



Evaluation of effect of atrifel (product of traditional Iranian medicine) on patients with migraine headaches associated with gastrointestinal symptoms

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General Note

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ABSTRACT

Background: Migraine is an acute non-communicable psychiatric disease, which causes many problems for affected patients, creating defects in the life process of these individuals. This complication is often collaborative, and treatment of the participated member can be an effective step to overcome the disturbances of migraines. This study aimed to evaluate the effect of atrifel on patients with migraine headaches associated with gastrointestinal symptoms. **Materials and Methods:** This double blind randomized clinical trial was conducted on 124 patients, August 2017 till July 2018, who referred to Neurology Clinic of Shahid Sadoughi Hospital, Yazd, Iran. Patients were randomly and equally divided into control and intervention groups. While subjects of the control group received a daily dose of sodium valproate 200 mg, the participants of the intervention group received both the mentioned tablet and atrifel sagir 50 mg pill before lunch and dinner. The relevant parameters were measured before and eight weeks after the intervention. **Results:** In this research, stress, fatigue, overeating, hearing loud voices, insomnia and consumption of high-calorie foods were more involved in the emergence of migraine, compared to other factors. According to the results, the integrated use of atrifel sagir and sodium valproate significantly reduced the severity of pain, duration of headache and the time required for rest ($P < 0.001$). **Conclusion:** According to the results of the study, atrifel sagir along with sodium valproate had considerable impacts on reduction of severity of pain, duration of headache and time required for rest in patients.

Keywords: Migraine, Participatory Gastric Headache, Atrifel Sagir, Valproate.

1. INTRODUCTION

Headache is one of the most common complaints among people, in a way that more than 90% of human beings experience this condition at least once in life. As the most extreme clinical manifestation of headache, migraine is the main cause of referral of patients to specialized neurosurgical centers. Generally, the prevalence of migraine, which has many causes, has been reported at 7% and 24% in men and women, respectively (Evans et al., 2000). In the past, the only cause of this disease was related to vascular disorders by physicians of that time. Today, it is believed that a neurovascular phenomenon is involved in this condition. In fact, this condition is a progressive spontaneous wave of neuronal and glial depolarization in the cerebral cortex, which leads to prehistoric stimulation, trigeminal nerves stimulation, and changes in permeability of the blood-brain barrier. The arrival of this wave to the ganglion is associated with the release of the tri-germinal neuropeptides, which create neurogenic inflammation and lead to vascular dilation and plasma protein leakage. All of these processes eventually create pain in individuals (Giglia, 2011).

In this regard, the headache international association divides this condition into primary and secondary types in its second edition of categorization of headache disorders published in 2004. The primary type of headache is not caused by another disease, whereas other factors are involved in the emergence of the secondary type of headache (Shinkeigaku, 2004). In this regard and according to the documents of Iranian traditional medicine, some physicians (e.g., Avicenna and Razi) have considered gastrointestinal disorders as one of the causes of headache, introducing it as "participatory gastric headache", which is often improved by medication affecting the gastrointestinal system (The Greatest Elixir and Azam Khan, 2008 and Nasser et al., 2009 and Hawi and Ibn Zakariya al-Razi, 2007). Meanwhile, headache is divided into 28 types in the resources of traditional medicine based on their causes (The Greatest Elixir and Azam Khan, 2008).

In addition, participatory gastric headache is divided into seven main categories: A type of headache is created by abnormal quality of humors, which is changed due to factors such as medication and food. In addition, having a heavy stomach after overeating causes headache, this is treated after the digestion of food (Mahroozade and Abdolahadi, 2017 and Sharh al-Asbab et al., 2015). Another headache is caused by excess safra (choler or yellow bile), which is associated with the production or increase of safra, has a warm and dry quality, and has the symptoms of nausea (Nasser et al., 2009 and Mahroozade and Abdolahadi, 2017 and Sharh al-Asbab et al., 2015 and The Canon of Medicine and Ibn Sina, 1973), anorexia, bitter taste in the mouth, smelly burp (Hawi and Ibn Zakariya al-Razi, 2007), excess thirst (Mahroozade and Abdolahadi, 2017 and Sharh al-Asbab et al., 2015 and The Canon of Medicine and Ibn Sina, 1973), and poor digestion. Headache caused by excess balgham (phlegm) has a cold and wet quality and is accompanied by symptoms, including poor digestion, sour burp, flatulence, increased salivation, and nausea when the stomach is full (Mahroozade and Abdolahadi, 2017 and Sharh al-Asbab et al., 2015 and The Canon of Medicine and Ibn Sina, 1973).

