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GENERAL GYNECOLOGY

Efficacy of *Crocus sativus* (saffron) in treatment of major depressive disorder associated with post-menopausal hot flashes: a double-blind, randomized, placebo-controlled trial

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Abstract

Purpose Due to concerns regarding the side effects of hormone therapy, many studies have focused on the development of non-hormonal agents for treatment of hot flashes. The aim of this study was to evaluate the efficacy and safety of saffron (stigma of *Crocus sativus*) in treatment of major depressive disorder associated with post-menopausal hot flashes.

Methods Sixty women with post-menopausal hot flashes participated in this study. The patients randomly received either saffron (30 mg/day, 15 mg twice per day) or placebo for 6 weeks. The patients were assessed using the Hot Flash-Related Daily Interference Scale (HFRDIS), Hamilton Depression Rating Scale (HDRS) and the adverse event checklist at baseline and also at the second, fourth, and sixth weeks of the study.

Results Fifty-six patients completed the trial. Baseline characteristics of the participants did not differ significantly between the two groups. General linear model repeated measures demonstrated significant effect for time × treatment interaction on the HFRDIS score [F (3, 162) = 10.41, $p = 0.0001$] and HDRS score [F (3, 162) = 5.48, $p = 0.001$]. Frequency of adverse events was not significantly different between the two groups.

Conclusions Results from this study revealed that saffron is a safe and effective treatment in improving hot flashes and depressive symptoms in post-menopausal healthy women. On the other hand, saffron, with fewer side effects, may provide a non-hormonal and alternative herbal medicine option in treatment of women with hot flashes.

Keywords *Crocus sativus* · Depression · Hot flashes · Saffron · Trial

Introduction

Hot flashes, as the most prominent vasomotor symptom of menopause, are characterized by a feeling of intense warmth throughout the upper body [1]. Hormone replacement therapy (HRT), as a treatment for hot flashes, may be unsuitable for some women including those at increased risk of cardiovascular disease, increased risk of thromboembolic disease or increased risk of some types of cancer such as breast cancer [2–4]. Due to this concern associated with hormone therapy, there is need for non-hormonal agents to alleviate hot flashes. Hence, there are different clinical trials that demonstrate the efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) in the treatment of hot flashes [5–8]. However, the most common side effects reported by using these drugs include dry month, constipation, nausea, and loss of appetite [8, 9]. On the other hand, herbal medicines can improve hot flashes. Anise (*Pimpinella anisum*), licorice (*Glycyrrhiza glabra*), soy, black cohosh, red clover, evening Primrose, flaxseed, *Salvia officinalis*, St. John's wort (*Hypericum perforatum*), and valerian are a few examples of such herbal medicines [10]. Saffron, the dried stigma of

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the plant *Crocus sativus* L., has been used as a medicinal plant in traditional medicine [11]. Three major constituents, including crocin, picrocrocin, and safranal, have been found in saffron [12]. Different clinical trials show that saffron is effective in treatment of depression [13–15]. To date, effects of saffron in treatment of hot flashes have not been studied. The aim of this study was to evaluate the efficacy and safety of saffron in treatment of major depressive disorder associated with post-menopausal hot flashes.

Materials and methods

Trial design

A 6-week, multicenter, randomized, double-blind, parallel-group clinical trial was conducted in the outpatient clinics of Arash and Baharloo Hospitals (all affiliated with Tehran University of Medical Sciences, Tehran, Iran) between March 2016 and March 2017.

The trial protocol was approved by the institutional review board (IRB) of Tehran University of Medical Science (Grant no.: 30324) and conducted consistent with the Declaration of Helsinki and its subsequent revisions. The trial was registered at the Iranian registry of clinical trials (http://www.irct.ir; registration number: IRCT201602031556N85) prior to study commencement. Written informed consent was obtained from all eligible participants and/or their legally authorized representatives. Patients were informed that they are free to withdraw from the trial at any time during the course of the study.

Participants

Post-menopausal women, with a clinical diagnosis of hot flashes were eligible to participate in the trial. Patients were post-menopausal women, over 40 years of age with no menstrual period in the last 12 months. Patients were required to have at least moderate hot flashes at time of randomization, having a score ≥ 40 in Hot Flash-Related Daily Interference Scale (HFRDIS) [16]. Patients were assessed to have major depressive disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria and mild-to-moderate depression based on a score of ≤ 22 in the 17-item Hamilton Depression Rating Scale (HDRS) [17].

