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Original Article

The effect of combined administration of Ginger (*Zingiber officinale* Roscoe) and Depakene on pain reduction in patients with migraine headaches compared to Depakene alone

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Abstract

Background and aims: Migraine is known as one of the most debilitating diseases with high prevalence worldwide. This study aimed to compare between combined administration of ginger and Depakene (sodium valproate) capsules (intervention group) and the use of Depakene (control group) alone to evaluate the therapeutic efficacy of ginger in the treatment of migraine.

Methods: This randomized one-blind clinical trial was conducted with 80 patients suffering from migraine headaches. A total of 40 patients in the intervention group received two ginger capsules of 250mg manufactured by Zintoma (Gol Darou Co.) along with 500 mg Depakene orally daily for sixteen weeks, and 40 patients in the control group received Depakene (500 mg/d) alone. The variables included the severity of the headache, the number of headaches per month, and the sleep quality of patients. Data were analyzed using descriptive statistics: frequency, percentage, mean and standard deviation, and analytical statistics: χ^2, independent *t* test, and pair *t* tests.

Results: For pain intensity, the mean score of pain after the intervention in the intervention group was significant so that it was lower than the mean score in the control group ($P<0.05$). Moreover, there were significant differences in disability severity induced by migraine headaches between the two groups after the intervention so that it was lower in the intervention group than in the control group ($P<0.05$).

Conclusion: Administration of the ginger capsule (500 mg) with Depakene (500 mg) was considered to improve pain severity, disability, and sleep pattern in patients with migraine compared to administration of Depakene alone. Therefore, this combination therapy can be considered a choice in the treatment of these patients.

Keywords: Headache, Migraine, Ginger

Introduction

Migraine is a severe disorder with a characteristic of mild or severe headaches consequently and is often associated with symptoms in the autonomic nervous system. This type of headache is unilateral and affects half of the head naturally; it occurs by pulsating and lasts from 4 to 72 hours. The severity of pain, duration of headaches, and frequency of attacks are different in different patients. Headaches that are lasting more than 72 hours are called migraine status. Symptoms associated with migraine headaches can include nausea, vomiting, feeling sensitive to light, and fearful sounds that are increased sensitivity to noise, and generally, it increases with high physical activity (1). Migraine is a periodic headache with hereditary and familial backgrounds and begins in childhood, adolescence, or early middle age and recurrences during the next years. Moreover, migraine is the most prevalent type of headache in all human societies and 12%-15% of individuals suffer in the world (2). The onset of migraine is more in young ages and decreases its prevalence and frequency by increasing age (3). Studies have shown that the dorsal hippocampus plays an important role in controlling headaches (4), and increases the production of endorphins, which is the most important analgesic hormone in the body (5). The first recommendation to control these headaches is to use pills such as ibuprofen and acetaminophen and to use antiemetics to prevent nausea. More specific migraine drugs include triptans and ergotamines recommended for patients who do not have any effect other than simple pills (6). In general, different methods have been mentioned to treat migraine including drug therapy and psychotherapy. The more common drug therapies include 5-hydroxytryptamine medications from sumatriptan selective categories, ergotamine and dihydroergotamine from non-selective categories, and aspirin, ibuprofen, and acetaminophen for reducing pain. Moreover, other different drugs have been mentioned to treat migraine including metoclopramide, propranolol, verapamil, and amitriptyline (7). Moreover, non-opioid analgesics like aspirin and nonsteroidal anti-inflammatory

compounds are used to treat migraine. However, due to the harmful effects of these chemical drugs, some efforts have begun to find palliative and analgesic drugs with less harm. Chemical drugs have their side effects, specific contraindications for consumption, and limitations for individuals with hypertension, cardiovascular diseases, and pregnant women (7,8).

Therefore, these factors reduce the patient's willingness to accept this drug regimen (3). Therefore, the use of alternative methods and the use of medicinal plants in the treatment and prevention of migraine is considered necessary. The tendency towards medicinal plants has expanded due to their availability, recently. Medicinal plants reduce stress and anxiety in different ways including increasing blood serotonin levels, decreasing levels of cortisol and adrenaline hormones, strengthening the immune system, and reducing blood pressure (7,8). The ginger plant (*Zingiber officinale*) has a long history. This plant has been important in Asia for long years and since the Middle Ages in Europe (9,10).