In this regard, another type of headache is emerged due to excess soada (melancholer or black bile), where the presence of excessive amount of soada in the stomach leads to epigastric burning and food craving, as well as sour burp and mouth (Mahroozade and Abdolahadi, 2017 and Sharh al-Asbab et al., 2015 and The Canon of Medicine and Ibn Sina, 1973) due to its cold

and dry quality, resulting in increased stress and depression (The Canon of Medicine and Ibn Sina, 1973). Excess luminal gas is responsible for another category of headache, which creates gastric pain and flatulence in patients by increasing gas due to consumption of gas-producing foods or weakness in natural heat of the patient (Mahroozade and Abdolahadi, 2017 and Sharh al-Asbab et al., 2015 and The Canon of Medicine and Ibn Sina, 1973). Another headache is caused by the formation of excess vapors in the stomach because of consuming vapor-producing foods, such as garlic, onion, chili and spicy vegetables, which creates pounding headaches and gastric heat without a feeling of being heavy (Mahroozade and Abdolahadi, 2017 and Sharh al-Asbab et al., 2015 and Fazljou et al., 2013). In addition, a headache is created because of the weakness of the gastric fundus and the cardia, which has the most effectiveness due to inappropriate muscular strength, compared to any internal or external simulator (Mahroozade and Abdolahadi, 2017 and Sharh al-Asbab et al., 2015 and The Canon of Medicine and Ibn Sina, 1973). Smelling bad odors leads to nausea and headache in these patients (Mahroozade and Abdolahadi, 2017 and Sharh al-Asbab et al., 2015 and The Canon of Medicine and Ibn Sina, 1973 and The Greatest Elixir and Azam Khan, 2010). It should be noted that each of the mentioned headaches has its own specific treatment.

Generally, treatment of migraine is carried out in two acute and preventive stages. In acute treatments, serotonin receptor agonists, or triptans (e.g., sumatriptan and rizatriptan), acetaminophen, nonsteroidal anti-inflammatory drugs and ergot alkaloids are used. On the other hand, beta blockers (propranolol), calcium-channel blockers (verapamil), antidepressants (e.g., amitriptyline and nortriptyline), and anticonvulsants (sodium valproate) are exploited to prevent migraine attacks (Khayat Kashani and Ghanadi, 2012). In the present study atrifel along with sodium valproate was assessed as one of the effective medications to treat migraine. Atrifel is a combination of various herbs with equal amounts of the major components of terminalia chebula, terminalia bellerica, and phyllanthus emblica (Javadi et al., 2013). Sheikh Al Rais defines atrifel as a combination of terminalia chebula, phyllanthus emblica and skin of terminalia bellerica, retained by a 40-mesh sieve and combined with honey and cow oil (Al-Jurjani et al., 1977). This medication has a cold and dry temperament and is significantly beneficial in defeating gastric moist conditions and stomach weakness. Moreover, this medication is a base for proper integration of other medical combinations in traditional medicine. Therefore, atrifel is used in various treatments of diseases (Javadi et al., 2013).

Given the necessity of this issue, the present study aimed to test a treatment protocol based on traditional medicine to treat migraine headache with gastric origin, so that the effectiveness of the mentioned medication in improvement of this condition is assessed.

