International Journal of Epidemiologic Research
doi:10.34172/ijer.2020.23 2020 Summer;7(3):129-135 http://ijer.skums.ac.ir

Original Article

Effects of Pomegranate Peel Extract and Vitamin E on Quality of Life in Hemodialysis Patients: A Randomized Placebo-Controlled Clinical Trial

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Received: 7 May 2020
Accepted: 10 Aug. 2020
ePublished: 28 Sep. 2020

Abstract

Background and aims: Quality of life (QOL) is poor in hemodialysis (HD) patients. High oxidative stress and inflammatory conditions disturb their normal physiological, emotional, and physical functions. This study aimed to assess the effects of pomegranate peel extract (PPE) alone and in combination with vitamin E (Vit E) as anti-oxidant and anti-inflammatory substances on QOL of HD patients using Short-form 36 (SF-36) QOL questionnaire.

Methods: This study was a double-blinded, placebo-controlled randomized clinical trial on HD patients. A total of 100 HD patients were randomly divided into 4 equal groups as follows: Pom+Vit E group, which received 2 PPE tablets + 1 Vit E soft gel daily, Pom group, which received 2 PPE tablets+1 Vit E placebo soft gel daily, Vit E group, which received 1 Vit E soft gel+2 PPE placebo tablets daily, and Placebo group, which received 2 PPE placebo tablets + 1 Vit E placebo soft gel daily. The intervention duration was 8 weeks. The stratified block randomization method based on sex, age, HD duration, and employment status was used for randomization.

Results: The mean age of participants ranged between 51 and 57 years with an HD duration of 9-11.2 months. Bodily pain score and general health score significantly increased in the Pom group and Pom+Vit E group. The emotional role functioning score of the Pom+Vit E group was significantly higher than that of the placebo group ($P<0.05$).

Conclusion: The consumption of PPE and Vit E had beneficial effects on mental components but not the physical components of QOL. Moreover, combination therapy was more effective than single therapy.

Keywords: Hemodialysis, Pomegranate, Vitamin E, Quality of life, Clinical trial

Introduction

Hemodialysis (HD) improves the survival of patients with end-stage renal failure. Many of these patients, who were previously threatened with death, experience a relatively normal life with HD procedure later and are more or less able to perform their personal tasks. However, health-related outcomes can still be poor in HD patients. Their morbidity and mortality rate are higher compared to the general population.[1] Studies have shown that the quality of life (QOL) is poor in HD patient population.[1,2] In addition to the chronic nature of underlying kidney disorder which influences physical, emotional, and social abilities of HD patients, higher incidence of cardiovascular events also affects their general health status.[2] It has been reported that HD patients are in high levels of oxidative stress and chronic inflammatory status.[3] Clinical trials have shown that the consumption of anti-inflammatory agents or antioxidants in patients with chronic disorders not only ameliorates the inflammation but also improves the health status and QOL of these patients.[4,5]

Fruits are good sources of polyphenols, tannins, and carotenoids which are known as powerful antioxidants. Pomegranate (*Punica granatum* L.), a valuable source of polyphenols and anthocyanins, is shown to have beneficial effects on human health and reduce the risk of chronic diseases like diabetes, atherosclerosis, and malignancies.[6] Recently, researchers tend to use natural antioxidants in HD patients in order to improve their health status. Pomegranate peel is the thin interior layer of the fruit that covers the pomegranate seeds. It is the richest source of flavonoids and tannins in this fruit which is characterized as a powerful natural antioxidant and anti-inflammatory substance.[7] Vitamin E (Vit E) is also a well-known antioxidant and anti-inflammatory drug.[8] The beneficial effects of single therapy with pomegranate or Vit E for HD patients have been studied before.[9,10] We hypothesized

that the consumption of pomegranate and vitamin E may have beneficial effects on the health status of HD subjects. This study aimed to assess the effects of pomegranate peel extract (PPE) alone or in combination with Vit E on QOL of HD patients.

Materials and Methods

Patient Selection

This study was a double-blinded, placebo-controlled randomized clinical trial which assessed the effects of PPE and Vit E on the health status of HD patients referred to HD centers in Chaharmahal-va-Bakhtiari province, Iran. Regarding one of the oxidative stress markers (malondialdehyde) as a key variable in this project, 17 subjects were needed in each group. We enrolled 25 subjects in each group. The inclusion criteria were as follows: HD duration ≥3 months and 3 times a week, not having any disorders or using medicines that interfere with our intervention like liver diseases, and not using antioxidant and anti-inflammatory drugs. During the intervention, we excluded the participants who could not tolerate the medicines or change their dietary patterns.

