

Effectiveness of Vitamin B2 versus Sodium Valproate in Migraine Prophylaxis: a randomized clinical trialAbolghasem Rahimdel¹, Ahmad Zeinali², Pouria Yazdian-anari³, Rahele Hajizadeh³, Ehsan Arefnia³

¹ Neurologist, Assistant Professor, Department of Neurology, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

² Psychiatrist, Assistant Professor, Department of Neurology, Shahid Sadoughi Hospital, Yazd University of Medical Science, Yazd, Iran

³ Medical student, Student Research Committee, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Type of article: Original

Abstract

Background: Migraine headache is a prevalent periodical and neurological impairment that is associated with functional disorders. Regarding the side effects of available medications, research is continuing in an effort to identify new, effective pharmaceutical regimens with limited side effects.

Objective: The aim of this study was to compare the effectiveness of vitamin B2 versus sodium valproate in migraine prophylaxis.

Methods: This was a single-blind clinical trial conducted on 90 migraine patients in two parallel groups. The first group underwent vitamin B2 treatment (400 mg/day) for three months, and the second group was treated with sodium valproate (500 mg/day). The patients were examined at the beginning of the study and 4, 8, and 12 weeks later. After the administration of the drugs in both groups, we recorded the duration of migraine pain, the frequency of migraine episodes, and the severity of the headaches. Potential complications of this study that were measured were weight gain, dizziness, and gastrointestinal problems.

Results: The findings showed that the frequency, median duration per month, and severity of the headaches decreased in both groups, but the difference between them was not significant ($p > 0.05$). However, there were significantly fewer side effects in the vitamin B2 group ($p = 0.005$).

Conclusion: Sodium valproate and vitamin B2 have similar effects on the reduction of migraine attacks, but vitamin B2 had fewer complications and fewer adverse effects; therefore, vitamin B2 can be administered to patients who are prohibited from taking sodium valproate or who have adverse side effects when they take it.

Trial registration: The trial is registered at the Thailand Clinical Trial Registry (<http://www.clinicaltrials.in.th>) with the TCTR identification number TCTR20150924001.

Funding: This study received no funding from external sources.

Keywords: migraine, sodium valproate, vitamin B2

1. Introduction

Migraine headaches are prevalent and periodical neurological disorders, and they can cause disability, impaired quality of life, and adverse effects on the daily activities of life (1). The most common types of treatment are beta-blockers (2), anti-convulsants, calcium channel blockers (3), serotonin antagonists, tricyclic antidepressants (TCA), and monoamine oxidase inhibitors (MAOs) (2, 3). Among drugs for migraine prophylaxis, sodium valproate has been used extensively in recent years. According to earlier studies, it reduces the severity or frequency of migraine attacks in 50-60% of the patients (2-4). It is noteworthy that sodium valproate is accompanied by side effects in nearly 30% of the patients who take it. These complications mainly include gastrointestinal complications, changes of liver enzymes, weight gain, hand tremors, and hair loss (4, 5). Therefore, it is essential to identify highly effective

Corresponding author:

Pouria Yazdian-Anari, Student Research Committee, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Tel: +98.9385101025, Fax: +98.3536230354, E-mail: pouria_yazdiana_a@yahoo.com

Received: July 10, 2015, Accepted: August 14, 2015, Published: October 19, 2015

iThenticate screening: September 25, 2015, English editing: October 02, 2015, Quality control: October 05, 2015

© 2015 The Authors. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

and acceptable treatment methods that have fewer adverse side effects. Vitamin B2 is a new drug that is being used to treat migraine headaches. The initial studies have reported that it has a profound and beneficial effect compared to other vitamins. This study was designed and conducted to compare the effectiveness of vitamin B2 and sodium valproate in migraine prophylaxis.

2. Material and Methods

2.1. Trial Design

This was a single-blind, randomized clinical trial conducted on 90 migraine patients who were seeking treatment. The patients were divided into two parallel treatment groups and investigated for 12 months.

2.2. Participants

The statistical population included patients who sought medical care for their migraine symptoms at the Neurology Clinic of Shahid Sadoughi Hospital in Yazd, Iran. The majority of the patients had photophobia and nausea. The inclusion criteria were patients whose ages were 15-55 and who had migraine headaches with or without aura for at least six months before the study, who had two or more headache attacks over the last three months, and who had not taken sodium valproate in the last six months. Patients with systemic and underlying diseases, such as diabetes, hepatic disease, or malignancy, as well as pregnant and/or breastfeeding women were excluded from the study.