2. MATERIALS AND METHODS

This double blind clinical trial was conducted on 124 patients, August 2017 till July 2018, who referred to the Neurology Clinic of Shahid Sadoughi Hospital, Yazd, Iran. Patients were randomly selected through simple sampling and were divided into intervention and control groups (32 cases per group) using coded envelopes. While subjects of the control group received a daily dose of sodium valproate 200 mg, the participants of the intervention group received both the mentioned tablet and atrifel sagir 50 mg pill before lunch and dinner. Subjects were evaluated before and eight weeks after the intervention using global physician evaluation, visual analog scale for pain (VAS pain), and daily notes and questionnaires filled by patients. In addition, subjects were followed up four weeks after the initiation of intervention to assess the level of response to treatment and possible complications. In addition, lack of continuing the treatment by patients was followed up to recognize the cause of this act and obtain information about response to treatment. Moreover, tests of CR, BUN, SGPT, SGOT, and CBC were performed on all patients in order to evaluate their health and impact of possible complications of the therapeutic method on blood factors, as well as their liver and kidney function.

The research result was defined as the level of effectiveness of the therapeutic protocol of traditional medicine on reduction of severity, duration and tolerance of migraine headache attacks. The severity of headache was assessed based on visual analog scale (VAS), whereas changes in the duration and recurrence of headache were evaluated using forms by the researcher, which was designed based on principles of history-taking of traditional medicine in patients with participatory gastric headache presented in the reference book of traditional medicine. Inclusion criteria included age range of 18-65 years, confirmation of participatory gastric headache according to diagnostic criteria included in the authentic texts of traditional medicine and HIS diagnostic criteria, awareness of the patient about his disease, being Iranian and Persian-speaking, having a minimum of four migraine headache attacks in a month for more than 30 minutes and with intensity \geq four (according to VAS) and patients' willingness to participate.

Exclusion criteria were pregnancy before or during the research, abnormal neurological examination before or during the study, being treated with infertility drugs and known allergic diseases and migraine prophylaxis drugs, previous consumption of atrifel sagir, and being a medical staff (e.g., nurse), addiction to drugs and alcohol, consumption of other herbal medications, undergoing acupuncture treatment before and during the research, emergence of complications of the treatment method in patients who required the discontinuing of the treatment, and when it is demonstrated that the primary diagnosis was wrong.

3. RESULTS

Evaluation of demographic characteristics of patients demonstrated no significant difference between the intervention and control groups regarding age ($P=0.65$), height ($P=0.46$), weight ($P=0.99$), patient age at diagnosis ($P=0.15$), gender ($P=0.57$), marital status ($P=0.20$), level of education ($P=0.76$), and occupational status ($P=0.36$) (table 1).

Table 1 Summary of descriptive information of demographic distribution of samples

		Control	case	total	p
Age(year)		26.33±78.8	02.34±19.10	64.33±47.9	65.0
Hight(cm)		±38.7 25.165	26.164±44.7	±40.7 76.164	46.0
Weight(kg)		±29.12 16.66	17.66±46.9	±94.10 17.66	99.0
Age of catch(year)		75.26±64.6	04.24±27.7	92.25±91.6	15.0
Sex	female	39 (5.31)	42 (9.33)	81 (3.65)	0.57
N (%)	male	23 (5.18)	20 (1.16)	43 (7.34)	
Marital status N (%)	Married	28 (6.22)	29 (4.23)	57 (46)	20.0
	Single	31 (25)	26 (21)	57 (46)	
	Divorced	3 (4.2)	3 (4.2)	6 (8.4)	
	Widow	0	4 (2.3)	4 (2.3)	
Level of education N (%)	Illiterate	4 (3.3)	3 (4.2)	7 (7.5)	72.0
	Primary school	10 (1.8)	14 (4.11)	24 (5.19)	
	Junior high school	1 (8.0)	0	1 (8.0)	
	Diploma	28 (8.22)	28 (8.22)	56 (5.45)	
	Higher education	19 (4.15)	16 (16)	35 (5.28)	
Occupational status N (%)	Self-employed	14 (2.11)	16 (8.12)	30 (24)	36.0
	Governmental position	20 (1.16)	14 (2.11)	34 (3.27)	
	Unemployed, housewife	12 (6.9)	21 (8.16)	33 (4.26)	
	School, University student	10 (1.8)	9 (2.7)	19 (3.15)	
	Physician, engineer	6 (8.4)	2 (6.1)	8 (4.6)	