Randomization, Blinding, and Study Design

Group allocation was performed by stratified block randomization based on sex, age, HD duration, and employment status using Random Allocation software. The random sequence was generated by someone who was not involved in the intervention. Subjects were divided into 4 equal groups as follows: Pom + Vit E group, which received 2 PPE tablets + 1 Vit E soft gel daily, Pom group, which received 2 PPE tablets + 1 Vit E placebo soft gel daily, Vit E group, which received 1 Vit E soft gel + 2 PPE placebo tablets daily, and placebo group, which received 2 PPE placebo tablets + 1 Vit E placebo soft gel daily. Participants and investigators were blinded to the randomization, group allocation, and content of the intervention. The allocation was concealed until the end of the study. The intervention duration was 8 weeks.

Drug Preparation

Pomegranate tablets (225 mg PPE) were obtained from Amin Pharmaceutical Company, Iran, and Vit E 400 IU soft gels (dL-Alpha-Tocopheryl Acetate) were purchased from Zahravi Pharmaceutical Company, Iran. The placebos were also prepared by the same companies and were identical with the main drugs in size, shape, color, and packaging. The drugs were coded with sequential numbers by someone not involved in the intervention. The patients used the tablets after dialysis.

QOL Assessment

The QOL was assessed by widely used Short-form 36 (SF-36) QOL Questionnaire. The SF-36 questionnaire is a standard method designed by Ware et al. for evaluation of the QOL in patients and healthy subjects.[11] It has 36 questions, which assess the QOL in 8 domains of vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. For each question, there are a minimum of 2 and a maximum of 6 options to answer. The options are graded from 0 to 100, which show the lowest and the highest levels of performance, respectively. The final score of each option is the sum of the scores for each of the questions in that option divided by the number of the questions. Therefore, the final score of each domain ranges from 0 (the lowest score) to 100 (the highest score). The scores range from 0–49, 50–74, and ≥75, which are considered as poor, relatively favorable, and favorable, respectively. This questionnaire can also be summarized in 2 components: the physical component scale (including physical functioning and physical role functioning domains) and the mental component scale (including the other domains). The acceptable reliability of the questionnaire for HD patients was previously assessed.[12,13] The validated Persian version of SF-36 QOL questionnaire was used in this study.[14] The QOL questionnaires were completed by 2 persons who were not aware of group allocation and the content of the intervention. Demographic data and the duration of HD were collected from the participants.

Statistical Analysis

Quantitative data were represented as mean ± SD while qualitative data were expressed as numbers and percentages. Normality of variables was examined by Kolmogorov-Smirnov test and Q-Q plot (Table 1). Within-group changes from baseline were assessed by analysis of paired samples *t* test. Pearson's chi-square test was used to compare categorical variables. Multivariate analysis of covariance (MANCOVA) was used to show between-group differences after adjusting the baseline variables, age, and dialysis duration. Analyses were performed by SPSS version 20.0. A *P* value ≤0.050 was considered statistically significant.

Results

At first, 120 HD patients were evaluated. According to the inclusion criteria, 100 HD patients were selected for the study and randomly divided into 4 equal groups. Demographic data and baseline characteristic variables of participants are shown in Table 2. There were no statistically significant differences in age, sex, body mass index (BMI), and other baseline variables between the groups. During the 8-week intervention, 3 subjects were excluded from the study (one person died in the second week, one withdrew, and one person changed the treatment) and 97 participants completed the study. The CONSORT flow diagram of the study is shown in Figure 1. Except for the score of emotional role functioning that

Table 1. Results of Kolmogorov-Smirnov Test

QOL Domain	Intervention Groups							
	Placebo[a]		Pom[b]		Vit E[c]		Pom + Vit E[d]	
	Z	*P*-value[e]	Z	*P*-value[e]	Z	*P*-value[e]	Z	*P*-value[e]
Vitality	0.793	0.907	0.543	0.153	0.111	0.788	0.444	0.899
Physical functioning	0.554	0.123	0.556	0.276	0.836	0.855	0.856	0.133
Bodily pain	0.765	0.453	0.135	0.356	0.323	0.464	0.999	0.777
General health perceptions	0.738	0.456	0.764	0.666	0.333	0.855	0.453	0.677
Physical role functioning	0.346	0.738	0.455	0.203	0.888	0.693	0.323	0.870
Emotional role functioning	0.523	0.273	0.957	0.744	0.489	0.243	0.522	0.168
Social role functioning	0.759	0.254	0.777	0.229	0.854	0.677	0.434	0.155
Mental health	0.240	0.530	0.486	0.932	0.456	0.753	0.512	0.240