Inclusion criteria were: hot flash attacks ≥ 14 times per week for at least 2 months. If history for oophorectomy was positive, more than 6 weeks should have elapsed from surgery and the level of serum FSH should be equal or more than 40 U per ml.

Exclusion criteria included: ingestion of any psychotropic and antidepressant medications, any Selective Estrogen Receptor Modulator medications (e.g., tamoxifen and raloxifen), any Aaromatase inhibitor medications (e.g., anastrozole, letrozole, and exemestane), leuprolide acetate, clonidine, gabapentin, pregabalin, amino acid supplements, over the counter (OTC) medications that reduced hot flashes during the last 4 weeks, ingestion of estrogen and progesterone based medications, history of suicidal thoughts, substance or alcohol dependence (with the exception of nicotine dependence) during the last 3 months and Electroconvulsive therapy (ECT) during the last 2 months. Patients who were suffering from any diagnoses other than depression on the DSM-IV-TR axis I were also excluded.

Interventions

Patients underwent a standard clinical assessment comprised of a psychiatric evaluation and a structured diagnostic interview and medical history. Eligible participants were randomized to receive either a saffron capsule (SaffroMood®, Green Plant Life, containing 15 mg of saffron extract) or a placebo capsule (twice daily) for 6 weeks. The saffron used in this study was donated by Green Plants of Life Co. Each capsule has 15 mg dried extract of saffron as: the plant stigma's extract was prepared as follows: 120 g of dried and milled petal was extracted via 1800 mL ethanol (80%) by percolation procedure in three steps. Subsequently, the ethanol extract was dried by evaporation in temperature between 35 and 40 °C. Each capsule had dried extract of the *C. sativus* stigma (15 mg), lactose (filler), magnesium stearate (lubricant), and sodium starch glycolate (disintegrant). Cronin value was expressed as direct reading of absorbance at about 440 nm. Each capsule had 1.65–1.75 mg crocin. Participants were not allowed to use any psychotropic drugs or receive any behavioral intervention therapy during the trial.

Outcome

The HFRDIS was used for assessment of patients at baseline and at weeks 2, 4, and 6. The HFRDIS is a ten-item scale measuring the degree to which hot flashes interfere with nine daily activities and the tenth item measures the degree to which hot flashes interfere with quality of life [16]. The HDRS contains 17 questions (on a three-point or five-point scale) which assesses severity of depressive symptoms and it was also used at baseline and at weeks 2, 4, and 6. This scale has been applied in many clinical trials in Iran [14, 17–19]. The primary outcome measure was difference in HFRDIS and HDRS score change from baseline to the end of the trial between the two groups using the general linear repeated measure model. Secondary outcome measures were comparing changes in HFRDIS and HDRS scores from baseline to each time point between the two groups, partial

response rates (25–50% reduction in the HDRS score) and complete response rates (≥ 50% reduction in HRDS score) and remission rates (HRDS score ≤ 7).

In terms of adverse events, a 25-item checklist was provided to systematically record the adverse events during the course of the trial [20, 21]. All participants were asked about any adverse event which was not mentioned in the checklist. Participants were also asked to immediately inform the research team about any unexpected symptom during the study period. A thorough physical examination was performed at the screening session and at weeks 2, 4, and 6.

Sample size estimation

Assuming a mean difference of 2 on the HDRS score between the saffron and placebo groups, with a standard deviation of 3.5 on the HDRS score, a power of 85% and a two-tailed significance level of 0.05, 50 patients (each group 25) were needed. Considering a 20% attrition rate, a final sample size of 60 was achieved.

Randomization, allocation concealment, and blinding

Generation of randomization codes was conducted via permuted randomization blocks (blocks of four, allocation ratio 1:1) by an independent party who was not involved elsewhere in the trial. Concealment of allocation was performed using sequentially numbered, sealed opaque envelopes. An aluminum foil inside the envelopes kept them impermeable to intense light. Study participant, investigator, and rater were all blinded to treatment allocation. Saffron and placebo capsules were indistinguishable in their shape, size, texture, color and odor.