In this research, 19% of the participants in the control group had a family history of migraine, 52% and 7.8% of whom had a history in the first and second-degree family members, respectively. In the intervention group, 12.9% reported a positive family history of migraine, 28.6% and 10.4% of whom had a history in the first and second-degree family members, respectively. In total, no significant difference was observed between the subjects in terms of family history of migraine ($P=0.12$) and family relationship ($P=0.49$). In addition, 63% of the subjects in the control group had migraine aura, whereas 4.9% and 1.2% had aura and hemiplegic migraine, respectively. The mentioned criteria were reported at 23.5%, 7.4% and 0% in the intervention group, respectively. In general, no significant difference was observed between the groups in terms of the type of diagnosed migraine ($P=0.08$) (table 2).

Table 2 Evaluation of frequency distribution of type of migraine and related factors

Family history of diagnosis of migraine		Control	case	total	p
family history		24 (4.19)	16 (9.12)	40 (3.32)	0.12
Relationship with the family members with migraine	First degree	20(52)	11 (6.28)	31 (6.80)	0.49
	Second degree	3 (8.7)	4 (4.10)	7 (2.18)	
Type of diagnosed migraine	Without aura	51 (63)	19 (5.23)	70 (4.86)	0.08
	With aura	4 (9.4)	6 (4.7)	10 (3.12)	
	Hemiplegic migraine	1 (2.1)	0(0)	1 (2.1)	

On the other hand, no significant difference was observed between the intervention and control groups in terms of stress ($P=0.09$), intense sunlight ($P=0.28$), brilliant and dazzling light ($P=0.58$), bad odors ($P=0.26$), loud voice ($P=0.20$), travel ($P=0.34$), fatigue ($P=0.46$), hunger ($P=0.85$), overeating ($P=0.56$), insomnia ($P=0.85$), timeless sleep ($P=0.24$), hot weather ($P=1.00$), long baths ($P=0.39$), going to crowded places ($P=0.35$), sexual activity ($P=0.82$), menstrual cycle ($P=0.82$), specific foods ($P=0.98$) and taking birth control pills ($P=0.69$). In terms of headache-reducing factors, no significant difference was observed between the groups in the variables of rest ($P=0.44$), sleep ($P=0.08$), darkness and silence ($P=0.36$), oral analgesic ($P=0.08$), serum and injectable medicine ($P=0.83$), and vomiting ($P=0.15$). According to the results, the highest impact was observed in consumption of oral analgesics followed by sleep (table 3).

Table 3 Evaluation of distribution frequency of factors aggravating and reducing headache

factors		Control	case	total	p
Aggravating factors	Stress	35 (2.28)	44 (5.35)	79 (7.63)	09.0
	Severe sunlight	29 (4.23)	35 (2.28)	64 (6.51)	28.0
	Bright light	25 (2.20)	28 (6.22)	53 (7.42)	58.0
	Odd or strong odors	20 (1.16)	26 (21)	46 (1.37)	26.0
	Loud voices	32 (8.25)	39 (5.31)	71 (3.57)	20.0
	Travel	18 (5.14)	23 (5.18)	41 (1.33)	34.0
	Fatigue	36 (29)	40 (3.32)	76 (3.61)	46.0
	Hunger	40 (3.32)	39 (5.31)	79 (7.63)	85.0
	Overeating	44 (5.35)	41 (1.33)	85 (5.68)	56.0
	Insomnia	35 (2.28)	36 (29)	71 (3.57)	85.0
	Timeless sleep	16 (9.12)	22 (7.17)	38 (6.30)	24.0
	Warm weather	28 (6.22)	28 (6.22)	56 (2.45)	00.1
	Long baths	12 (7.9)	16 (9.12)	28 (6.22)	39.0
	Going to crowded places	25 (2.20)	20 (1.16)	45 (3.36)	35.0
	Sexual activity	13 (5.10)	12 (7.9)	25 (2.20)	82.0
	Menstrual cycle	10 (1.8)	9 (3.17)	19 (3.15)	80.0
Specific foods	6 (8.4)	6 (8.4)	12 (7.9)	98.0	
	25 (2.20)	24 (4.19)	49 (5.39)		
Reducing factors	Using contraceptives	4 (2.3)	3 (4.2)	7 (6.5)	69.0
	Rest	22 (7.17)	18 (5.14)	40 (3.32)	44.0
	Sleep	37 (8.29)	47 (9.37)	83 (4.66)	08.0
	Darkness and silence	32 (8.25)	27 (8.21)	59 (6.47)	36.0
	Oral analgesics	49 (5.39)	56 (2.45)	105 (7.84)	08.0
	Serum and injectable medications	16 (9.12)	17 (7.13)	33 (6.23)	83.0
	Vomiting	14 (3.11)	8 (5.6)	22 (7.17)	15.0