2.3. Interventions

The subjects were divided into two groups (#1 and #2) using a random number table. The study was initiated after obtaining informed consent forms that had been signed by the patients. Group #1 received vitamin B2 treatments of 400 mg/day for 12 weeks, and group #2 received 500 mg/day of sodium valproate for the same period of time. The type of treatment was decided by the respective physicians. The patients also were trained to measure their pain levels. After the patients' first visit to the health center, they used a questionnaire to record the severity, duration, and frequency of their headaches after periods of 4, 8, and 12 months. They also recorded probable complications of the medicine on the questionnaires. This process was conducted either through telephone interviews or during the patients' monthly visits to the center. Also, their liver enzymes were assessed once per month, and all of the results were within the acceptable range. The severity of their headaches was measured based on the visual analog scale (VAS).

2.4. Outcomes

Before beginning the intervention, demographic parameters, age, and gender were recorded. Twelve weeks after the initiation of the drug treatment, we recorded the duration, pain, frequency, and severity of migraine episodes in both groups. We also measured the patients' weight gain, dizziness, and gastrointestinal problems as possible complications of this study.

2.5. Sampling and blinding

According to relevant studies and by using of the sample size formula " $n = \sigma^2(Z^\alpha + Z^\beta)^2/d^2$," the sample size of this study was determined to be a total of 90 patients. Thus, this was a single blinded study that included 90 patients with migraine headaches. The follow-up data sampling and recording was done by the researcher, who was unaware of the medicine that was administered to each patient.

2.6. Statistical methods

SPSS version 16 (SPSS, Inc., Chicago, Illinois, USA) was used to analyze the statistical data. The t-test analysis was used to analyze the quantitative data, and the chi-squared analysis was used to analyze the qualitative data. A confidence level of 0.95 was used in this project.

2.7. Research ethics

The Medical Ethics Committee at Shahid Sadoughi University of Medical Sciences approved this study. The patients were included in the study after being informed about the treatment methods.

3. Results

This study was performed on 90 migraine patients, who were randomly divided into two equal groups. The first group was treated with vitamin B2, and the second group was treated with sodium valproate. During the study, five patients (two from group 1 and three from group 2) were removed from the study either because they were not present at the scheduled times or because they developed serious complications related to the medication. The t-test

indicated that there was no significant difference between the mean ages of group 1 and group 2 (30.2 ± 9.3 and 32.9 ± 9.8 years, respectively; p -value = 0.2). The chi-squared test did not show any significant difference between the two groups with respect to gender; there were 40 and 38 females in groups 1 and 2, respectively (93% versus 90.5%; p -value = 0.8). According to ANOVA, both medications had profound reductions of the frequency, duration, and severity of the patients' migraine headaches, pre- and post-intervention. In addition, the frequency of nausea and vomiting decreased, and the response to the analgesic was improved; however, the two groups were not significantly different in this regard. In this study, the frequency of headaches during the follow-up stages decreased from about 9.2 ± 6.2 to 2.4 ± 1.6 times/month in group 1 (vitamin B2 group) and from about 6.5 ± 3.1 to 2.1 ± 1 times/month in group 2 (sodium valproate group). Although the reduction was greater in group 2, the difference was not significant (Figure 1).