Data shows the results of Z and *P* value of each variable in K-S test.
[a] Received 3 placebo pills.
[b] Received 2 pomegranate peel extract (PPE) tablets +1 vitamin E (Vit E) placebo.
[c] Received 1 Vit E + 2 PPE placebo.
[d] Received 2 PPE tablets + 1 Vit E.
[e] Obtained from K-S test, showing normal distribution of variables.

Table 2. Baseline Characteristics of Participants

Variable	Intervention Group				*P*-value[e]
	Placebo[a]	Pom[b]	Vit E[c]	Pom + Vit E[d]	
Age (year)	56.45 ± 16.14	57.50 ± 17.02	52.04 ± 16.94	51.16 ± 12.92	0.285
Gender (female/male)	12/12	14/11	13/11	10/14	0.933
BMI (kg/m^2)	23.08 ± 3.90	23.58 ± 3.16	23.40 ± 3.17	24.63 ± 3.38	0.430
HD duration (month)	11.00 ± 6.74	9.33 ± 5.34	11.21 ± 7.44	10.83 ± 6.00	0.765
Marital status (married/single)	23/1	25/0	24/0	23/1	0.816
Urban/rural	6/18	6/19	5/19	6/18	0.509
Employment status (employed/unemployed)	9/15	12/13	11/13	12/12	0.322
Insurance status (yes/no)	24/0	24/1	23/1	24	0.750

Data are expressed as mean ± SD.
[a] Received 3 placebo pills.
[b] Received 2 pomegranate peel extract (PPE) tablets +1 vitamin E (Vit E) placebo.
[c] Received 1 Vit E + 2 PPE placebo.
[d] Received 2 PPE tablets + 1 Vit E.
[e] Obtained from ANOVA.

was relatively favorable (>50), the rest of pre-intervention QOL scores of HD patients were poor (<50 in most of the domains), which represented that the participants were not in a good condition. The baseline scores of QOL are shown in Table 3.

Effect of Interventions on Vitality

After 8-week interventions, the vitality score significantly increased in Pom + Vit E group while it did not significantly change in the other groups. Results of the MANCOVA test revealed that there were no significant differences between the groups in the vitality domain after the interventions (Table 3).

Effect of Interventions on Physical Functioning

Results of the paired samples *t*-test showed that physical functioning scores did not significantly change in the groups after the intervention. Results of the MANCOVA test showed that 8-week interventions could not significantly increase the physical functioning score of the patients (Table 3).

Effect of Interventions on Bodily Pain

Bodily pain score significantly increased in the Pom group and Pom + Vit E group, while it decreased in the placebo group compared to the baseline. Comparison of between-group differences (MANCOVA test) revealed that our interventions significantly altered the bodily pain scores (Table 3). Post hoc analyses demonstrated that a significant difference was found between Pom + Vit E and placebo groups (MANCOVA test, post hoc analyses, $P < 0.01$).

Effect of Interventions on General Health Perception

Results of paired *t* test revealed that after 8-week interventions, the score of general health perception significantly decreased in the placebo group while it increased in the other groups and its increase was more considerable in the Pom + Vit E group. There was also