Statistical analyses

The Statistical Package of Social Science Software (SPSS version 22; IBM Company, USA) was used for statistical analysis and SigmaPlot 12.2.0 (SYSTAT Software, Incorporated) for drawings. Continuous variables were reported as mean ± standard deviation (SD) and categorical variables were reported as frequency (percentage). The independent *t* test was used to compare baseline continuous variables. Mean difference between the saffron and the placebo group was reported as mean difference [MD, 95% confidence interval (CI)]. A general linear model repeated measure was used to evaluate time × treatment interaction considering the treatment group (saffron vs. placebo) as the between subject factor and the study measurement as the within subject factor (time). Whenever Mauchly's test of sphericity was significant, Greenhouse–Geisser adjustment was used for degrees of freedom. To compare the score change from baseline between the two groups, the independent *t* test and Cohen's *d* effect size were used. Categorical variables were compared using the Chi square or Fisher's exact test where appropriate. All analyses were performed two-sided, and a *p* value of less than 0.05 was considered statistically significant.

Results

Patients

Among 74 patients who were screened for the eligibility criteria, 60 patients entered the trial and were randomized to receive either saffron ($n = 30$) or placebo ($n = 30$). Four patients discontinued the trial (2 patients in each group at week 1) and a total number of 56 patients (28 patients in each group) completed the trial (Fig. 1). Baseline characteristics of the participants did not differ significantly between the two groups (Table 1).

Outcomes

The HFRDIS score

Baseline HFRDIS scores were not significantly different between the saffron and the placebo groups [MD (95% CI) = 3.21 (− 7.41 to 13.84), $t(54) = 0.60$, $p = 0.54$] (Table 1). General linear model repeated measures demonstrated significant effect for time × treatment interaction on the HFRDIS score [$F(3, 162) = 10.41$, $p = 0.000$] (Fig. 2). An independent *t* test demonstrated significantly greater reduction in HFRDIS

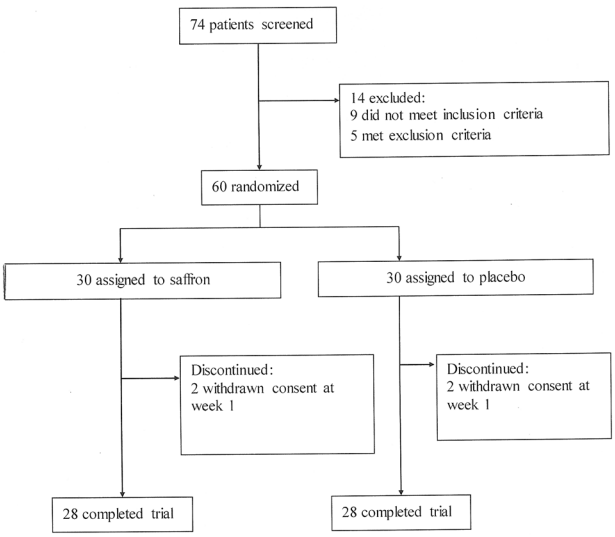

Fig. 1 Flow diagram of the study

Table 1 Baseline characteristics of the patients

Variable	Saffron group ($n = 28$)	Placebo group ($n = 28$)	p value
Age, years, mean ± SD	55.71 ± 6.57	55.43 ± 5.46	0.86
Duration of the disease (months), mean ± SD	32.92 ± 25.74	29.64 ± 20.89	0.60
Presence of seasonal pattern	8 (28.6%)	10 (35.7%)	0.56
History of psychiatry disorder	9 (32.1%)	8 (28.5%)	Non significant
Education			
Illiterate	5 (17.9%)	13 (46.4%)	Non significant
Primary	10 (35.7%)	3 (10.7%)	
Secondary	8 (28.6%)	7 (25.0%)	
High school and diploma	5 (17.9%)	5 (17.9%)	
Higher	0 (0%)	0 (0%)	
Job			
House maker	25 (89.3%)	22 (78.6%)	Non significant
Clerk	3 (10.7%)	6 (21.4%)	
Marital status			
Married	27 (96.4%)	28 (100.0%)	Non significant
Single	0 (0%)	0 (0%)	
Separated	0 (0%)	0 (0%)	
Widow	1 (3.6%)	0 (0%)	
Baseline HFRDIS score, mean ± SD	69.29 ± 20.53	66.07 ± 19.11	0.54
Baseline HDRS score, mean ± SD	15.29 ± 6.05	15.96 ± 4.26	0.63