Some studies have been performed on the analgesic effect of ginger. The analgesic effects of ginger extract, ibuprofen, and placebo were compared in patients with knee and elbow osteoarthritis in a double-blind randomized clinical trial. Three-week consecutive treatment sessions and an additional one-week session were held in this study using treatment with ginger extract, ibuprofen, and placebo. The results of this study showed that the analgesic effect of ibuprofen was better than the analgesic effect of ginger extract during three treatment sessions through pain measurement, and the ginger extract was better than the placebo. This study showed that no side effect has been reported with ginger in this human study (11). In the other animal study, 2.5 g of ginger per kilogram of the body weight was administered daily to determine acute poisoning for 7 days, and no side effects were observed during this period, but using the amount of 3 to 3.5 grams per kilogram of the body weight on a daily basis caused the death of 10%-30% of animals (11). Considering the high prevalence of migraine and the possibility of its effect on each individual in the community, it is necessary to prevent initial progress and ultimately provide mental health in the community. In addition, due to the increasing desire of individuals to use herbal medicines and the high side effects of analgesic chemical drugs and due to all the therapeutic advantages of ginger and its capsules, its effect on reducing migraine has not been studied. This study aimed to compare between combined administration of ginger and Depakene (sodium valproate) capsules (intervention group) and the use of Depakene (control group) alone to evaluate the therapeutic efficacy of ginger in the treatment of migraine.

Methods

This one-blind clinical trial was conducted within 16 weeks. Samples were patients with migraine headaches referred to private physician offices and Neurology Clinics for headaches in Shahrekord in 2019 treated with Depakene (sodium valproate). Eighty migraine patients referred to private physician offices and Neurology Clinics were selected by convenience sampling after receiving ethics permission, informed consent from the patients, and given inclusion and exclusion criteria. They were randomly assigned to the two groups. The patients were matched based on age, gender, and medication. At the beginning of the study, all clinical and neurological examinations were performed. Then, they received the medications. The control group received 500 mg/d of Depakene daily. The intervention group received 500 mg/d of ginger (two capsules of 250 mg Zintoma (Gol Darou Co.) along with 500 mg/d of Depakene. Patients were allowed to take 500 mg of acetaminophen if they had mild and severe pain, and their pain continued for 4 hours and was written it down and reported the number of medications in subsequent referrals to the researcher. The single blindness of the study was that the mentioned drugs received a code without any label and the patient selected one of the two drugs randomly. Then, the name of each person and the drug code provided to him were registered by the secretary. Neither the patient nor the doctor knew the type of medication, and when analyzing the data just, the name of each person and his drug was declared, and the patients' information profile was completed by mentioning the name of the drug received by them. Inclusion criteria were age 18 to 65 years, history of migraine headache before the study based on International Headache Society (IHS) criteria, headache from moderate to severe less than six days by visual analog scale score, normal vital signs and results of normal neurological examinations, having no disease such as renal failure, liver disease, heart disease, active stomach ulcer, and diabetes. In addition, patients who had been treated twice with drug regimens with effective doses before referring and did not have a suitable treatment response, patients who had reported an overdose of analgesics (more than 6 times the use of analgesics and more than eight times the use of other analgesics) and patients who were treated with calcium channel blockers, tricyclic antidepressants were not included in the study. In addition, patients who were treated using Antiepileptic drugs, monoamine oxidase inhibitors, nonsteroidal anti-inflammatory drugs, local anesthetics, corticosteroids, and botulinum toxins were not included in the study. Exclusion criteria included abnormal vital signs during the study, new abnormal findings during the CT scan, patient dissatisfaction to continue in the study, and observation of drug sensitivity. Ginger capsules of Gol Darou Co. with the brand name Zintoma were used in this study. It should be noted that according to the company's drug order, this drug has no specific side effect in therapeutic amounts of 1g and may only increase gastrointestinal secretions in large quantities. Patients are advised to take two capsules of 250 mg daily. The possible side effects and therapeutic benefits of both

drugs were described for all patients who participated in this study and if a patient requested to participate in the study, written consent was received from them. Data were collected using the questionnaires of demographic information, Visual Analog Scale (VAS), Pittsburgh sleep quality index (PSQI), and Migraine Disability Assessment Scale (MIDAS). The variables included the severity of the headache which was determined by VAS by the physician, the number of headaches per month using the MIDAS questionnaire, and the sleep quality of patients measured by the PSQI questionnaire that was performed before and 30 days after treatment. Data were collected and entered into SPSS 18 software. Data were analyzed using descriptive statistics: frequency, percentage, mean and standard deviation) and analytical statistics: χ^2, independent *t* test, and paired *t* test.

