The Effectiveness of Combination of *Viola odorata* L., *Rosa damascena* Mill. and *Coriandrum sativum* L. on Quality of Life of Patients with Migraine Headaches: A Randomized, Double Blinded, Placebo - Controlled Clinical Trial

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Abstract

Headache is one of the most common public health problems in the world, which causes patients to see a doctor. Migraine is the second most common cause of headaches after tension headaches. This study is a randomized, double blinded, placebo - controlled clinical trial, using SF36 questionnaire, to evaluate the effect of combination of *Viola odorata* L*., Rosa damascena* Mill. and *Coriandrum sativum* L. on the quality of life, in patients with migraine after 4 weeks. In all domains of the SF36 questionnaire, the scores after intervention in the drug group were significantly higher than the control group after 4 weeks. This study showed that, combination of *V. odorata, R. damascena* and *C. sativum*, improves the quality of life of patients with migraine.

Keywords: Persian medicine; Viola; Migraine; Headache; SF36; Traditional iranian medicine; CAM; Quality of life

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Introduction

Headache is one of the most common pain complaints and half of visits to physicians is due to headache [1], and the hardly curable ones are the main challenge [2]. Migraine is the second prevalent headache after tension headache [3]. The prevalence of migraine among adults is more that 10% [4]. It is a common, debilitating, recurrent, and hereditary headache that is involved in various causes and is caused by neurovascular disorders [5]. The first attack of migraine usually happens when people are around 40 years old [6], which is a productive age in anyone's life [7]. The symptoms of migraine include nausea and sensitivity to light and sound affecting the daily performance of patients [8-11] and decresing their productivity [12]. By the same token, it has an effect on their attendance at school and workplace [13]. The quality of life includes spiritual / physical health, personality, social relationships and self-esteem [14]. Evidence shows that standard tools can be employed to investigate the effects of diseases on social and personal life [15]. 36-item Short Form survey (SF-36) is a set of generic, coherent, and easily administered quality of life measures. It investigates the effects of diseases on personal and moral performance of patients [16-20]. Patients with migraine have a lower score of SF-36 than patients without migraine [8,10,21]. The investigations through SF-36 reveals that the negative effects of migraine on different aspects of health are equal or even more harmful than other diseases such as backache, congestive cardiac failure [16], depression [16,21], diabetes, hypertension [22], myocardial infarction [16] and osteoarthritis [22]. Regarding the importance of migraine as a worldwide health problem [23], various preventive treatments have been employed [6]. Many patients complain about the side effects of medications they take and some patients report drug resistance [24-26]. This jus-

tifies the regular use of complementary and alternative medicine (CAM) among patients with migraine [27]. According to the World Health Organization (WHO), alternative medicine has a long history in the treatment of chronic diseases [28]. One of the most beneficial forms of Complemantary and Alternative Medicine is Persian Medicine [29]. Ancient Iranian physicians used some medicinal herbs that had sedative, pain killing and preventive effects [30] for headaches [30, 31]. The reference books for Persian Medicine highlight some of these herbs as medications for headaches [32,33]. The combination of *Viola odorata* L.*, Rosa damascena* Mill. and *Coriandrum sativum* L. is a prescribed medication [34-36]. The current study aimed to investigate the effectiveness of the combination of *V. odorata, R. damascena* and *C. sativum* on the quality of life of patients with migraine headaches using SF-36 in a double-Blind clinical trial. This study was performed during a six-month period in Besat 4 clinic affiliated with Kerman University of Medical Sciences from September 2016 to march 2017. In addition, our study provides scientific documentaries concerning the efficacy of beliefs and experiences of traditional Iranian medicine.