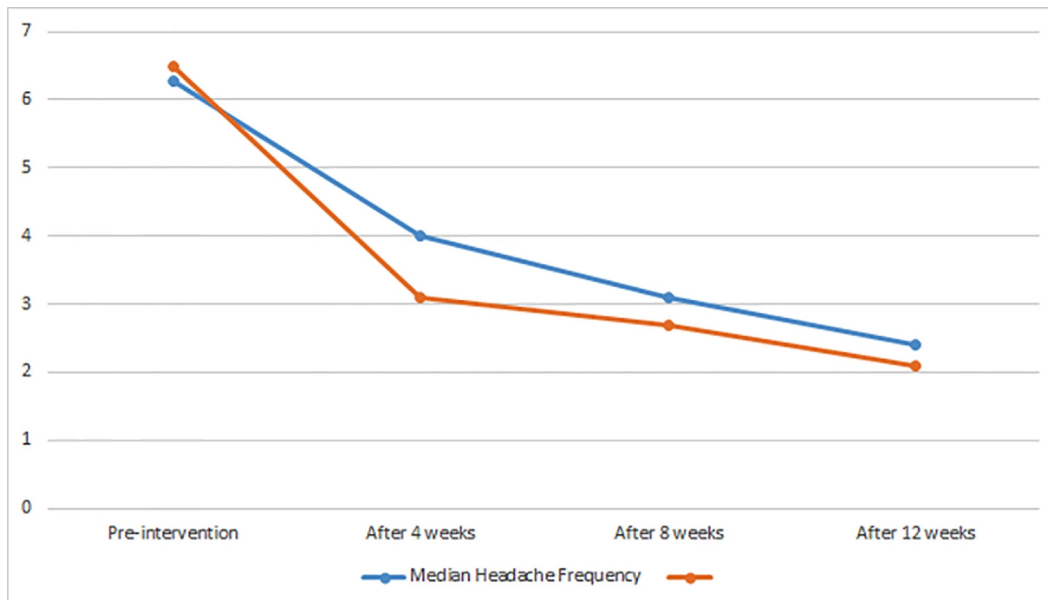


Figure 1. Changes in the frequency of headaches in the two groups, i.e., group 1 (vitamin B2 group) and group 2 (sodium valproate group)

Also, the duration of headaches decreased from about 15.1 ± 7.1 to 4.2 ± 2.6 hr/month in group 1 (vitamin B2 group) and from 16.2 ± 10.6 to 8.2 ± 4.7 hr/month in group 2 (sodium valproate group). Although there was a greater reduction in group 1 (vitamin B2 group), the difference was not statistically significant. Moreover, the severity of the patients' headaches was decreased in 71.8 and 76.2% of the patients in group 1 and group 2, respectively. Although this reduction was slightly greater in group 2, the difference was not statistically significant ($p = 0.9$). Nine patients developed complications during the research. The observed complications included weight gain, dizziness, and gastrointestinal problems. Examination of the data with Fisher's exact test showed a significantly higher frequency of complications in group 2 ($p = 0.005$).

4. Discussion

As stated earlier, initially, 90 patients were included in the study. The mean ages of the patients in groups 1 and 2 were 30.2 ± 9.3 and 32.9 ± 9.8 , respectively. The frequency and duration of headaches decreased in both groups, but the difference between them was not significant. The mean reduction in the severity of the headaches in the follow-up stage compared to the baseline stage was 71.8 and 76.2% in groups 1 and 2, respectively, which indicated that there was no significant difference between the two medications in this regard. However, vitamin B2 had significantly fewer side effects than sodium valproate (2.3 versus 17.7%). Other studies related to the migraine prophylactic effect of vitamin B2 and sodium valproate have reported similar results. For example, Hering & Kuritzky, in a study on sodium valproate, concluded that the administration of 400 mg of this drug twice per day for eight weeks decreased the duration and frequency of headaches in 86% of the patients. Our findings were consistent with theirs even though the prescribed amounts of the medication and the duration of the treatment were different. In addition, they did not discuss the drug's complications (6). Taylor et al., in a study in America, investigated the

effect of sodium valproate and reported an 85% favorable response to the treatment, which was slightly greater than our findings (7). Alizadeh et al. compared the effectiveness of sodium valproate with topiramate and found that 91.9% of patients who took sodium valproate responded to the treatment, but 14% of them developed treatment-induced complications (8). They reported degrees of headache and complications that were higher and lower than our findings, respectively. Schoenen et al. (1994) showed that the administration of vitamin B2 (400 mg) reduced the frequency and severity of headache attacks in 69% of patients (9). Despite our study's being consistent with theirs, this reduction was slightly greater in our study. Boehnke et al. showed that the administration of 400 mg of vitamin B2 decreased the frequency of attacks from four times per month to two times per month. In addition, the durations of the attacks were reduced from 50 hr/month to 22-28 hr/month after three months, but the intensity of the headaches did not change (10). Our study was consistent with this study except that we demonstrated a reduction in frequency of attacks (four attacks in baseline vs. two attacks) and the duration of the headaches (16.2 hr/month in baseline vs. 4 hr/month), and the severity of the headaches was reduced by 71.8%.

Maizels et al. also showed that the administration of a 400 mg/day of vitamin B2 decreased the severity of headaches in 50% of patients (11). Our findings were consistent with theirs except that we observed an improvement of better than 50%. There was a significant difference between the groups in terms of drug-induced complications. Eight patients (17.7%) in group 2 developed complications, which led to the discontinuation of medication in three of the patients (6.6%). However, this only occurred in one subject in group 1. In general, vitamin B2 was associated with significantly fewer complications than sodium valproate. Togha et al. investigated cinnarizine and sodium valproate and concluded that 14% of the patients (nine patients) in the sodium valproate group developed complications that led to the discontinuation of the medication (12). Our findings were consistent with their study except that we found fewer cases with such complications. In a study by Erdemoglu et al., there were mild sodium valproate-induced complications that did not lead to discontinuation of medication (6). Our study was not consistent with that outcome. Moreover, Schoenen et al. observed one case with vitamin B2-induced complications that led to diarrhea (13).

