The Effects of Combination Herbal Medicine Tablet on Migraine Headache: A Randomized, Double-blind, Placebo, Controlled Study

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Abstract

Background: Migraine is the second most common cause of headache, various methods have been mentioned for the treatment of migraine, including herbal medicine. Iaraj Fiqra is a combination of Aloe, saffron, cinnamon, mustalci, balsam incense and asaroon and claim to be effective in migraine. The present study aims to compare the effect of Iaraj Fiqra and placebo tablets on migraine headache.

Methods: In this randomized, controlled trial, patients with migraine (based on the International Headache Society definition) received Iaraj Fiqra (500mg/daily) or placebo tablets for two months. Headache characteristics were measured using the Migraine Disability Assessment (MIDAS) and Headache Impact Test-6 (HIT-6).

Results: Iaraj Fiqra reduced significantly the frequency (P=0.007), the severity (P=0.000) and the duration (P=0.000) of attacks compared to placebo. MIDAS and HIT-6 scores were significantly reduced in the drug group other than the placebo group (P=0.014 and P=0.000 respectively). Analgesic use also reduced. No significant difference was observed between the two groups in term of side effects (P=0.23).

Conclusion: This study showed that Iaraj Fiqra had significant effects on reducing headache characteristics and analgesic use and given its limited side effects, it is recommended for the treatment of migraine.

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Keywords: Migraine; Herbal Medicine; Iaraj Fiqra

Introduction

Headache is one of the most common types of pain which cause many discomforts if it is repeated. Headache is the complain of more than 50% of the patients who are visited by doctors (1). The international headache society classifies headache into more than 150 types of primary and secondary headaches. Migraine is the second most common after tension headache (2). The Migraine headache is moderate to severe and throbbing headaches that usually affect one side of the head and are often associated with nausea, vomiting, photophobia and fatigue (3). According to the report of the World health organization (WHO), migraine ranks 19th among all disorders that cause disability and diminished quality of life (4).

The prevalence of migraine is higher in young people and decrease with age. The prevalence of migraine headache is 19% in women and 6% in adult men (5). The overall prevalence of migraine in Iran is 14%(6).

Various medications are used to managed migraine pain. The treatment strategy includes management of acute migraine attack, prophylaxis and combined treatment. Common treatments for pain control include triptans, ergotamine derivatives, analgesics (e.g. NSAIDs and acetaminophen), anti-nausea (metoclopramide) and corticosteroid (7). Prophylactic treatment is recommended in case of frequent occurrence of headache between 8 to 12 attacks per month, high consumption of analgesics or contraindications for acute stage treatment and occurrence of side effects. Beta blockers, TCAs, Ca-channel blockers, SSRIs are recommended for prophylaxis of migraine attack (8).

All medications use for migraine control pose a variety of side effects in long term use and besides, their costs are

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inconsistent with their degree of effectiveness (9). The need for a definitive, efficient and low cost method with fewer side-effect is therefore deeply felt.

The use of alternative medicine and herbal plants have been of interest for a long time in the treatment and prevention of migraine (10). Iran's traditional medicine recommends several medications for the treatment of different types of headache (11). The effect of "Sodae" capsule (Booali daru) was evaluated on migraine headache by Rezaei et al., in 2020. The results indicated that this capsule has an effective therapeutic option in migraine headache (12). Tanacetum parthenium (feverfew) (13) and peppermint extract (14) are example of other Iranian herbal plants that show effectiveness in studies.

Iaraj Fiqra tablet is a product derived from traditional Iranian medicine, which consist of rose flower powder, cinnamon, ginger, and sabrezard (Aloe) and is scientifically prepared and formulated (15). Another name of Aloe is Fiqra, so the product named Fiqra and Iaraj is one of the Socrates' inventions. The Iranian traditional sources (including Abu Ali sina's (law of medicine), Razi (Al-Hawi) and Ismail jorjani (Zakhira kharazm shahi) introduced Iaraj Fiqra (collection of plants) as one of the treatment of headaches (16). This collection includes, Aloe, saffron, cinnamon, mustalci, balsam incense and asaroon, which first mix all except Aloe with a ratio of 1:1 and then mix Aloe with a ratio of 2:1.