Methods

In this study, patients were selected based on the criteria from the International Headache Society [IHS] [37,38], and a neurologist approved that patients suffered from migraine. The inclusion criteria were as follows: age between 15 and 45 years, being informed of the disease, and experiencing at least four migraine attacks during past few months. The exclusion criteria encompassed: a decision to be pregnant, being pregnant, breastfeeding, suffering from other chronic diseases [heart, liver, kidney, other neurological disorders except migraine, hypertension, diabetes, depression, etc.], and suffering from other types of headaches except migraine,

treatment with a conventional migraine medication, not properly taking prescribed medications and lack of cooperation [39]. SF-36 quality of life questionnaire, investigates the effects of migraine on eight domains regarding patients' performance including physical function, physical disabilities, physical pain, general health, mental health, and emotional instabilities, social and physical performance. Each domain ranges from 0 [the worst performance] to 100 [the best performance]. The questionnaire was translated into Persian and its validity and reliability were confirmed [40]. This is a block Randomized in a 1:1 ratio, Double Blind, and Placebo - Controlled Clinical Trial designed by an epidemiologist. Before the initiation of the study, we explained the details and objectives of the study to patients. Informed written consent was granted from patients and they were assured that their information will be kept confidential. The protocol of the study was confirmed by the ethics committee of Kerman University of Medical Sciences with code number: IR.KMU. AH.REC.1395.18. Besides, this study was approved by the center for clinical researches with code number: IRCT2012122511876N. This study is based on the Declaration of Helsinki as a statement of ethical principles for medical research, October 2013 [41]. The herbarium number for each herb at Kerman University of Medical Sciences is as follows: *V. odorata* (Kf 1425), *R. damascene* (Kf 132), and *C. sativum* (Kf 1524). The quality control tests were performed at Barij Esans lab, Kashan, Iran. The tests included total ash content determination, acid-insoluble ash determination, tannin and polyphenol determination in gallic acid through spectrophotometry (UV-VIS) and microbial contamination detection including Salmonella, Escherichia coli, Aerobic Mesophilic Bacteria, Yeast and Mold Count. The medications were produced according to methods by Iranian traditional medicine [32-36]. Medicinal herbs were powdered with an electric grinder. Then 500 mg capsules were made each having the same amount of *V. odorata, R. damascena and C. sativum*. We filled the same capsules with starch to make placebos. According to similar studies, the standard deviation of the number of headache attacks was higher than other variants; therefore, we considered this variant to calculate the sample size [42]. Based on similar studies and the above-mentioned formula, the sample size in this study for the intervention and control group was at least 43 and 86 patients, respectively. The intervention group took one 500-mg capsule (*V. odorata, R. damascena and C. sativum)* three times a day [1.5 g daily intake] and one propranolol 20 two times a day after meals for four weeks and the control group took one placebo capsule three times a day and one propranolol 20 two times a day in the same way as the intervention group. Demographic data of patients were collected. SF-36 questionnaires were completed in the beginning and at the end of week four. This information was kept in patients' files. Data analysis was performed using SPSS software version 21. We used descriptive statistics (frequency, mean ±Standard Deviation (SD)) as well as inferential statistics (Chi-square, two independent T-test and regression model) to determine the efficacy of herbs on the quality of life of patients with migraine headaches. There was a significant level of 0.05 for two-tailed tests. A pharmacist performed the random allocation and all the participants received their medicine from the pharmacist. Patients knew that they were divided into two groups, but they were not aware of the treatment method. Interviewers and patients were not aware of the allocation method for the intervention group during the study period.

Findings

In this study, we divided 88 patients with migraine into two groups of intervention and con-

trol. One patient in the intervention group and one patient in the placebo group were excluded because they did not take their medications properly. Finally, we performed the study with 43 patients in each group. The mean (±SD) of age for patients was 33 ± 5.7 years. Also, the mean (±SD) of age for the intervention group and the placebo group was 32 ± 5 and 34 ± 4 years, re2 spectively. There were 30 women (69%) in the intervention group and 32 women (74%) in the control group. There was no significant difference between the two groups in terms of age (P = 0.09), sex (P = 0.63), marital status [single or married] and the type of migraine (with and without aura) (P = 0.56). (Table 1)