HFRDIS Hot Flash-Related Daily Interference Scale, *HDRS* Hamilton Depression Rating Scale

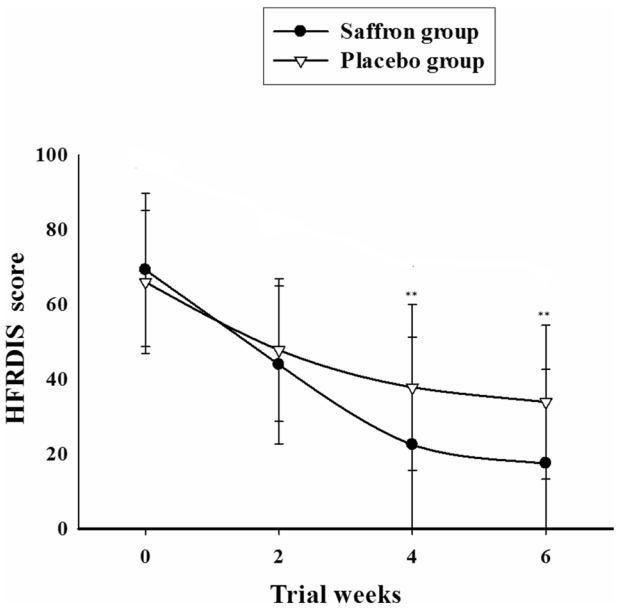

Fig. 2 Comparison of mean ± SD of the Hot Flash-Related Daily Interference Scale (HFRDIS) scores at baseline and post-intervention with saffron or placebo over time. $^{**}p \leq 0.01$

score in the saffron group than the placebo group at weeks 2, 4, and 6 (Table 2).

The HDRS score

Baseline HDRS scores were not significantly different between the saffron and the placebo groups [MD (95% CI) = − 0.67 (− 3.49 to 2.13), $t(48.49) = -0.48$, $p = 0.63$] (Table 1). General linear model repeated measures demonstrated significant effect for time × treatment interaction on the HDRS score [$F(3, 162) = 5.48$, $p = 0.001$] (Fig. 3). An independent t test demonstrated significantly greater reduction in HDRS score in the saffron group than the placebo group at weeks 2, 4, and 6 (Table 2). There was significant difference between the two groups in terms of complete response rate at weeks 4 and 6, and remission rate at weeks 2, 4, and 6 (Table 3).

Side effects

Frequency of adverse events was not significantly different between the two groups (Table 4). No serious adverse event or death occurred.

Table 2 Comparison of changes in Hot Flash-Related Daily Interference Scale (HFRDIS) and Hamilton Depression Rating Scale (HDRS) scores from baseline between the two groups

	Saffron group ($n = 28$)	Placebo group ($n = 28$)	Mean difference saffron–placebo (95% CI)	Cohen's d	p value
HFRDIS (week 2)	25.35 ± 9.61	18.21 ± 9.44	7.14 (2.03–12.25)	0.74	0.007
HFRDIS (week 4)	46.78 ± 17.43	28.21 ± 18.86	18.57 (8.83–28.30)	1.02	0.001
HFRDIS (week 6)	51.78 ± 19.25	32.14 ± 20.43	19.64 (9.00–30.28)	0.98	0.001
HDRS (week 2)	3.39 ± 1.72	2.42 ± 1.70	0.96 (0.04–1.88)	0.56	0.04
HDRS (week 4)	5.17 ± 2.68	3.64 ± 2.07	1.53 (0.25–2.82)	0.63	0.02
HDRS (week 6)	7.10 ± 4.38	4.39 ± 2.64	2.71 (0.76–4.66)	0.74	0.007

HFRDIS Hot Flash-Related Daily Interference Scale, *HDRS* Hamilton Depression Rating Scale