Aloe vera (sabrezard) with the scientific name Aloe ferox from Xanthorrhoeacea family proven to has compounds with anti-inflammatory properties that reduce pain (17). Also, Aloe has muscle relaxant properties which suitable for muscle spasm around the head and neck in migraine (18).

Cinnamon (cinnamomum verum) belongs to the Lauracea family and its essential oil relief pain and has anti-rheumatic effects (19). Some studies confirm that cinnamon could be effective option in management of migraine headache through its anti-inflammatory properties (20-22).

Other products in Iaraj Fiqra including saffron, cinnamon castia, pistacia lentiscus, commiphora opobalsamum (belsam) showed have analgesics, sedative effects which could be beneficial in the treatment of migraine (23-25). Based on the evidence obtained from previous studies and increasing trend of people towards herbal medicines, we aim to compare the effects of Iaraj Fiqra and placebo tablets on migraine headache. No study has been done with this drug before.

Methods

This study was designed as a double-blind, placebo-controlled, randomized study which was performed during October 2020 to September 2022. The study protocol was approved by Ethics committee of Isfahan University of Medical Sciences (IUMS). The trial was registered at IRCT (Iranian registry of clinical trial) with the code number of IRCT20081208001497N9. The informed consent was obtained from all patients. The participants were selected from those patients who were visited project collaborating physicians to alleviate their headache.

Patients were eligible for inclusion if they met all of the following criteria: migraine without aura headaches (as defined by international headache society (2), which diagnosed by collaborating physician); age between 18 and 65 years; more than three attacks per month in the last three months; the onset of migraine at least a year before the study, the onset of migraine before the age of 50 and MIDAS (Migraine Disability Assessment) score more than 6. Exclusion criteria were defined as follows: experience headaches between any two migraine attacks that cannot be distinguished from the migraine attacks, chronic tension headaches or other headaches more than 15 days per month, daily use of migraine prevention medication less than one month before the study, the use of more than three types of migraine prevention medications over the last ten years, having underlying heart problems (e.g. arrhythmia), having biliary problems, inflammatory bowel diseases (crohn's disease and ulcerative colitis), hemorrhoids, simultaneous use of sedative drugs (such as phenobarbital), and use of diuretics, and oral corticosteroids, consumption of laxatives (e.g. polyethylene glycol, magnesium hydroxide), pregnancy, breast feeding, and dependent on alcohol and other illegal substances.

A research coordinator conducts the randomization and delivered the study drug. The participant and collaborating physician blinded to the treatment assignment. Eligible participants randomly assigned 1:1 to either the treatment group or the placebo group in accordance with the predefined randomization list with a block size of four.

The treatment group received 500mg (one tablet) of Iaraj Fiqra (Niac company, Gorgan, Iran) orally, every night before sleep for two months. Patients in the control group received placebo (which was prepared with Niac company) with the same dose for two months. The placebo tablet was similar in size and color with the Iaraj Fiqra tablet. The investigator delivered drug or placebo in the same packaging containers. Investigator evaluated drug compliance by counting pills and patients with less than 80% compliance removed from the study. During the study, the patients were monitored for medication intake and possible side effects through phone calls made by the investigator. The product contains Aloe, saffron, cinnamon, mustalci, balsam incense and asaroon. All the patients continue their treatment regimen for migraine.

The primary outcome was to evaluate the effect of Iaraj Fiqra on the frequency, duration and severity of attacks. Secondary outcomes included assessment of the migraine disability assessment (MIDAS) and headache impact test-

6 (HIT-6) at baseline and one and two months later (26). The MIDAS contains five item and items and determines the number of days of absenteeism from social or family activities or days in which the patient has performed poorly in these activities over the last three months as a result of migraine headaches. The MIDAS score is the sum of the number of days given by the patient in response to each item (27).

The HIT-6 was containing six questions with 5-option items, and the options include 'never' (6 points), 'rarely' (8points), 'sometimes' (10 points), 'very often' (11 points) and 'always' (13 points). The HIT-6 score is the sum of the scores of the options chosen by the patient for each item (28). The test-retest reliability of the MIDAS was obtained with a correlation coefficient of r = 0.991(29), and the HIT-6(30) had a correlation coefficient of r = 0.50, which suggests acceptable convergence validity.