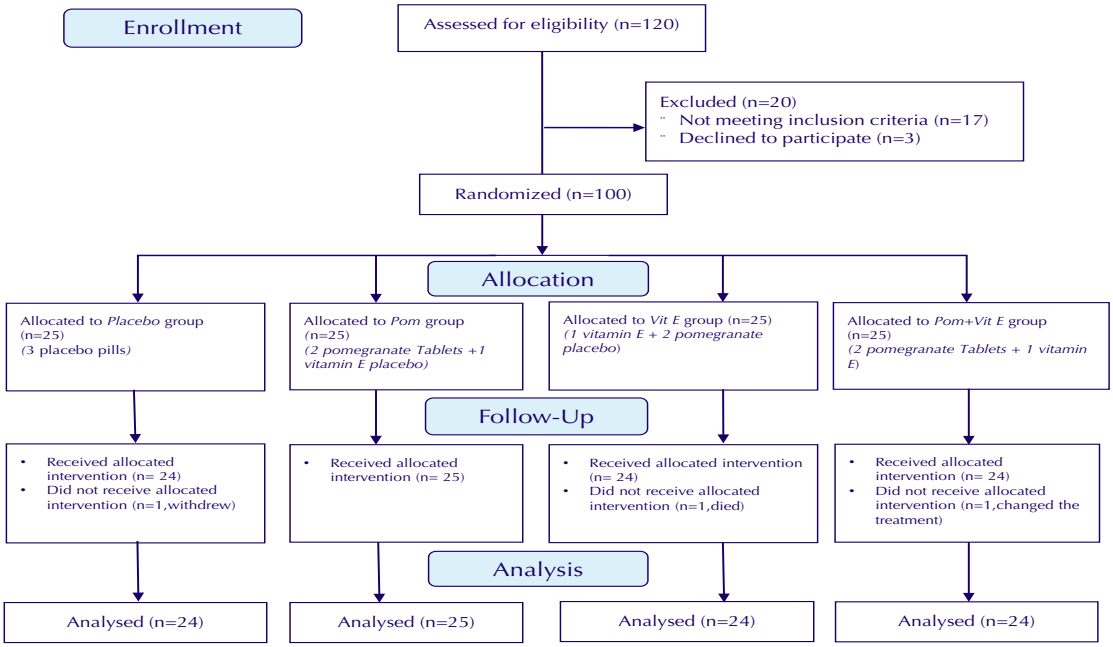

Figure 1. CONSORT Flow Diagram of Study Design

a significant between-group difference according to MANCOVA tests (Table 3), and based on post hoc analyses, all the scores were significantly higher in intervention groups compared to the placebo group (MANCOVA test, post hoc analyses, $P<0.05$).

Effect of Interventions on Physical Role Functioning

Eight-week interventions did not significantly change the scores of physical role functioning. Results of the MANCOVA test also revealed that there was no significant between-group difference in this domain after the interventions (Table 3).

Effect of Interventions on Emotional role Functioning

Table 3 shows that the interventions did not significantly change the scores of emotional role functioning after 8 weeks, while the MANCOVA test indicated a significant difference in post-intervention scores among the groups (Table 3). Results of post hoc analyses showed that this score was significantly higher in Pom + Vit E group than in the placebo group (MANCOVA test, post hoc analyses, $P<0.050$).

Effect of Interventions on Social Role Functioning

Our interventions did not significantly change the scores of social role functioning. The MANCOVA test also indicated that there were no significant differences between the groups in post-intervention scores of this domain (Table 3).

Effect of Interventions on Mental Health

As shown in Table 3, the score of mental health significantly increased in the Pom group while it did not significantly change in the other groups. Results of the MANCOVA test showed that our intervention significantly altered the post-intervention scores (Table 3). Post hoc analyses revealed that the mental health score was significantly higher in Pom + Vit E group compared to the placebo group (MANCOVA test, post hoc analyses, $P<0.050$).

The Overall Effects of Interventions on the Physical Component Scale and Mental Component Scale

Our 8-week interventions did not significantly change the physical component scale, while they significantly changed the scores of the mental component scale (Table 4). Results of the post hoc analyses represented that mental component scale significantly increased in the Pom + Vit E, Pom, and Vit E groups compared to the placebo group after the interventions (Figure 2), while there were no significant differences in the physical component scale among the groups (Figure 3).

Discussion

Our study indicated that the consumption of PPE alone or in combination with Vit E did not improve the physical-related domains, while it significantly ameliorated the mental-related domains of QOL in HD subjects. Few studies have evaluated the QOL scores in HD patients and reported poor QOL in these patients.[12-16] Ibrahim and El Salamony evaluated 60 HD patients in Egypt and reported that their QOL scores were poor (<50 score in all domains). They also found that the high prevalence of depression in these patients was associated with poor QOL.[16] Gencer et al studied 109 HD subjects in Turkey. They reported poor QOL status in these patients, which was related to high malnutrition status. [17]

Table 3. Quality of Life (QOL) Scores of Hemodialysis Participants Before and after 8 weeks of Intervention