Results

Forty patients with migraine headaches in the intervention group were treated with the combination of ginger and Depakene and 40 patients in the control group were only treated with Depakene. Regarding gender, most individuals in the intervention and control group were females, 26 (65.0%) and 28 (0.70%), respectively. The mean and standard deviation of age in patients in the intervention group, and control group was 41.90 ± 8.99 and 40.30 ± 10.05 years old, respectively. The two groups were matched by gender and age ($P > 0.05$). According to pain intensity status, the mean score of pain after the intervention in the intervention group was significant and it was lower than the mean score in the control group ($P < 0.05$). Moreover, there were significant differences in the mean score of disability severity induced by migraine headaches between the two groups after the intervention and it was lower in the intervention group than it in the control group ($P < 0.05$). In addition, a significant improvement in sleep patterns in patients in the intervention group was observed ($P < 0.05$) (Table 1).

Discussion

In this study, a clinical comparison was conducted between the administration of ginger combined with Depakene capsules and the use of Depakene alone. The results were received for three variables of pain intensity, the severity of the disability, and sleep pattern disorder in patients. The results of this study showed that the use of combined treatment of ginger and Depakene compared to Depakene alone led to more reduction in pain intensity, a more reduction in the severity of a physical disability, and an improvement of sleep patterns in patients

Table 1. Comparison of the results in the studied groups

Variables	Intervention group	Control group	*P* value
Pain severity score (VAS)			
Pre intervention	7.20 ± 1.14	7.70 ± 1.02	0.042*
Post intervention	2.75 ± 0.95	5.90 ± 0.96	0.000**
P value	0.000**	0.000**	
Pain severity score changes	4.45 ± 1.22	1.80 ± 1.09	0.000**
The score of migraine number monthly			
Pre intervention	22.75 ± 4.37	22.75 ± 5.17	1.000
Post intervention	8.20 ± 3.35	11.70 ± 4.25	0.000**
P value	0.000**	0.000**	
Score changes of the migraine number	14.55 ± 5.93	11.05 ± 6.99	0.018*
The score of sleep quality monthly (PSQI)			
Pre intervention	18.45 ± 1.99	19.15 ± 1.48	0.078
Post intervention	10.00 ± 1.11	15.40 ± 2.59	0.000**
P value	0.000**	0.000**	
PSQI Score changes	8.45 ± 2.63	75.3 ± 2.37	0.000**
The disability score of pre-intervention			
Very mild	0 (0.0)	0 (0.0)	
Mild	0 (0.0)	0 (0.0)	1.000
Moderate	10 (25.0)	10 (25.0)	
Severe	30 (75.0)	30 (75.0)	
The disability score of post-intervention			
Very mild	12 (30.0)	6 (15.0)	
Mild	18 (45.0)	14 (35.0)	0.047*
Moderate	10 (25.0)	20 (50.0)	
Severe	0 (0.0)	0 (0.0)	

*$P < 0.05$, **$P < 0.001$.

observed. Although the patients received treatment protocols, adding ginger to the usual treatment regimen (Depakene) completely, serious side effects of using both of them did not increase and patients improved rapidly. This is the main finding of the present study. The use of ginger as a complementary herbal medicine helps rapid improvement without increasing the side effects in patients with migraine headaches. Of course, it should be noted that the dose of ginger and the duration of administration can be effective factors in the effectiveness of this herbal medicine.

In a study conducted by Oliveira et al on the side effects of three plants, they did not report any side effects or hematologic and biochemical changes after 28 days. Researchers in most studies have observed that migraine headaches are neurological disorders with vascular challenges. Ginger is useful for the treatment of neurological disorders because of its anti-inflammatory effects (12).

The studies of Martins et al in 2019 showed that patients treated with 400 mg ginger extract, ultimately decreased their pain severity and improved their physical activity in the treated group with ginger. Their study also showed that even treating headaches with ginger alone could be very effective (13). Their study is in line with our study and emphasizes the effect of ginger on decreasing pain severity and improving physical activities. In addition, In Cady et al. study, the improvement in migraine pain severity in the group treated with ginger was evaluated to be much higher than placebo (14). Although the therapeutic effects of ginger or sumatriptan were similar, ginger administration was more satisfying due to fewer side effects (15). Although their study compares ginger and sumatriptan, its results show at first, the effect of ginger on the reduction of migraine, and secondly, it shows the fewer side effect of ginger. These findings are in agreement with our study as well as a study conducted in 2005 by Cady et al who studied the effect of gel state (containing ginger) on migraine sufferers (15). Thirty men and women with a 1-year history of migraine headaches were treated with gel state. The results showed that out of 29 patients who cooperated until the end of the study, after 2 hours of treatment, 48% reported no pain and 34% reported mild to severe pain. Twenty-nine percent had a recurring headache within 24 hours. No side effects were reported in this study. Fifty-nine percent of them were satisfied with the gel state and 41% reported no difference with pre-treatment (16). In the present study, no complaints about ginger consumption were reported, which is in line with the results of other studies. Safavi Naeine et al in 2002 investigated the effect of ginger on headaches caused by oral contraceptive pills in women. 46 patients in the intervention group and 25 in the control group were divided into their study. Then, they examined and interviewed before and during two cycles after ginger consumption and completed a questionnaire. The results of this study showed that ginger consumption led to a significant reduction in the rate of headaches in the intervention group. The analgesic effects of ginger in this study have been attributed to its strong antioxidant and anti-inflammatory properties, which is in line with the results of the present study. According to the results of this study, probably the analgesic effects observed in migraine patients can be due to the antioxidant and anti-inflammatory properties of ginger. In general, it can be argued that ginger with antioxidant and anti-inflammatory properties could improve patients with migraine headaches (17).