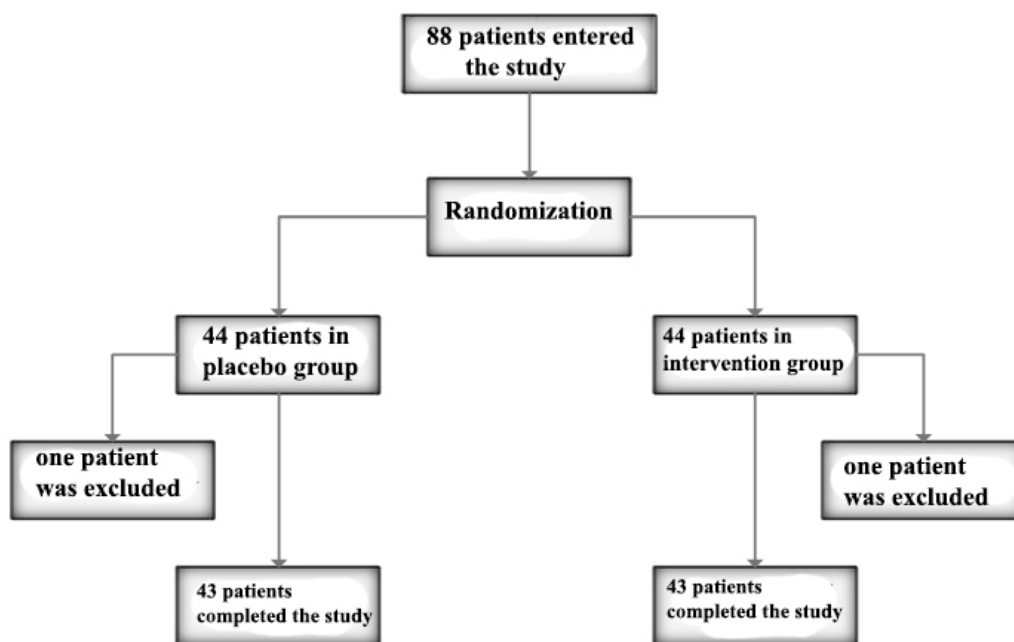The process of entering and leaving patients participating in the research is presented in Figure 1.

Figure 1: Flow diagram of the study design and randomization

Table 1: Demographic characteristics of groups under study

variables	intervention (Mean ± SD)	control (Mean ± SD)	Sig*
sex			0.63
female	30 (69%)	32 (74%)	
male	13 (30%)	11 (25%)	
Marital status			0.43
single	11 (25%)	8 (18%)	
married	32 (74%)	35 (81%)	
Type of migraine			0.56
Without aura	35 (81%)	37 (86%)	
With aura	32 (18%)	6 (13%)	
Age (years old)	32±5	34±4	0.093

*Chi square test and t-test

We employed the regression model to compare the two groups. Table 2 shows the comparison of scores for the quality of life in all domains in the two groups before and after the treatment. In the intervention group, in all domains of life quality, the score for quality of life significantly increased (P < 0.05). In the control group, except the scores for general health there was a significant difference between the scores for quality of life before and after the treatment (P < 0.05) (Table 3). At the end of the study, the average of quality of life scores in the intervention group for all domains was significantly higher than the control group (P < 0.05). We observed a significant difference for the emotional role in which the average score in the intervention group (46.12) for quality of life was (95% C.I: 37.53-54.70) more than the control group. Furthermore, the least difference was for physical function in which the average score for quality of life in the intervention group (3.47) was (95% C.I: 1.52- 5.41) more than the control group.