5. Conclusions

Both vitamin B2 and sodium valproate had similar impacts on relieving migraine pain. Since vitamin B2 resulted in minimum complications, it can be administered to patients who have sodium valproate-induced complications or those who are prohibited from taking it. Regarding the results, future studies are recommended to assess the effectiveness and complications of vitamin B2 and sodium valproate in migraine prophylaxis in children. We also recommend that studies be conducted to compare the effectiveness of vitamin B2 with the effectiveness of other vitamins in migraine prophylaxis.

Acknowledgments:

We thank the library of Shahid Sadoughi University of Medical Sciences for their help in literature review, and Dr. Marzie Vaghefi for her constructive comments on the manuscript.

Funding: This study was a self-funded research.

Trial Registration: The trial is registered at the Thailand Clinical Trial Registry (<http://www.clinicaltrials.in.th>) with the TCTR identification number TCTR20150924001.

Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

References

- 1) Togha M, Rahmat M, Nilavary K, Ashrafian H, Razeghi S. Efficacy of Cinnarizine and Sodium Valproate in migraine prophylaxis: a clinical trial. *Tehran University Medical Journal*. 2006;64(6):121-30.
- 2) Longo D, Fauci A, Kasper D, Hauser S. *Harrison's Principles of Internal Medicine* 18th edition: McGraw-Hill Professional; 2011.
- 3) Ropper AH. *Adams and Victor's principles of neurology*: McGraw-Hill Medical New York; 2009.

- 4) Rozen T, Oshinsky M, Gebeline C, Bradley K, Young W, Shechter A, et al. Open label trial of coenzyme Q10 as a migraine preventive. *Cephalalgia*. 2002;22(2):137-41. doi: 10.1046/j.1468-2982.2002.00335.x, PMID: 11972582
- 5) Sandor P, Di Clemente L, Coppola G, Vandenheede M, Fumal A, Agosti R, et al., editors. A randomized controlled trial of coenzyme Q10 in migraine prophylaxis. *Neurology*; 2004: LIPPINCOTT WILLIAMS & WILKINS 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
- 6) Kunsman GW, Levine B, Smith ML. Vitamin B~ 2 Interference with TDx Drugs-of-Abuse Assays. *Journal of forensic sciences*. 1998;43:1225-7, doi: 10.1520/JFS14390J. PMID: 9846401
- 7) Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001;41(7):646-57. doi: 10.1046/j.1526-4610.2001.041007646.x, PMID: 11554952
- 8) Göbel H, Heinze A, Heinze-Kuhn K. [Prophylactic measures and acute treatment of migraine]. *Schmerz (Berlin, Germany)*. 2006;20(6):541-54; quiz 55-6, doi: 10.1046/j.15264610.2001.041007638.x. PMID: 11554952
- 9) Sándor PS, Áfra J, Ambrosini A, Schoenen J. Prophylactic Treatment of Migraine With β - Blockers and Riboflavin: Differential Effects on the Intensity Dependence of Auditory Evoked Cortical Potentials. *Headache: The Journal of Head and Face Pain*. 2000;40(1):30-5, doi: 10.1046/j.1526-4610.2000.00005.x. PMID:10759900
- 10) Matson JL, Bamburg JW, Mayville EA, Pinkston J, Bielecki J, Kuhn D, et al. Psychopharmacology and mental retardation: a 10 year review (1990-1999). *Research in developmental disabilities*. 2000;21(4):263-96. doi: 10.1016/S0891-4222(00)00042-1
- 11) Raymond D. Adams RD, Victor M, Principle of neurology. New York Mc Graw Hill; 1993.
- 12) Goadsby PJ, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. *N Engl j Med*. 2002;346(4):257-70, doi: 10.1056/NEJMra010917. PMID:11807151
- 13) Freitag F, Collins S, Carlson H, Goldstein J, Saper J, Silberstein S, et al. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. *Neurology*. 2002;58(11):1652-9, doi: 10.1212/WNL.58.11.1652. PMID: 12058094