Different groups of compounds in ginger have phenolic structures and can illustrate benzoic acid and cinnamic acid derivatives, quinines, and polyphenolic compounds (13). Ginger contains large amounts of polyphenols and vitamins. Moreover, ginger contains various antioxidant compounds, mainly benzoic acid, and cinnamic acid derivatives. One of these derivatives is called 3 and 4 dihydroxy benzaldehyde which has an active ingredient with determined antioxidant properties (18). Ferulic acid in ginger also has anti-inflammatory effects (19). In addition, fatty acids in ginger can cause antibacterial, antifungal, and anti-inflammatory effects (20). Fatty acids directly affect T lymphocytes and regulate immune responses (15,16). It has also been reported that linoleic acid can produce anti-inflammatory responses by reducing the production of inflammatory mediators such as PGE2, IL-6, IL-1β, TNF-α, and nitric oxide (20,21). Another analgesic and anti-migraine mechanism of medicinal plants can lead to reducing platelet activity (7). Ginger reduces platelet aggregation and inhibits prostaglandin and thromboxane production. One of these chemical compounds also prevents the release of serotonin. For this reason, ginger did not recommend for individuals who consume anticoagulants (7,21). Another mechanism involved in the occurrence of analgesic and anti-migraine activity of medicinal plants is minimizing damage to the vascular endothelium (7). The role of serotonin can also be mentioned in these investigations (7). Serotonin is produced during the day and is converted to melatonin in later stages (7). Melatonin rises rapidly in the middle of darkness and decreases before the onset of light to return to daily doses (7). These hormones have their effects on central nervous system function, cardiovascular, renal, and many physiological activities such as mechanisms of anxiety, thoughts, appetite, and sleep cycle (22).

It is believed that the anti-migraine effects of these compounds are similar to methysergide (a serotonin antagonist) and prevent the release of granules from platelets and neutrophils (7). It has been also reported that herbal extracts that affect migraine can be effective in the reduction of pain intensity with an effect on pain receptors and increasing their stimulation threshold (23). One of the causes of migraine is the increase in the construction and secretion of prostaglandins. Vitamin E is also able to prevent the secretion of prostaglandins due to its antioxidant properties (24,25). In addition,

considering that ginger is a rich source of vitamin E, the presence of this vitamin that has antioxidant properties can also justify the antioxidant mechanism of ginger (20). Some researchers reported that the antioxidant activity of ginger is due to its ability to chelate Iron ions, remove radicals of hydroxyl and superoxide and prevent lipid peroxidation of liver substance (26). The results of Sadoughi et al study in 2008 showed that vitamin E and placebo reduced the pain severity mean of menstrual migraine and improved factors associated with menstrual migraine, but the effect of vitamin E was significant and higher than placebo (27). According to the results of the present study, the analgesic effects observed in people with migraine can be due to ginger's antioxidant and anti-inflammatory properties. With its antioxidant and anti-inflammatory properties, ginger improves the symptoms of people suffering from migraine headaches. On the other hand, no life-threatening complications were reported by the patients.

Conclusion

Administration of ginger capsules (500 mg) with Depakene (500 mg) resulted in a considerable improvement in pain severity, disability, and sleep pattern in patients with migraine headaches compared to Depakene alone. Therefore, further studies on its effective compounds may help us to use it as a complementary drug along with other drugs affecting migraine.

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Authors' Contribution

Conceptualization: Nahid Jivad.
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Visualization: Nahid Jivad.
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Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

This study was approved by the Deputy of Research and Technology of Shahrekord University of Medical Science (IR.SKUMS.REC.1398.018) and registered in the Iranian Registry of Clinical Trials (identifier: IRCT20220818055740N2 (https://www.irct.ir/trial/65453).

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