In this research, no significant difference was observed between the groups regarding the onset and severity of headache in the fasted state in mornings ($P=1.00$), relief with vomiting ($P=0.28$), worry, nausea and vomiting ($P=0.51$), tenesmus and stomachache ($P=0.54$), heartburn ($P=0.57$), weak digestion ($P=0.53$), acid reflux. Burp ($P=0.50$), and after consuming vapor-creating foods ($P=0.29$). However, there was a significant difference between the study groups in terms of after food. Heavy stomach ($P=0.002$). In general, the most complaints of the subjects were related to migraine accompanied by heavy stomach after food, acid reflux and burp, weak digestion and relief with vomiting (table 4).

According to the results, a significant difference was observed between the groups in terms of mean severity of pain ($P<0.001$). While no significant difference was observed between the intervention and control groups before the intervention ($P=0.24$), there was a significant difference between the groups eight weeks after the intervention ($P<0.001$). According to the means obtained in the control and intervention groups, the combination of aripiprazole and sodium valproate was more-able to inhibit pain, compared to

independent use of sodium valproate. Moreover, an equal level of significant reduction was observed in the duration of headache and rest time in both groups after the intervention ($P < 0.001$) (table 5, figure 1 & 2).

Table 4 Participatory Headache

Participatory Headache	Control	case	total	p
Onset.intensification in the fasted state in mornings	11 (9.8)	11 (9.8)	22 (7.179)	00.1
Relief with vomiting	17 (7.13)	12 (7.9)	29 (4.23)	28.0
After food.heavy stomach	24 (4.19)	9 (3.7)	33 (6.26)	002.0
Worry.indigestion.vomiting	12(7.19)	15 (11.12)	27 (8.21)	51.0
Tenesmus.stomachache	7 (6.5)	5 (4)	12 (7.9)	54.0
Heartburn	6 (8.4)	8 (5.6)	14 (3.11)	57.0
Weak indigestion	17 (7.13)	14 (3.11)	31 (25)	53.0
Acid reflux.burp	20 (1.16)	13 (5.10)	33 (6.26)	50.0
After consuming a vapor-creating food	6 (8.4)	3 (4.2)	9 (3.7)	29.0

Table 5 Evaluation of mean of duration before and eight weeks after the intervention across the study groups

Parameter		Control	case	p
Severity of pain (vas)	before intervention	77.6±47.1	11.6±54.2	24.0
	After intervention	98.4±78.1	00.4±91.1	004.0
	p	<0.001	<0.001	
Duration of headache	before intervention	34.10±69.8	58.10±72.7	67.0
	After intervention	53.5±11.5	33.5±92.4	69.0
	p	<0.001	<0.001	
Time required for rest	before intervention	26.1±61.0	69.1±01.1	08.0
	After intervention	87.0±40.0	94.0±48.0	69.0
	p	<0.001	<0.001	