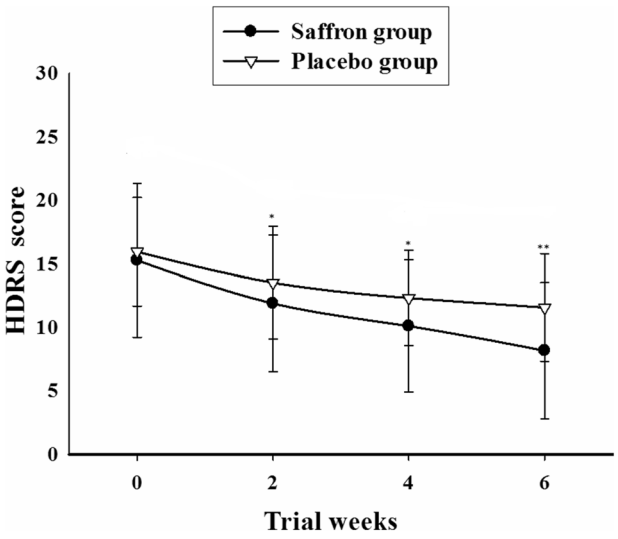

Fig. 3 Comparison of mean ± SD of Hamilton Depression Rating Scale (HDRS) for Depression scores at baseline and post-intervention with saffron or placebo. *$p \leq 0.05$ and **$p \leq 0.01$

Discussion

To the best of our knowledge, this study was the first double-blind clinical trial to evaluate the efficacy and safety of saffron in the treatment of women with post-menopausal hot flashes. The findings in this study indicate that saffron provides a non-hormonal option that is both effective and safe in alleviating hot flashes after 6 weeks of treatment (15 mg, two capsules per day).

The pathophysiology of hot flashes still remains unclear. Hot flashes have been suggested to be the result of central thermoregulatory center dysfunction caused by changes in estrogen levels during the menopausal period [22]. The decrease in estrogen levels alone is not adequate to describe the pathophysiology of hot flashes. Central sympathetic activation through central α_2-adrenergic receptors is also elevated in symptomatic women that decrease the thermoneutral zone. Hot flashes are triggered by elevations in core body temperature acting within this narrowed thermoneutral zone [23].

Clonidine decreases central sympathetic activation, widens the thermoneutral zone, and improves hot flashes [24]. Hormonal replacement therapy (HRT), especially estrogen therapy, is the most effective therapy for alleviating

Table 3 Comparison of outcome indexes in depression between the two groups

Outcome	Saffron group	Placebo group	p value	Power	Odd's ratio (95% CI)
Number (%) of partial responders at week 2	11 (39.3%)	4 (14.3%)	0.03	0.43	3.88 (1.05–14.27)
Number (%) of partial responders at week 4	14 (50.0%)	11(39.3%)	0.42	0.07	1.54 (0.53–4.46)
Number (%) of partial responders at week 6	11 (39.3%)	9 (32.1%)	0.57	0.04	1.36 (0.45–4.09)
Number (%) of complete responders at week 2	2 (7.1%)	1 (3.6%)	1.00	0.02	2.07 (0.17–24.31)
Number (%) of complete responders at week 4	7 (25.0%)	1 (3.6%)	0.05	0.47	9.00 (1.02–78.94)
Number (%) of complete responders at week 6	13 (46.4%)	5 (17.9%)	0.02	0.51	3.98 (1.17–13.49)
Number (%) of remitters at week 2	8 (28.6%)	1 (3.6%)	0.02	0.59	10.80 (1.24–93.44)
Number (%) of remitters at week 4	8 (28.6%)	1 (3.6%)	0.02	0.59	10.80 (1.24–93.44)
Number (%) of remitters at week 6	15 (53.6%)	4 (14.3%)	0.002	0.82	6.92 (1.90–25.22)

Table 4 Frequency of adverse events in the two groups

Adverse event	Saffron group ($n = 28$)	Placebo group ($n = 28$)	p value
Headache, n, %	2 (7.1)	1 (3.6)	1.00
Dry mouth, n, %	3 (10.7)	2 (7.1)	1.00
Nausea, n, %	3 (10.7)	1 (3.6)	0.61
Daytime drowsiness, n, %	2 (7.1)	2 (7.1)	1.00
Constipation, n, %	3 (10.7)	2 (7.1)	1.00
Sweating, n, %	2 (7.1)	1 (3.6)	1.00

menopausal vasomotor symptoms, including hot flashes [25]. The risks of hormonal therapy were assessed in different studies. Holmberg et al. reported that after extended follow-up, the risk of new breast cancer was significantly increased in survivors who took hormone replacement therapy. They reported that the cumulative incidence at 5 years was 22.2% in the hormone replacement therapy group vs. 8.0% in the control group [3]. A daily dose of 0.1 mg of clonidine is effective in treatment of hot flashes in postmenopausal women with breast cancer [26]. Manson et al. provides a comprehensive report of findings from the intervention and extended post-intervention phases of the conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) and CEE alone trials of the Women's health initiative (WHI).