QOL domain	Intervention Groups												Between Group *P* value[f] (Before)	Between Group *P* value[g] (After)
	Placebo[a]			Pom[b]			Vit E[c]			Pom + Vit E[d]				
	Before	After	*P*-value[e]	Before	After	*P*-value[e]	Before	After	*P*-value[e]	Before	After	*P*-value[e]		
Vitality	44.8±20.6	44.9±17.7[x]	0.907	43.1±13.9	45.3±13.0[x]	0.113	47.9±19.5	49.2±16.6[x]	0.288	44.5±14.0	47.7±13.0[x]	<0.001	0.791	0.727
Physical functioning	44.0±21.1	46.0±17.6[x]	0.738	41.9±14.1	46.7±13.3[x]	0.226	46.0±19.9	44.8±20.6[x]	0.856	39.8±10.9	46.1±13.6[x]	0.100	0.623	0.981
Bodily pain	42.8±25.2	39.3±23.5[x]	0.030	39.4±11.2	48.4±17.3[xy]	<0.01	45.6±17.4	53.0±18.4[xy]	0.064	47.5±20.4	59.9±19.5[y]	<0.001	0.468	<0.01
General health perceptions	40.4±16.8	36.5±15.7[x]	0.013	45.0±14.0	53.4±16.5[y]	<0.01	50.0±22.3	53.9±22.7[y]	<0.01	47.0±13.5	54.3±12.1[y]	<0.001	0.255	0.001
Physical role functioning	46.0±17.6	44.0±21.1[x]	0.738	46.9±13.2	42.0±14.1[x]	0.203	44.8±20.6	47.4±20.4[x]	0.693	46.7±13.3	39.9±10.9[x]	0.070	0.968	0.461
Emotional role functioning	54.3±12.1	42.7±18.1[x]	0.075	53.4±16.5	50.4±14.9[xy]	0.288	54.6±21.6	53.1±21.5[xy]	0.267	54.3±12.1	58.9±19.8[y]	0.160	0.118	0.031
Social role functioning	44.0±22.1	44.3±16.8[x]	0.636	41.9±14.0	46.6±13.3[x]	0.229	46.0±19.9	42.7±18.3[x]	0.607	39.8±10.9	46.0±13.7[x]	0.106	0.640	0.795
Mental health	42.8±25.2	46.8±18.0[x]	0.240	39.4±11.2	46.5±17.3[xy]	<0.01	45.5±17.4	49.1±18.2[xy]	0.063	47.5±20.47	53.0±23.4[y]	0.240	0.471	0.048

Data are expressed as mean ± SD.
[a] Received 3 placebo pills.
[b] Received 2 pomegranate peel extract (PPE) tablets +1 vitamin E (Vit E) placebo.
[c] Received 1 Vit E + 2 PPE placebo.
[d] Received 2 PPE tablets + 1 Vit E.
[e] Obtained from paired *t*-test, showing within group changes.
[f] Obtained from ANOVA.
[g] Obtained from MANOVA.
[x,y] Post-intervention values with different superscript letters are significantly different among the groups ($P<0.05$).

Table 4. Overall Effects of Interventions on Quality of Life (QOL) Scales

QOL scale	Intervention Groups				Between Groups *P*-value[e]
	Placebo[a]	Pom[b]	Vit E[c]	Pom + Vit E[d]	
Physical component	45.0 ± 13.0	44.3 ± 9.6	46.1 ± 12.5	43.0 ± 8.1	0.246
Emotional component	41.2 ± 9.7	48.4 ± 8.1	50.1 ± 10.2	53.0 ± 10.4	<0.001

Data are expressed as mean ± SD.
[a] Received 3 placebo pills.
[b] Received 2 pomegranate peel extract (PPE) tablets +1 vitamin E (Vit E) placebo.
[c] Received 1 Vit E + 2 PPE placebo.
[d] Received 2 PPE tablets + 1 Vit E.
[e] Obtained from MANOVA.

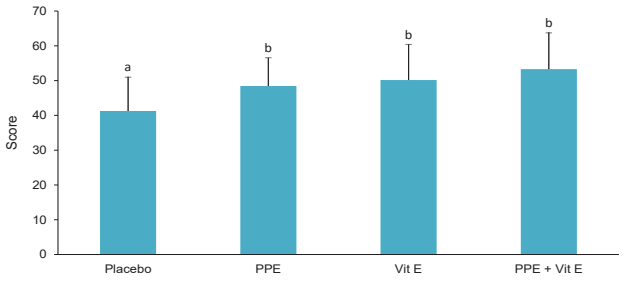

Figure 2. The Overall Effects of Pomegranate Peel Extract (PPE) and Vitamin E (Vit E) on Mental Component Scale. Means ± SD with different letters are significantly different ($P<0.001$).