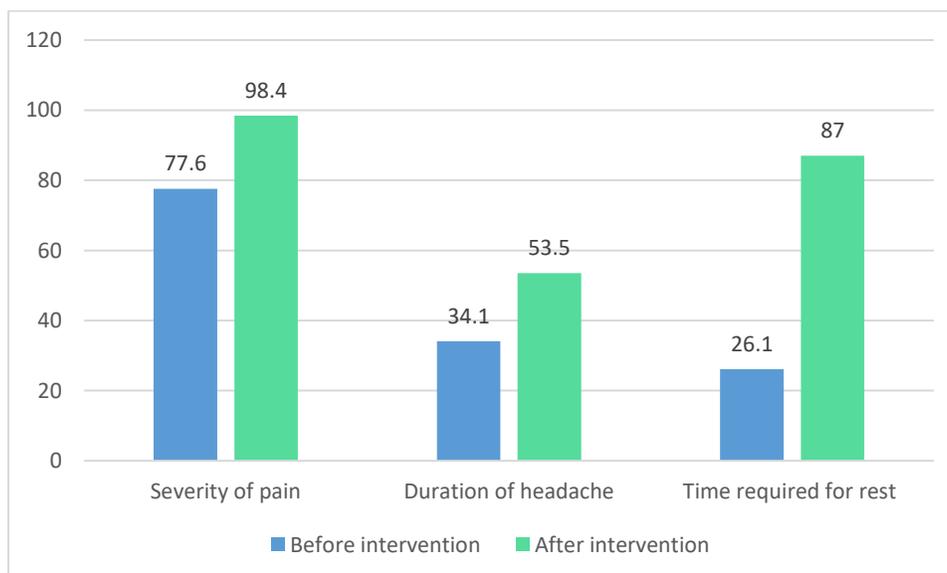


Figure 1 Mean of duration before and after the intervention in the control group

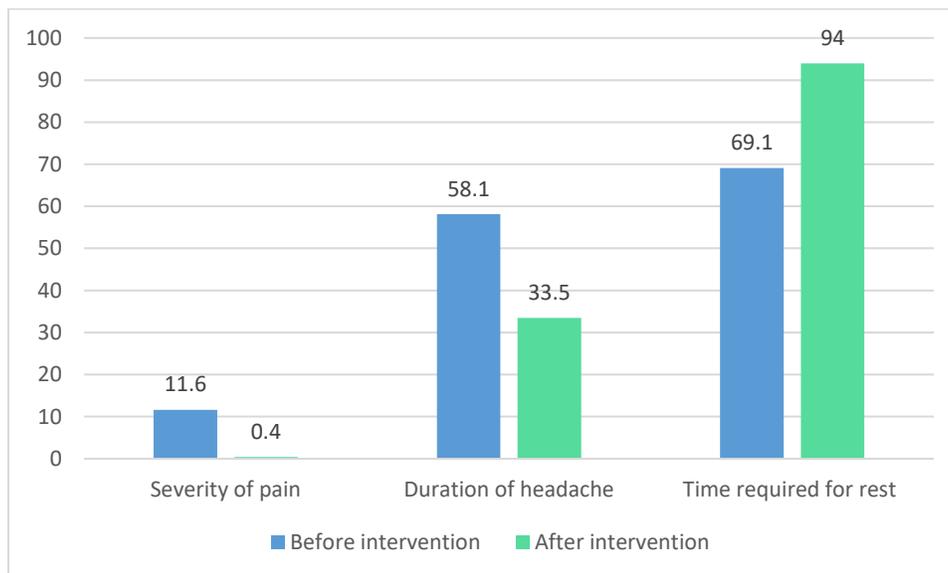


Figure 2 Mean of duration before and after the intervention in the case group

While no significant difference was found between the intervention and control groups (except for increased appetite [P=0.04]) in the area of emerged complications, a closer look at the matter demonstrated that the diversity of complications was significantly lower in the intervention group, compared to the control group. Nevertheless, this difference was not statistically significant.

