnaires (i.e., the Migraine Disability Assessment [MIDAS] and Headache Impact Test-6 [HIT]) were used to obtain clinical information. *The paper diary* which used to record information about the attacks of migraines during baseline and treatment period, including; Wong-Baker Faces Pain Rating Scale for severity assessment besides data about the frequency, duration, days with migraines per month, and the number of painkillers used per month. The patient should complete the Diary daily and the research assistant *contacted* the *patient* by telephone every week to ensure from patient compliance.

primary efficacy measures : The three groups were evaluated to compare the efficacy of three treatment schedules at the end of baseline, as well as the first, second, and third months after the treatment. Migraine frequency, severity and duration of attack as well as number of painkiller used per month were compared between the three treatment groups

Secondary efficacy measures: Changes in the MIDAS and HIT-6 scores from the baseline were calculated after a 3-month treatment in each group. The HIT-6 was used to assess the severity of headache impact on the patient life, and the HIT-6 score ranges from 36 to 78 (Shin, Park et al. 2008). The MIDAS questionnaire was also used to determine migraine-related disabilities over a 3-month period. The MIDAS scores include 0 to 5 (MIDAS grade I: little or no disability), 6 to 10 (MIDAS grade II: mild disability), 11 to 20 (MIDAS grade III: moderate disability), and 21 or higher (MIDAS grade IV: severe disability) (Bigal, Rapoport et al. 2003, Holla, Darshan et al. 2019).

Inclusion and exclusion criteria

The inclusion criteria were the diagnosis of migraine according to the latest International Headache Society criteria (Arnold 2018), history of migraine with or without aura for at least 6 months, age range of 18-65 years, and experience of at least four monthly attacks. The exclusion criteria were non-migraine headaches, the total number of headache days per month higher than 15, overuse of

analgesics in migraine attacks (i.e., the use of ergots, nonsteroidal anti-inflammatory drugs, and triptans higher than 8 days a month), substance and alcohol dependence, illiteracy of patients and their family (unable to fill diaries), pregnancy and nursing, history of magnesium or sodium valproate intolerance, history of renal, liver, and chronic diseases, elevated liver enzymes in the first sampling more than two times the normal, neurologic disorders other than migraine, use of supplements containing magnesium, use of herbal antimigraine, as well as use of antidepressant and antipsychotic medications.

Randomization and blinding

Block randomization sampling was used in the present study. Each subject received an ID code, and the medications were delivered to the patient based on the order of the blocks in completely identical containers without the label, marked as A, B or C to complete sample size. Clinicians and patients were blinded to receiving drugs during the study period.

Sample size and Statistical methods

The required sample size for the study was calculated at least 67 in each group with a power of 80% and the significance level of 5%, whereas the recovery rate in the two groups of the study were 65% and 38.1%, respectively based on the previous trials (Keyvan and Abolfazl 2009). Therefore, 260 patients were divided into three groups via random divisions (A=88, B=86, C=86) considering the dropout rate.

All statistical analyses were performed using SPSS software (version 20). Firstly, the normal distribution of data at the beginning of the study was investigated by the Kolmogorov-Smirnov test. Descriptive characteristics, such as mean and standard deviation, were used to explain the statistical results. Patient characteristics (sex, migraine type, family history) were analyzed using Pearson's chi-square test. Intergroup comparisons were performed using a paired student's t-test. The analysis of variance (ANOVA) and Tukey's post-hoc test were used to compare values between three treatment groups. *P*-value less than 0.05 was considered statistically significant.

Results

A total of 298 patients with recurrent migraine were enrolled in the present study. After careful screening, 260 patients were randomized to different treatment groups (i.e., A, B, and C). Finally, 222 patients (125 females and 97 males) completed the study. The consort diagram of the study is presented in Figure 1. As shown in Table 1, there was no significant difference in demographics, migraine type, and headache history at the baseline in various treatment groups.