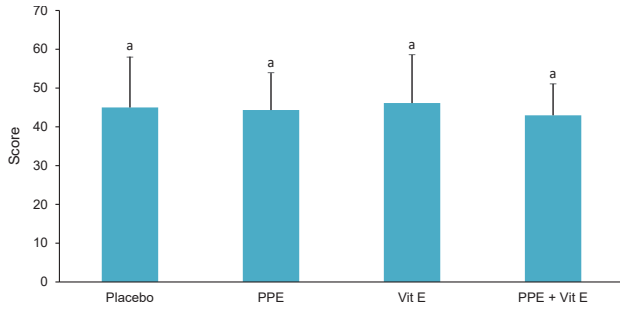

Figure 3. The Overall Effects of Pomegranate Peel Extract (PPE) and Vitamin E (Vit E) on Physical Component Scale. Means ± SD with the same letter are not significantly different ($P > 0.05$).

Oxidative stress is characterized by an imbalance between the body antioxidant defense and the accumulation of oxidative products such as reactive oxygen and nitrogen species.[18] In this situation, oxidative molecules trigger the oxidation of the biological substance and molecules such as carbohydrates, proteins, nucleic acids, and lipids and, therefore, destroy the physiological functions of the organism.[19] Oxidative stress is almost always associated with chronic inflammation. Inflammation is a vital physiologic response of organisms against pathogens and life-threatening factors. In some conditions, this response is prolonged and destructive, and high levels of inflammatory markers in addition to oxidative products promote disorders such as chronic kidney disease.[4,20,21] The number of patients with chronic renal failure is increasing worldwide. HD is a way to compensate for the loss of kidney function and increases the patients' survival. HD patients also have high levels of inflammation and oxidative stress, which affect their health status. High serum levels of free radicals, reactive oxygen species, as well as inflammatory markers are associated with a reduction in mental health and physical functions.[22,23]

Due to the valuable antioxidative capacity of pomegranate, many studies have used this fruit and its extracts in order to improve the health status of patients with chronic or metabolic disorders.[7,24,25] It seems that the improvement of antioxidative defense and reduction of the inflammation in HD patients ameliorate their health status, thereby improving their QOL score. As it was revealed in this study, the consumption of antioxidant and anti-inflammatory substances (PPE alone or in combination with vitamin E) for 8 weeks ameliorated the domain of mental health, especially when the participants used both PPE and vitamin E. It can be concluded that the combination of PPE and Vit E strengthens the antioxidative and anti-inflammatory properties of each other. To our knowledge, this is the first study that evaluated the effects of antioxidants and anti-inflammatory drugs on QOL in HD patients. Considering the health conditions of our participants, we were not able to have a longer intervention period and this can be a limitation of this study.

Conclusion

The current study revealed that the consumption of PPE and Vit E had beneficial effects on the mental components of QOL in HD patients. We also concluded that combination therapy has more benefits compared to single therapy. We suggest further studies in this field with longer period of intervention as well as evaluation of other antioxidant and anti-inflammatory drugs.

Conflict of Interest Disclosures

None of the authors have any personal or financial conflict of interests.

Ethical Approval

Human rights were fully respected according to the Helsinki declaration 1975 and its revision (1983). The study protocol was approved by the Ethics Committee of Shahrekord University of Medical Sciences (IR.SKUMS.REC.1395.235). It was also registered at the Iranian Registry of Clinical Trial (identifier: IRCT20180816040814N1; https://irct.ir/trial/33944) with the approval date of December 5, 2016. An informed consent form was filled

out by all participants.

Authors' Contribution

TJ designed the study and conducted the project. TJ and LM helped in drafting. MB and MS contributed to data collection, screening, and sampling. TJ, LM, MB, and MS supervised the participants, and AAF prepared the drugs and placebos. TJ and AAF contributed to the statistical analyses, data interpretation, and manuscript writing. All of the authors approved the submitted manuscript.

Acknowledgements

This study was financially supported by Vice Chancellor for Research, Shahrekord University of Medical Sciences, Shahrekord, Iran (1395-01-75-3111). The authors would like to express their thanks to Medical Plant Research Center for approving the project and Mr. Aman A. Jafari for editing the manuscript.

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