The record pain intensity, a visual pain measurement tool (visual pain scale) (31) was used, which is one of the most reliable tool for pain measurement. This tool is the simplest tool to measure the level pain that can be easily understand by the patients' basic information of patients including age, sex, past medical history and status of migraine attacks (frequency, duration, severity) and use of analgesics has been recorded.

According to the previous study (12), we calculated the required sample size for an estimated dropout rate of 10%, a one sided level of significance of α=5%, and a power of 80%, assuming the standard deviation (SD) of 0.25 and mean difference of 1.81 to reduce frequency of attacks. A sample size of 25 patients in each group was estimated to be sufficient to detect a significant difference in reduction of attack frequency.

Statistical analysis was performed based on the intention to treat (ITT) principle. Continuous data were assessed for normality by the Shapiro-Wilk test. Normally distributed and non-normally distributed data are presented as the mean ± SD. Independent-samples t test and repeated measure analysis ANOVA were performed in order to compare normally distributed variables between and within groups, respectively. Mann-Whitney U test and Wilcoxon Signed-Ranks test were performed on non-normally distributed and ordinal variables for evaluating between and within- group differences, respectively. Categorical variables are expressed as frequencies and percentages, and comparisons between groups were assessed by means of the Chi-square test or Fisher's exact test, as appropriate. A value of $P \leq 0.05$ considered statistically significant. All analyses performed using SPSS statistics software V24.0 (SPSS Inc; Chicago, IL, USA).

Results

Over the study period, of 160 patients who were assessed for eligibility, 60 were randomly assigned (30 patients to drug and 30 to placebo group) with a ratio of 1:1. 23 patients in each group completed the protocol. Reasons for interrupting the treatment are reported to Figure 1.

Figure 1. Progress through the stage of trial.