The patients were evaluated in terms of headache frequency, headache severity, headache duration and number of painkillers taken per month after the onset of the treatment for 3 months. The intergroup and intragroup analyses of the data were performed. The obtained results showed a significant reduction in the measured parameters in three arms of the study, compared to that reported at the baseline after a 1, 2 and 3-month treatment ($P<0.001$) . However, a significant reduction in headache duration in group C was not demonstrated during the first month of the study ($P=0.153$) (Table 2).

Intragroup data analysis indicated that there was no statistically significant difference in headache frequency between groups A and B in the first ($P= 0.972$) and third months ($P=0.525$), but group B revealed a significant reduction in the second month compared with A ($P=0.029$). Furthermore, Group C indicated a significant difference in headache frequency compared with A and B over three months ($P<0.001$) (Table 3).

No significant difference in headache severity was observed in the first month between the three groups but severity reduction was significant in B group compared with A ($P=0.01$ and $P=0.002$) and C ($P<0.001$) groups in the second and third month respectively. Severity reduction was also better in A group compared to C in the second and third months ($P< 0.001$) (Table 3).

Three groups had no significant difference in headache Duration in the first month but A and B were both significantly better than C group with *P*-value of 0.006 and <0.001 respectively in the second month and *P*-value of 0.004 and <0.001 respectively in the third month. Headache duration also differed significantly between A and B in the second (*P* value= 0.019) and third month (*P* value= 0.013) (Table 3).

Paine killer number had no statistically significant difference between A and B groups in the first month (*P* value= 0.871) but it was lower significantly in A (*P* value=0.031) and B (*P* value= 0.010) compared to C group in the first month. The pain killer number was

significantly lower in B compared to A group in the second and third months (P< 0.001). A and B group used both significantly lower pain killers than the C group in the second (P value=0.017 and <0.001 respectively) and third month (P value<0.001) (Table 3).

The MIDAS and HIT-6 scores (Table 4) were significantly lower in all treatment groups in comparison to those measured at the baseline (P<0.001). Intragroup analysis of MIDAS and HIT-6 changes also indicated that groups A and B had significantly higher scores changes than group C (P<0.001). However, no significant difference was observed between groups A and B in HIT score change (P-value = 0.999). MIDAS score changes were significantly different between two groups (A vs B, P-value= 0.023) (Figure 3).

Discussion

The current study compared the efficacy of sodium valproate (group A), sodium valproate plus magnesium oxide (group B), and magnesium oxide (group C) in the migraine prophylaxis of patients within the age range of 18-65 years. Besides, MIDAS and HIT6 scores were compared between three treatment groups. The obtained results showed that the combination of magnesium and sodium valproate had an appropriate efficacy in migraine prophylaxis, as headache severity, duration of headache, and amount of utilized painkillers were significantly lower in group B, compared to those reported in group A. Moreover, the MIDAS score reduced more in B group than A and HIT score changes were not significantly different between A and B. Furthermore, by the addition of magnesium to valproate (group B), the sodium valproate dose reduced significantly, compared to group A.

Sodium valproate belongs to an antiepileptic drug class with an important role in the treatment of migraine. Increasing GABA activity and inhibiting NMDA-evoked neuroexcitatory signals are two main mechanisms of valproate in blocking cortical spreading depression during a migraine attack. It can inhibit GABA-degrading enzymes (i.e., aminotransferase and succinic semialdehyde) and increase the neuro-inhibitory activity of GABA. In addition, the active metabolites of valproate can activate the GABA-synthesizing enzyme (i.e., glutamic acid decarboxylase) and increase GABA activity more over time. Furthermore, valproate decreases neurogenic inflammation by debilitating plasma extravasation of vasoactive neuropeptides, such as substance P, CGRP, and neurokinin A (Parikh and Silberstein 2019, Waldrop and Kolb 2019).