Table 2: The comparison of scores for quality of life before and after intervention in different groups of medication and placebo

variables	before	after	t	p-value
	Mean ± SD	Mean ± SD		
General health				
intervention	35.10 ± 00.80	38.10 ± 83.28	5.62	<0/001
control	35.12 ± 00.80	35.11 ± 34.46	0.19	0.84
Physical function				
intervention	77.15 ± 90.36	83.10 ± 95.94	5.38	<0/001
control	76.9 ± 74.25	79.8 ± 88.20	5.22	<0/001
vitality				
intervention	35.9 ± 52.18	51.5 ± 56.23	10.07	<0/001
control	41.8 ± 39.04	46.7 ± 39.50	7.08	<0/001
Emotional role				
intervention	3.9 ± 10.70	55.21 ± 81.48	14.17	<0/001
control	0 ± 0	10.15 ±15.44	4.31	<0/001
Social function				
intervention	42.11 ± 44.29	51.7 ± 16.62	5.49	<0/001
control	41.11 ± 51.26	46.5 ± 51.67	3.05	0/004
Bodily pain				
intervention	38.11 ± 89.79	58.10 ± 43.05	10.01	<0/001
control	39.8 ± 30.71	42.5 ± 03.46	0.008	0/008
Physical role				
intervention	16.20 ± 86.20	58.23 ± 13.60	10.85	<0/001
control	13.13 ± 95.69	23.19 ± 25.96	4.98	<0/001
Mental health				
intervention	35.9 ± 72.00	50./5 ± 97.92	11.01	<0/001
control	37.8 ± 67.15	40.8 ± 85.18	6.71	<0/001

Table 3: The comparison of scores for quality of life after intervention in the two groups of medication and placebo with moderated scores before intervention and demographic characteristics

variables	Mean ± SD	moderation Coefficient regression 95%)*.C.I.**)	t	p-value
General health				
intervention	38.83 ± 10.28	3.69 (2.19, 5.73)	4.40	<0/001
control	35.34 ± 11.46	standard		
Physical function				
intervention	83.95 ± 10.94	3.47 (1.52, 5.41)	3.55	<0/001
control	79.88 ± 8.20	Standard		
vitality				
intervention	51.56 ± 5.23	7.59 (4.78, 10.39)	5.38	<0/001
control	46.39 ± 7.50	standard		
Emotional role				
intervention	55.81 ± 21.48	46.12 (37.53, 54.70)	167	<0/001
control	10.15 ± 15.44	standard		
Social function				
intervention	51.16 ± 7.62	4.60 (1.80, 7.40)	3.27	0/002
control	46.51 ± 5.67	standard		
Bodily pain				
intervention	58.43 ± 10.05	16.20 (12.97, 19.43)	9.99	<0/001
control	42.03 ± 5.46	standard		
Physical role				
intervention	58.13 ± 23.60	34.06 (25.65, 42.47)	8.06	<0/001
control	23.25 ± 19.96	standard		
Mental health				
intervention	50.97 ± 5.92	11.45 (8.97, 13.93)	9.20	<0/001
control	40.85 ± 8.18	standard		

*With moderated scores before intervention and demographic characteristics
** Confidence interval

Discussion and Conclusion

According to the results, the combination of *V. odorata, R. damascena* and *C. sativum* significantly increases the SF-36 scores in a short time without having any side effect on migraine patients and taking this medication for four weeks has a positive effect on the quality of life of patients with migraine. In this study, 62 females and 14 males participated with a relative frequency of 71.5% and 27.5%, respectively. Evidence shows that migraine is more prevalent among women than men with a 2 to 1 or 3 to 1 ratio [43,44]. In the study carried out by Ozdemir et al. to determine the prevalence of migraine, 69.5% of patients were women and 30.5% were men [4645 In addition, the average age of participants was 33 ± 5.7. Also, the average ages of patients in intervention and control groups were 32 ± 5 and 34 ± 4, respectively. The results from a study performed by Ramage-Morin shows that the most prevalence of migraine was among 31-49-year-old people [46]. So far, there has been no study to evaluate the effects of *V. odorata, R. damascena* and *C. sativum* on the quality of life of patients with migraine and this is the first clinical trial to investigate the effects of this medication on the quality of life of patients with migraine in comparison with a