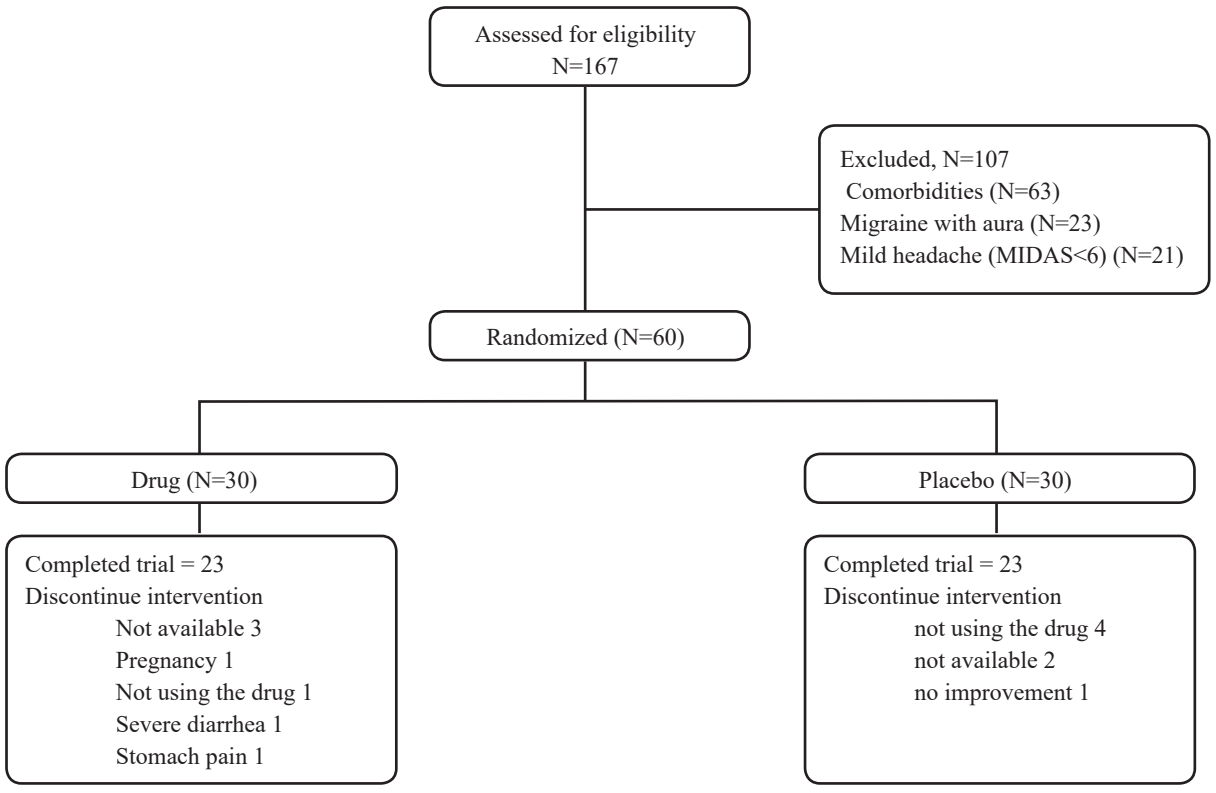

Table 1 shows the baseline demographics and headache characteristics of the patients. As shown, the patients of two groups were matched in terms of demographic details and headache characteristics except of severity.
Table 2 shows the effects of interventions on the headache characteristics and MIDAS and HIT-6 scores after 1 and 2 months in the study subjects. As seen, despite the reduction of the headache
characteristic and the scores in both groups, the reduction was significantly higher in the intervention (drug) group compared to the placebo group.

The MIDAS score (showing the degree of disability causes by headache) showed a significant reduction in both groups (within groups); although, between group analysis showed a significant effect of drug compared to placebo (P=0.01). The subjects' frequency distribution in to the different classes of the MIDAS score was measured. This score showed a significant reduction in both groups, although, more in the drug group. (Table 3)

Table 1. The demographic details and headache characteristics in the intervention and placebo groups at baseline.

	Drug (N=23)	**Placebo (N=23)**	**P value**
Age, mean±SD	39.6±9.1	35.2±8.2	0.05
Gender (Male/Female)	11/19	12/18	0.5
Headache characteristics			
Frequency/month	7.1±3.2	8.4±3	0.1
Severity	8.2±1.6	8.9±1.1	0.03
Duration, hour	10.7±1.1	16.5±1.4	0.05
MIDAS	30.1±11.6	32.6±9.6	0.37
Treatment			
Sumatriptan	11	15	0.15
Ergotamine-C	0	2	
Without	19	13	
Prophylaxis			
Nortrityline	2	6	0.032
Valperoic acid	3	0	
Propranolol	2	6	
Citaloperam	2	0	
Past medical history			
Anxiety	6	2	0.36
Cardiac diseases	0	1	
Gastrointestinal diseases	1	1	
Hypothyroidism	1	0	

Table 2. A comparison of the mean headache characteristics and MIDAS and HIT-6 scores in the two groups at measurement time (mean±SD)

	Groups	0	1 month	2 month	P value*
Frequency/months	Drug (N=23)	7.1±3.2	2.9±0.65	1.9±0.53	0.000
	Placebo (N=23)	8.4±3	5±0.72	5.3±0.87	0.011
	P value**	0.007			
Severity	Drug (N=23)	8.2±1.6	4.2±0.54	3.3±0.48	0.000
	Placebo (N=23)	8.9±1.1	6.7±0.49	6.4±0.5	0.002
	P value**	0.000			
Duration, hour	Drug (N=23)	10.7±1.1	3.5±0.59	3.7±1.04	0.012
	Placebo (N=23)	16.5±1.4	10.8±1.8	10.3±1.8	0.003
	P value**	0.000			
MIDAS	Drug (N=23)	30.1±11.6	15.9±3.1	11.6±2.8	0.000
	Placebo (N=23)	32.6±9.6	25.9±2.7	23.8±2.7	0.031
	P value**	0.014			
HIT-6	Drug (N=23)	63.1±9.7	51.7±9.5	48.6±10.5	0.006
	Placebo (N=23)	48.8±9.9	44.4±6.8	41.5±5	0.001
	P value**	0.000			
Analgesics, N	Drug (N=23)	30	-	7	76.6% reduction
	Placebo (N=23)	30	-	11	63.4% reduction
	P value**	0.06			

Table 3. A comparison of the disability caused by headache in the intervention and placebo groups at the measurement time.

Group		0	1 month	2 month	P value*
Drug	0-5 (without disabilities)	-	6	9	
	6-10 (weak disabilities)	-	7	5	
	11-20 (moderate disabilities)	9	4	4	
	≥21 (severe disabilities)	21	6	3	
Placebo					
	0-5 (without disabilities)	-	3	2	
	6-10 (weak disabilities)	-	1	1	
	11-20 (moderate disabilities)	3	3	2	
	≥21 (severe disabilities)	27	16	10	
P value		0.05	0.017	0.013	0.000

*between group analysis

The HIT-6 score shows the negative impact of headache in the personal lives of those affected. Drug significantly reduced score compared to the placebo (P=0.000).