There is much evidence that valproate is effective in the prevention of migraine attacks; however, different response rates were reported in various studies (Mathew, Saper et al. 1995, Shaygannejad, Janghorbani et al. 2006). Ichikawa et al. demonstrated that different factors, such as the history of hyperlipidemia, allergy, and psychiatric disorders, are involved in the clinical responses to valproate (Ichikawa, Katoh et al. 2016). Sodium valproate has been used in doses within the range of 500 to 1,000 mg/day in migraine prevention trials (Parikh and Silberstein 2019). Nevertheless, in the current study, a lower dose of 200 mg was prescribed twice a day for patients with an acceptable response. Other studies in Iranian population also revealed that the therapeutic effect is achieved using 200 to 500 mg sodium valproate daily in migraine prophylaxis (Bostani, Rajabi et al. 2013, Homam, Farajpour et al. 2016, Hesami, Shams et al. 2018).

The effectiveness of magnesium in migraine prophylaxis was firstly investigated by Facchinetti et al. in 1991 (Facchinetti, Sances et al. 1991). Other trials also reported different results of magnesium efficacy in migraine patients (Taubert 1994, Köseoglu, Talaslıoglu et al. 2008). Therefore, further clinical trials were suggested in studies to clarify the exact efficacy of magnesium in the prevention of migraine. It is proposed that magnesium is linked to migraine pathogenesis by counteracting both vascular and neurogenic mechanisms of migraine (Von Luckner, Riederer et al. 2018). Magnesium may be effective in migraine through the regulation of neuronal excitability because magnesium not only acts as a physiologic calcium-antagonist but also inhibits NMDA receptors and glutamate-dependent excitatory pathways (Dalla Volta 2017, Hoffmann and Charles 2018). In addition, magnesium can regulate neurotransmitter release and substance P release and reduce free radical accumulation within the cell and vasoconstriction (Altura and Altura 1980, Facchinetti, Sances et al. 1991, Weglicki, Phillips et al. 1992). Magnesium through modulating mitochondrial oxidative phosphorylation, 5-HT neurotransmission, and the NO system, regulating the uptake of glutamate into astrocytes, and blocking of NMDA receptor can be effective in migraine-preventive therapy (Sprenger, Viana et al. 2018).

Magnesium has numerous effects on the nervous system, and other mechanisms, including the inhibition of voltage-gated calcium channels, connexin channels, and other ion channels, can be involved in the prevention of migraine (Hoffmann and Charles 2018). Based on the evidence, magnesium was strongly recommended by the Canadian Headache Society in migraine prophylaxis. The Swiss Headache Society also suggests magnesium to children and pregnant women with migraine (Pringsheim, Davenport et al. 2012).

In a crossover study conducted by Karimi et al., the comparison of efficacy between magnesium oxide and sodium valproate was carried out for migraine prophylaxis. The results showed that 500 mg/day magnesium has comparable efficacy to 400 mg/day valproate in migraine prophylaxis (Karimi, Razian et al. 2019). However, the obtained results of the present study showed that valproate was significantly more effective than magnesium in the reduction of migraine frequency and severity, duration of attacks, pain killer number as well as the MIDAS and HIT scores.

According to the literature, it was shown that the addition of magnesium to valproic acid in magnesium valproate can reduce calcium ion conductance efficiently, activate the Na^+/K^+ ion pump, and modulate the NMDA receptors of the neuronal membrane, compared to valproate alone in epilepsy (Canger and Guidolin 2000). Animal studies also demonstrated that magnesium enhances the anticonvulsant potential of a subprotective dose of valproic acid in pentylenetetrazol-treated rats by the improvement of redox balance and modulation of some brain excitatory amino acids, such as aspartate, asparagine, and glycine (Safar, Abdallah et al. 2010).