placebo group. Migraine attacks radically decrease social function and productivity. An effective treatment should increase patients' productivity. The difference in terms of scores (by five scores or more) in most parts of the questionnaire is considered as a significant clinical difference [47]. The results of this study show that despite the low number of statistical population, this herbal medication increased most of the scores in quality of life questionnaire in the intervention group in comparison with the placebo group and also in the intervention group before and after the treatment. Comparing the standard deviation reveals that emotional role had the most increase in the intervention group after the treatment versus before treatment and also in comparison with medicinal herb and placebo groups after intervention. General health obtained the least score showing that migraine has the worst effect on emotional aspects of patients. Over years, various theories have been suggested to treat migraine. One of these theories is bone marrow failure that changes the sensational inputs and since in migraine treatment considering pathophysiology and its symptoms (such as pain, fatigue, mood change etc.) are of high importance, this theory justifies the negative effects of migraine on emotional aspects of patients [48]. A study conducted by Kamali et al. revealed that this herbal medicine significantly decreases the intensity, duration and the frequency of attacks in patients with migraine [40]. One of the characteristics of *V. odorata* is to cure migraine and no side effects have been reported [49]. *V. odorata* has salicylic acid. It is a natural aspirin and has been used to cure all types of headaches and migraines and physical pain for centuries as a sedative and anti-inflammatory medicine [50]. Feyzabadi et al. prescribed *V. odorata* oil for fifty patients with chronic insomnia to take two drops of oil in each nostril every night before sleep for one month. Comparing before treatment, the in-

crease of scores in terms of sleep and insomnia severity index (ISI) dramatically decreased. Therefore, *V. odorata* oil can be prescribed for patients with chronic insomnia as a healthy, tolerable and effective medicine [51]. In the study performed by Vishal Antil et al. the analgesic effects of methanolic and aqueous extracts of *V. odorata* at a dose level of 400 mg/kg had a significant effect on tail immersion and hotplate models [52]. Another study carried out by Alireza Monadi et al. showed that 100 and 200 mg/kg extracts of *V. odorata* has the same sedative effects as Diazepam but the same extract at a dose level of 400 mg/kg comparing Diazepam had a significant difference. This shows that viola extract leads to more sedative effects. We can conclude that *V. odorata* extract has more sedative effects than Diazepam but it is dependent upon the dose level [53]. One of the benefits of *C. sativum* in Iranian traditional medicine is to cure headache and no side effects have been reported [54]. Hossein Delvari Kazmaie et al. compared the effects of *C. sativum* syrup on migraine with placebos. *C. sativum* syrup dramatically decreased the intensity and frequency of migraine in the intervention group in comparison with the control group [55]. Hasan Rakhshandeh et al. investigated the analgesic effects of aqueous, ethanolic and chloroformic extract of R. damascena through heating and freezing methods in mice. The results showed that the ethanolic extract of *R. damascena* has significant analgesic effects comparing to morphine [56]. The findings of this study showed that the combination of *V. odorata, R. damascena* and *C. sativum* has positive effects on patients with migraine. The benefits of taking this medicine include its availability and having no side effects. Considering the analgesic, anti-inflammatory and sedative effects of this medicinal herb, we can state that this medicine has positive effects on the quality of life of patients with migraine. One of the strengths of this study

is the use of standard questionnaires. Conversely, the short period of monitoring the treatment process is a disadvantage of our study. In this regard, we cannot decide about the long-term treatment. After four weeks of intervention, our patients were not cured.Therefore, studies with higher sample sizes and longer lifespan are highly recommended. One of the shortcomings of this study is the use of medicinal herbs or sedatives as well as anti-inflammatory and analgesic medicines if the patients comply with these mediciations. We highly recommend that further studies be performed to find the advantages and disadvantages of the combination of these medicinal herbs for longer periods on human samples.

Conflict of Interest
None.

Acknowledgement

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