In the course of the study, the subjects reported that their use of analgesics has reduced at a rate similar to their rate of relief from pain; analgesics use had reduced 76.7% in the drug group and 63.4% in the placebo group, but the difference was not significant (P=0.06).

No serious side effects were reported in either of the group and there was no significant difference between the two groups regards of side effects (P=0.23). Stomach pain (N=6) and diarrhea (N=3) were the most reported side effects.

Discussion

This double-blind, placebo-controlled, randomized study showed that both the Iaraj Fiqra and placebo tablets were able to improve migraine headache, but this improvement was significantly better with Iaraj Fiqra tablets than with the placebo.

Iaraj Fiqra was most effective in reducing the severity, duration and frequency in respective order. The Iaraj Fiqra tablets was also very effective in reducing the MIDAS and HIT-6 scores. Also, the Iaraj Fiqra tablets was able to reduce headache –induced disability significantly, especially in most of the subjects with severe disability, and turned their disabilities into weaker ones. The Iaraj Fiqra was effective in reducing the use analgesics. There were no serious adverse effects with this tablet.

Some previous studies have reported the beneficial effect of various herbal medicine on migraine headache. Most of them conducted as single herb, but, a study by Rezaei et al., (12) investigated the effect of Sodae capsules (combination of Turpethum, Bdellium,Rhubarb, Terminalia chebula, and Eyaraj fighara) on migraine headaches compared with placebo. The study was conducted on74 migraine patients (720 mg Sodae for 3 months). The headache characteristic reduced significantly more in the intervention group and the capsule had limited side effects. The investigators mention that the laxative effect of Sodae capsule, the body and digestive tract of additives and toxins and create a lighter feeling in the head. Also, this drug reduces the bile and improve headache. The Iaraj Fiqra components (include Aloe, saffron, cinnamon, mustalci, balsam incense and asaroon) had anti-inflammatory, sedative and analgesic effect; however, we didn't evaluate any biomarkers but it seems that some of the beneficial effects of the Iaraj Fiqra related to its anti-inflammatory properties. As a combination of herbs, the laxative, sedative, analgesics effects of Iaraj Fiqra also is considerable.

Zarei et al.,(22) in a randomized, double-blind controlled trial on 50 patients with migraine show that cinnamon significantly reduce frequency and duration of migraine headache and also, reduce interleukin-6 and nitric oxide levels which shows that cinnamon had anti-inflammatory properties. As cinnamon is one of the main herb in Iaraj Fiqra, it could be explaining the positive effect on migraine through some anti-inflammatory actions.

Another ingredient, saffron (corcus sativus) have been used to treat fever, wounds and lower back pain(23). Aqueous and alcoholic extracts of stigmas and saffron petals have an anti-nociceptive and anti-inflammatory activity for both acute and chronic pain(32). Other studies showed the potential benefit of saffron as an analgesic, anti-inflammatory and anti-depressant(33, 34).

Pistacia lentiscus (mustic) is naïve plant from the Mediterranean area which its gum has been widely used in Persian medicine to treatment of gastrointestinal disorders (e.g. reflux)(35), also has antioxidant and antimicrobial and anti-inflammatory properties(36). Therefore, through these mechanisms could be effective in alleviating migraine

A review by Levin et al., (2012) on herbal treatment of headache showed that Butter bar and fever few are the two herbal oral preparations best studied and have real potential in alleviation of migraine. Also, coffee, tea, guarana berries, chamomile, ginger root, juniper, peppermint, kudzu, willow and brich claims to have anti-headache properties(37). Many studies in different parts of Iran and the world show positive effect of herbal medicine in reducing migraine pain and the results of the present study confirmed this.

The present findings showed that Iaraj Fiqra tablet reduce frequency, severity and duration of migraine headache compared to placebo. Also, it reduces use of analgesics by migrainous patients without significant side effects. Therefore, this herbal medicine could be used as an adjunct main treatment of migraine. At lease, overuse of analgesics will be diminished with its use.

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Conflict of Interest

None to be declared.

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