It should be noted that epilepsy and migraine have some similar pathophysiological mechanisms, including the imbalance between GABA-mediated inhibition, excitatory glutamate-mediated transmission, as well as the abnormal function of voltage-gated sodium and calcium channels (Shahien and Beiruti 2012). The results of in vitro studies demonstrated that magnesium improves valproic acid efficacy against 4-aminopyridine-induced ictal activity (Fueta, Siniscalchi et al. 1995). The findings of the present clinical study also confirmed this idea and indicated that a combination of magnesium and low-dose valproate (200 mg) have appropriate efficacy in migraine prophylaxis without any reported exacerbation of side effects.

Study limitations

Some participants in this study did not contribute to blood sampling. Lack of complete data about serum magnesium level limits our analysis about studying the correlation between serum levels of magnesium and the efficacy of treatment in three groups. Furthermore, adverse effects assessment during the study was not carried out completely due to faulty reports so the precise analysis was impossible.

Conclusion

The results of the present study revealed that combination treatment with a low dose of sodium valproate and magnesium has desirable efficacy in the reduction of migraine frequency, severity, duration, and utilized pain killer. Considering these promising results, it also indicated that by the addition of magnesium to valproate, the sodium valproate dose can be reduced and improve its efficacy. Consequently, the development of a new combination drug in this manner "Magnesium Valproate", can be a more potent and safe therapy for migraine prophylaxis.

Declarations

Acknowledgments

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References

1. Altura, B. T. and B. M. J. N. l. Altura (1980). "Withdrawal of magnesium causes vasospasm while elevated magnesium produces relaxation of tone in cerebral arteries." 20(3): 323-327.
2. Arnold, M. J. C. (2018). "Headache classification committee of the international headache society (ihs) the international classification of headache disorders." 38(1): 1-211.
3. Assarzadegan, F., H. Tabesh, S.-M. Hosseini-Zijoud, A. D. Beale, A. Shoghli, M. G. Yazdi, B. Mansouri, O. Hesami, N. B. Moghadam and H. D. J. I. R. C. M. J. Kasmaei (2016). "Comparing zonisamide with sodium valproate in the management of migraine headaches: double-blind randomized clinical trial of efficacy and safety." 18(9).
4. Bigal, M. E., A. M. Rapoport, R. B. Lipton, S. J. Tepper, F. D. J. H. T. J. o. H. Sheftell and F. Pain (2003). "Assessment of migraine disability using the migraine disability assessment (MIDAS) questionnaire: a comparison of chronic migraine with episodic migraine." 43(4): 336-342.