Table 6 Evaluation of complications of medications before and after the intervention across the study groups

complications	Control	case	total	p
Constipation	2 (6.1)	0	2 (6.1)	15.0
Vomiting	3 (4.2)	0	3 (4.2)	08.0
Headache	1 (8.0)	0	1 (8.0)	31.0
Hair loss	3 (4.2)	1 (8.0)	4 (2.3)	30.0
Drowsiness	7 (6.5)	3 (4.2)	10 (1.8)	18.0
Diarrhea	3 (4.2)	0	3 (4.2)	08.0
Buzz	2 (6.1)	0	2 (6.1)	15.0
Increased appetite	4 (2.3)	0	4 (2.3)	04.0
Excess hair	2 (6.1)	0	2 (6.1)	15.0
Liver conditions	2 (6.1)	0	2 (6.1)	31.0
Increased weight	1 (8.0)	6 (8.4)	7 (6.5)	57.0
Balance	0	1 (8.0)	1 (8.0)	31.0

4. DISCUSSION

According to the results of the current research, no significant difference was observed between the groups in terms of demographic variables. In addition, it was demonstrated that the severity of pain, duration of migraine attacks and time required for rest significantly reduced by treating gastric problems in patients with participatory gastric headache using atrifel (P=0.001). Other studies have shown that treatment of the participatory body part with migraine play a significant role in improvement of this condition. In this regard, Gasbarrini et al. conducted a research on patients with *Helicobacter pylori*, who complained of headache. According to their results, elimination of the mentioned bacteria led to complete treatment of headache attacks and signs in 17% of the participants. On the other hand, return, duration and intensity of headache decreased in 69% of the patients (Gasbarrini et al., 1998).

In another study by Spierings, which was carried out on migraine patients with reflux symptoms, it was observed that the headache was initiated by the onset of stomach reflux, and treatment of this condition significantly improved the headache of subjects (Spiering, 2002). In a research conducted by the same author on three patients with headache, medical history of patients showed that headache emerged due to reflux, dyspepsia and constipation, and treatment of these problems completely eliminated or significantly improved the headache of the participants (Spiering, 2002). In addition, Dong-Gyan Hon and Chang-Ju Lee conducted a research on patients with participatory headache with symptoms of functional disorders of the digestive tract, presenting a report on periodic vomiting and repetitive abdominal pain in children, which led to migraine. In this regard, visceral diseases are an important factor in the development of headache by stimulating the parasympathetic system and parasympathic referral pain (Dong-Gyun and Chang-Ju, 2009).

In the pain scale, treatment with atrifel was reported to have the most effectiveness. Literature review revealed that no study has been conducted on the effect of atrifel sagir on the reduction of migraine attacks. In a research by Hwang et al. on 58 children with primary headache and epigastric pain, it was shown that headache was eliminated in 64% of migraine patients and 53% individuals with tension headache due to the consumption of antacid (Hwang et al., 2008). Moreover, Choupannejad et al. presented a complete report on modification of lifestyle and reduction of migraine headache using atrifel cilantro in 45 migraine patients (Choupannejad et al., 2014). Fazljou et al. also conducted an intervention on 26 patients, who referred to the specialized clinic of headache (traditional medicine) in Imam Khomeini Hospital in Tehran, Iran. In this research, there was a significant reduction in the number and duration of headache attacks due to the consumption of atrifel cilantro (Fazljou et al., 2013). On the other hand, Falah et al. claimed that propranolol and cinnarizine medications significantly decreased the duration of headache (Fallah et al., 2013). In addition, Bidabadi et al. introduced propranolol, topiramate and sodium valproate as the most effective medications from the traditional medicine. This lack of consistency with our findings might be due to the type of the mentioned study, where a random intervention was performed to compare the effect of propranolol and sodium valproate in order to prevent headache in children (Bidabadi and Mehrvar, 2010). Therefore, there were some differences between the studies in terms of type and applied medications.

5. CONCLUSION

According to the results of the current study, atrifel sagir can be used as a supplementary medication along with sodium valproate to significantly improve the severity of pain and number of attacks.

Funding

This research received no external funding.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of Shahid Sadoughi University of Medical Sciences, Ardakan, Yazd (ethical approval code: IR.SSU.REC.1395.194).

Data and materials availability

All data associated with this study are present in the paper.

Peer-review

External peer-review was done through double-blind method.

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