They reported that women assigned to CEE plus MPA had a hazard ratio (HR) of 1.24 (95% CI 1.01–1.53) for breast cancer compared to the placebo group and the HRs progressively increased by time since randomization ($p = 0.005$ for time trend). In contrast, woman assigned to CEE alone had a HR of 0.79 (95% CI 0.61–1.02) in comparison with the placebo group [2].

During the cumulative 13-year follow-up, the HRs for coronary heart disease (CHD) were 1.09 (95% CI 0.96–1.24) for CEE plus MPA and 0.94 (95% CI 0.82–1.09) for CEE alone in comparison with the placebo group [2].

Another randomized trial showed that the rate of breast cancer and other cancer was not increased, although they suggested a longer follow-up to make definite conclusions [27].

The efficacy of SSRIs and SNRIs has been proven in randomized clinical trials. A prospective randomized clinical trial showed that paroxetine in doses of 10 and 20 mg reduced frequency and composite score of hot flashes in comparison to the placebo group [6]. Davari-Taha et al. reported that venlafaxine and citalopram significantly decreased the severity of hot flashes in comparison with the placebo group ($p = 0.02$) and the frequency of hot flashes were reduced more by citalopram than venlafaxine ($p = 0.03$) [8].

The mechanism of SSRI action in the treatment of hot flashes is not known. Bioinformatics analyses indicated that the minor allele of rs1042173 seems to disrupt a binding site for a microRNA. This disruption leads to higher expression of SLC6A4 (a gene encoding the serotonin and/or norepinephrine transporters). Higher expression of SLC6A4 leads to depletion of serotonin in synaptic clefts, and this triggers the presynaptic auto receptor feedback mechanism to produce more serotonin, which is protective against hot flashes [28]. It seems decline in brain 5-hydroxytryptamine (5-HT) should worsen hot flashes [29].

In the present study, we focused on the possible serotonergic effects of saffron. The findings of the present study are consistent with our previous clinical trials supporting the antidepressant effect of saffron [17–19, 30]. These effects are due to serotonergic, antioxidant, anti-inflammatory, neuroendocrine and neuroprotective effects [31]. According to the rat model studies, antidepressant effects of saffron may be as a result of increase in the levels of brain-derived neurotrophic factor (BDNF), VGF Neuropeptide, Cyclic-AMP Response Element Binding Protein (CREB) and phospho-CREB (p-CREB) in rat hippocampus [32, 33]. Wang et al. showed that oral administration of *C. sativus* significantly decreased the immobility time in comparison with the control group in the tail suspension test (TST) in mice [34].

The findings of another clinical trial showed that antidepressant effects of saffron extract are attributed to crocin [13].

Limitations of the present study include the small number of participants and the short period of follow-up. Further research in this area with a longer study period, an active agent such as venlafaxine and a higher sample size to consider patients with different biological and racial backgrounds is needed.

Conclusions

The results of this study emphasize the efficacy and safety of saffron in the treatment of post-menopausal hot flashes and depression. In addition, our study shows that saffron does not have any serious adverse effects in therapeutic doses and provides evidence that saffron is as safe and as effective as any alternative treatment in management of hot flashes.

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Author contributions LK and SA, principal investigator and data Management from March 2016 to March 2017, SE, FE, HS and EMZ, data collection and manuscript writing from March 2016 to March 2017; SS, TF and FE, data collection and data management from March 2016 to March 2017

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the current study were approved by the institutional review board of Tehran University of Medical Sciences (Approval number: 30324) and were in accordance with the 1964 Helsinki declaration and its later amendments in Brazil, 2013.

Informed consent Informed consent was obtained from all individual participants included in the study.

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