5. Bostani, A., A. Rajabi, N. Moradian, N. Razazian and M. J. I. J. o. N. Rezaei (2013). "The effects of cinnarizine versus sodium valproate in migraine prophylaxis." 123(7): 487-493.
6. Canger, R. and L. J. C. D. I. Guidolin (2000). "Clinical Efficacy and Tolerability of Magnesium Valproate as Monotherapy in Patients with Generalised or Partial Epilepsy." 20(4): 215-221.
7. Cutrer, F., V. Limmroth and M. J. C. Moskowitz (1997). "Possible mechanisms of valproate in migraine prophylaxis." 17(2): 93-100.
8. Dalla Volta, G. J. I. J. N. B. D. (2017). "Combi-nation of Tanacethum Partenium, 5-Hy-drossitriptophan (5-Http) and Magnesium in the Prophylaxis of Episodic Migraine without Aura (AURASTOP®)-An Obser-vational Study.(2017) Int J Neuro Brain Dis 4 (3): 1-4." 4(3).
9. Daniel, O. and A. J. C. t. o. i. n. Mauskop (2016). "Nutraceuticals in acute and prophylactic treatment of migraine." 18(4): 14.
10. Dolati, S., R. Rikhtegar, A. Mehdizadeh and M. J. B. t. e. r. Yousefi (2019). "The Role of Magnesium in Pathophysiology and Migraine Treatment." 1-9.
11. Facchinetti, F., G. Sances, P. Borella, A. R. Genazzani, G. J. H. T. J. o. H. Nappi and F. Pain (1991). "Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium." 31(5): 298-301.
12. Farhadi, Z., S. Alidoost, M. Behzadifar, R. Mohammadibakhsh, N. Khodadadi, R. Sepehrian, R. Sohrabi, M. T. Mirghaed, M. Salemi and H. J. I. R. C. M. J. Ravaghi (2016). "The prevalence of migraine in Iran: A systematic review and meta-analysis." 18(10).
13. Faryadi, Q. J. I. J. o. A. (2012). "The magnificent effect of magnesium to human health: a critical review." 2(3).
14. Fueta, Y., A. Siniscalchi, V. Tancredi and M. J. E. Avoli (1995). "Extracellular magnesium and anticonvulsant effects of valproate in young rat hippocampus." 36(4): 404-409.
15. Giorgio Dalla, V., P. Zavarize, G. Ngonga, A. Pezzini, G. J. I. J. o. N. Dalla Volta and B. Disorders (2017). "Combination of Tanacethum Partenium, 5-Hydrossitriptophan (5-Http) and Magnesium in the Prophylaxis of Episodic Migraine without Aura (AURASTOPÂ®) An Observational Study." 4(1): 0-0.
16. Ha, H. and A. J. A. f. p. Gonzalez (2019). "Migraine Headache Prophylaxis." 99(1).
17. Hesami, O., M. R. Shams, L. Ayazkhoo, F. Assarzadegan, B. S. Lima, H. D. Kasmaei and M. J. I. j. o. p. r. I. Sistanizad (2018). "Comparison of pregabalin and sodium valproate in migraine prophylaxis: a randomized double-blinded study." 17(2): 783.
18. Hoffmann, J. and A. Charles (2018). "Glutamate and Its Receptors as Therapeutic Targets for Migraine." Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics 15(2): 361-370.
19. Holla, R., B. Darshan, Y. Z. Ying, T. Raymond, E. Ponniah, K. S. San, N. Y. J. I. J. o. P. H. R. Yen and Development (2019). "Clinical Characteristics and Associated Disability of Headache among Medical Undergraduates." 10(8): 647-650.
20. Homam, M., A. Farajpour, S. Khadem and Z. J. C. J. o. N. S. Mostafavian (2016). "The experiential comparison of levetiracetam efficacy in migraine headache with sodium valproate." 2(2): 42-49.
21. Ichikawa, M., H. Katoh, T. Kurihara and M. J. J. o. C. N. Ishii (2016). "Clinical response to valproate in patients with migraine." 12(4): 468-475.
22. Karimi, N., A. Razian and M. J. A. N. B. Heidari (2019). "The efficacy of magnesium oxide and sodium valproate in prevention of migraine headache: a randomized, controlled, double-blind, crossover study." 1-7.
23. Keyvan, G. and M.-B. J. P. j. o. b. s. P. Abolfazl (2009). "Comparison of treatment effect of sodium valproate, propranolol and tricyclic antidepressants in migraine." 12(15): 1098-1101.
24. Köseoglu, E., A. Talaslıoglu, A. S. Gönül and M. J. M. r. Kula (2008). "The effects of magnesium prophylaxis in migraine without aura." 21(2): 101-108.
25. Mathew, N. T., J. R. Saper, S. D. Silberstein, L. Rankin, H. G. Markley, S. Solomon, A. M. Rapoport, C. J. Silber and R. L. J. A. o. N. Deaton (1995). "Migraine prophylaxis with divalproex." 52(3): 281-286.
26. Parikh, S. K. and S. D. J. C. t. o. i. n. Silberstein (2019). "Current Status of Antiepileptic Drugs as Preventive Migraine Therapy." 21(4): 16.
27. Pringsheim, T., W. Davenport, G. Mackie, I. Worthington, M. Aubé, S. N. Christie, J. Gladstone and W. J. J. C. J. N. S. Becker (2012). "Canadian Headache Society guideline for migraine prophylaxis." 39(2 Suppl 2): S1-59.
28. Romoli, M., C. Costa, S. Siliquini, I. Corbelli, P. Eusebi, C. Bedetti, S. Caproni, L. M. Cupini, P. Calabresi and P. J. C. Sarchielli (2018). "Antiepileptic drugs in migraine and epilepsy: Who is at increased risk of adverse events?" 38(2): 274-282.

29. Safar, M. M., D. M. Abdallah, N. M. Arafa and M. T. J. B. r. Abdel-Aziz (2010). "Magnesium supplementation enhances the anticonvulsant potential of valproate in pentylenetetrazol-treated rats." 1334: 58-64.
30. Shahien, R. and K. J. J. o. c. n. s. d. Beiruti (2012). "Preventive agents for migraine: focus on the antiepileptic drugs." 4: JCNSD. S9049.
31. Shaygannejad, V., M. Janghorbani, A. Ghorbani, F. Ashtary, N. Zakizade, V. J. H. T. J. o. H. Nasr and F. Pain (2006). "Comparison of the effect of topiramate and sodium valporate in migraine prevention: a randomized blinded crossover study." 46(4): 642-648.
32. Shin, H. E., J. W. Park, Y. I. Kim and K. S. J. J. o. c. n. Lee (2008). "Headache Impact Test-6 (HIT-6) scores for migraine patients: Their relation to disability as measured from a headache diary." 4(4): 158-163.
33. Skljarevski, V., M. Matharu, B. A. Millen, M. H. Ossipov, B.-K. Kim and J. Y. J. C. Yang (2018). "Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial." 38(8): 1442-1454.
34. Spasić, M., M. Živković and S. J. M. B. Lukić (2003). "Prophylactic treatment of migraine by valproate." 10(3): 106-110.
35. Sprenger, T., M. Viana and C. J. N. Tassorelli (2018). "Current prophylactic medications for migraine and their potential mechanisms of action." 15(2): 313-323.
36. Steiner, T. J., G. L. Birbeck, R. Jensen, Z. Katsarava, P. Martelletti and L. J. Stovner (2011). The global campaign, world health organization and lifting the burden: collaboration in action, BioMed Central.
37. Taubert, K. J. F. d. M. (1994). "Magnesium in migraine. Results of a multicenter pilot study." 112(24): 328-330.
38. Von Luckner, A., F. J. H. T. J. o. H. Riederer and F. Pain (2018). "Magnesium in migraine prophylaxis—is there an evidence-based rationale? A systematic review." 58(2): 199-209.
39. Waldrop, M. A. and S. J. J. C. t. o. i. n. Kolb (2019). "Current Treatment Options in Neurology—SMA Therapeutics." 21(6): 25.
40. Weatherall, M. W. J. T. a. i. c. d. (2015). "The diagnosis and treatment of chronic migraine." 6(3): 115-123.
41. Weglicki, W. B., T. M. J. A. J. o. P.-R. Phillips, Integrative and C. Physiology (1992). "Pathobiology of magnesium deficiency: a cytokine/neurogenic inflammation hypothesis." 263(3): R734-R737.

Tables

Table 1. Patient Demographic characteristics at baseline.

Characteristics		A (n=82)	B (n=70)	C (n=70)	p-value
Sex (Female), n		41	42	42	0.35
Age, y		35.16 ± 8.21	37.11 ± 6.56	34.41 ± 6.19	0.27
BMI (Kg/m^2)		24.78± 8.34	24.76± 8.54	24.42± 7.70	0.17
Migraine type, n	Without Aura	51	39	44	0.62
	With Aura	31	31	26	
Headache history, y		5.23 ± 2.49	5.73 ± 2.14	4.89 ± 3.14	0.25
Family history of migraine, n	Yes	55	43	47	0.71
	No	27	27	23	

Table 2. Migraine characteristics of the three groups (A: Sodium Valproate; B: Sodium Valproate +Magnesium; C: Magnesium) in different treatment periods; *P values≤ 0.05 were considered statistically significant vs baseline [measured using sample (paired) t test].

Group	A	*P*-value (vs baseline)	B	*P*-value (vs baseline)	C	*P*-value (vs baseline)
Migraine attack (n), mean±SD						
baseline	6.65 ± 1.65		6.89 ± 1.52		7.06 ± 1.54	
After 1 month	4.09 ± 0.99*	<0.001	4.04 ± 0.93*	<0.001	5.49 ± 1.45*	<0.001
After 2 month	2.83 ± 0.73*	<0.000	2.47 ± 0.71*	<0.001	4.21 ± 0.08*	<0.001
After 3 month	1.60 ± 0.76*	<0.000	1.46 ± 0.75*	<0.001	3.91 ± 0.86*	<0.001
Headache severity, mean±SD						
baseline	5.33 ± 0.67		5.27 ± 0.79		5.16 ± 1.02	
After 1 month	3.68 ± 0.81*	<0.001	3.68 ± 0.73*	<0.001	3.93 ± 1.24*	<0.001
After 2 month	2.51 ± 0.68*	<0.001	2.16 ± 0.67*	<0.001	3.32 ± 0.78*	<0.001
After 3 month	1.71 ± 0.55*	<0.001	1.26 ± 0.59*	<0.001	2.41 ± 1.15*	<0.001
Headache duration (h),mean±SD						
baseline	11.56 ± 3.53		11.96 ± 1.73		10.99 ± 2.49	
After 1 month	10.39 ± 2.87*	<0.001	9.95 ± 1.80*	<0.001	10.64 ± 1.96	0.153
After 2 month	8.19 ± 2.76*	<0.001	7.22 ± 1.66*	<0.001	9.30 ± 1.84*	<0.001
After 3 month	7.06 ± 2.53*	<0.001	6.08 ± 1.75*	<0.001	8.15 ± 1.83*	<0.001
Painkiller (n), mean±SD						
baseline	6.45± 0.95		6.27 ± 0.94		5.88 ±1.34	
After 1 month	4.15 ± 0.93*	<0.001	4.19 ± 0.69*	<0.001	3.82 ± 0.76*	<0.001
After 2 month	3.11 ± 0.68*	<0.001	2.16 ± 0.67*	<0.001	3.12 ± 0.67*	<0.001
After 3 month	1.72 ± 0.58*	<0.001	1.26 ± 0.59*	<0.001	2.37 ± 0.78*	<0.001

Table 3: Intragroup monthly basis analysis of Migraine attack, Headache severity, Headache duration and Painkiller number (A: Sodium Valproate; B: Sodium Valproate +Magnesium; C: Magnesium); *P values≤ 0.05 were considered statistically significant.

Group	A	B	C	A vs B			A vs C			B vs C		
				p-value	Mean Difference	95 % CI	p-value	Mean Difference	95 % CI	p-value	Mean Difference	95 % CI
Migraine attack (n), mean±SD												
baseline	6.65 ± 1.65	6.89 ± 1.52	7.06 ± 1.54	0.621	-0.24	-0.85 to 0.37	0.248	-0.41	-1.02 to 0.20	0.797	-0.17	-0.80 to 0.46
After 1 month	4.09 ± 0.99	4.04 ± 0.93	5.49 ± 1.45	0.972	0.05	-0.40 to 0.48	< 0.001	-1.40	-1.84 to -0.96	< 0.001	-1.45	-1.90 to 0.99
After 2 month	2.83 ± 0.73	2.47 ± 0.71	4.21 ± 0.08	0.029	0.36	0.03 to 0.69	< 0.001	-1.38	-1.71 to -1.06	< 0.001	-1.74	-2.08 to -1.40
After 3 month	1.60 ± 0.76	1.40 ± 0.75	3.91 ± 0.86	0.525	0.20	-0.17 to 0.45	< 0.001	-2.31	-2.62 to -2.01	< 0.001	-2.51	-2.77 to -2.14
Headache severity, mean±SD												
baseline	5.33 ± 0.67	5.27 ± 0.79	5.16 ± 1.02	0.885	0.06	-0.25 to 0.38	0.424	0.17	-0.15 to 0.49	0.732	0.11	-0.22 to 0.43
After 1 month	3.68 ± 0.81	3.69 ± 0.73	3.93 ± 1.24	0.999	-0.01	-0.37 to 0.35	0.243	-0.25	-0.61 to 0.11	0.287	-0.24	-0.62 to 0.13
After 2 month	2.51 ± 0.68	2.16 ± 0.67	3.32 ± 0.78	0.01	0.35	-0.06 to 0.61	< 0.001	-0.81	-1.08 to -0.54	< 0.001	-1.16	-1.44 to 0.87
After 3 month	1.71 ± 0.55	1.26 ± 0.59	2.41 ± 1.15	0.002	0.45	-0.13 to 0.75	< 0.001	-0.70	-1.00 to -0.39	< 0.001	-1.15	-1.46 to -0.82
Headache duration (h), mean±SD												
baseline	11.56 ± 3.53	11.96 ± 1.73	10.99 ± 2.49	0.649	-0.40	-1.45 to 0.66	0.403	0.57	-0.48 to 1.63	0.093	0.97	-0.12 to 2.07
After 1 month	10.39 ± 2.87	9.95 ± 1.80	10.64 ± 1.96	0.481	0.44	-0.45 to 1.31	0.779	-0.25	-1.13 to 0.63	0.185	-0.69	-1.60 to 0.23
After 2 month	8.19 ± 2.76	7.22 ± 1.66	9.30 ± 1.84	0.019	0.97	0.12 to 1.80	0.006	-1.11	-1.94 to -0.26	< 0.001	-2.08	-2.94 to -1.20

After 3 month	7.06 ± 2.53	6.08 ± 1.75	8.15 ± 1.83	0.013	0.98	0.17 to 1.77	0.004	-1.09	-1.90 to -0.29	< 0.001	-2.07	-2.90 to -1.23
Painkiller (n), mean±SD												
baseline	6.45± 0.95	6.27 ± 0.94	6.05 ±1.48	0.601	0.18	-0.26 to 0.62	0.083	0.40	-0.04 to 0.84	0.489	0.22	-0.24 to 0.68
After 1 month	4.15 ± 0.93	4.07 ± 0.73	4.55 ± 1.13	0.871	0.08	-0.29 to 0.44	0.031	-0.40	-0.76 to -0.03	0.010	-0.48	-0.85 to -0.09
After 2 month	3.11 ± 0.68	2.21 ± 0.75	3.46± 0.89	< 0.001	0.90	0.60 to 1.19	0.017	-0.35	-0.64 to -0.05	< 0.001	-1.25	-1.55 to -0.93
After 3 month	1.72 ± 0.58	1.26 ± 0.59	2.37 ± 0.78	< 0.001	0.46	0.20 to 0.71	< 0.001	-0.65	-0.89 to -0.39	< 0.001	-1.11	-1.36 to -0.84

Table 4. Analysis of MIDAS and HIT score in a different group (A: Sodium Valproate; B: Sodium Valproate +Magnesium; C: Magnesium) compared to baseline.

	A		P-value	B		P-value	C		P-value
	Pre-intervention	Post-intervention		Pre-intervention	Post-intervention		Pre-intervention	Post-intervention	
MIDAS	21.74 ± 4.44	17.11 ± 4.06	<0.001	21.68 ± 3.72	16.11 ± 3.87	<0.001	22.13 ± 1.88	18.81± 1.76	<0.001
HIT-6	56.72 ± 4.59	49.91 ± 4.58	<0.001	56.89 ± 3.84	50.50 ± 3.27	<0.001	57.54 ± 2.13	53.03 ± 1.88	<0.001

MIDAS: migraine disability assessment score

HIT-6: Headache Impact Test-6 score