

The effects of n-3 fatty acids and *Rosa damascena* extract on primary dysmenorrhea

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Summary. *Background:* Primary dysmenorrhea is painful contractions of the lower abdomen without abnormal pelvic pathology. *Aims:* Because high prevalence of dysmenorrhea and its effects on women's social activities, the purpose of this study was to investigate the effects of separate and concurrent supplementation of n-3 fatty acid and Rosa damascene extract (RDE) on primary dysmenorrhea complaints. *Study design:* Double blind clinical trial. *Methods:* In this study, 120 university students were randomly allocated with equal size into two groups [Fish oil (FO) Factor groups: one with one-gram soft gel capsule of fish oil (60) and other without it (60)], then each group was randomly allocated with equal size into two groups (RDE Factor groups: one with one-gram capsules of RDE (30) and other without it (30)), for 2 months. And all data was measured three times in these four groups, at the beginning of the study 30th day and 60th day. Pain intensity and quantity of bleeding were measured by visual analog scale (VAS), Higham Pictorial blood loss assessment charts methods respectively. *Results:* After 2 months treatment, pain intensity was decreased significantly in FO ($p=0.02$), and RDE ($p<0.01$) groups but remained high among those who received both of FO and RDE ($p=0.27$). Reduction of bleeding days was significant ($p<0.01$) with separate supplementation of FO and RDE but concurrent use of them has no significant effect ($p=0.75$) on bleeding duration. The amount of bleeding does not changed significantly in any groups. *Conclusion:* Our results suggest, omega-3 fatty acids and RDE separately have analgesic effect on pain severity and can decrease bleeding duration of dysmenorrhea as nutritional supplements only when used separately.

Key words: dysmenorrhea, Rosa, fish oils, pain

Introduction

Dysmenorrhea means painful contractions of the uterus during menstruation (1). Primary dysmenorrhea is painful contractions of the lower abdomen without abnormal pelvic pathology and secondary dysmenorrhea is pelvic pain associated with pathological conditions such as endometriosis and endometriosis (1, 2). Primary dysmenorrhea begin some hour before or simultaneously with the onset of bleeding and it take up to 72 hour associated with symptoms such as vomiting, diarrhea, headache, fatigue and syncope (2, 3).

The prevalence of dysmenorrhea is estimated to be 45-90% in different communities (3). For example, it has been reported in Turkey 87.7%, in Mexico 67% (1) and in Iran, more than 70% (1, 4). Dysmenorrhea is a major cause of impaired quality of life and social activities of young women, especially if associated with symptoms, such as headache, fatigue, nausea, vomiting, diarrhea, irritability, chills and muscle cramps. These symptoms cause the person's absence from work or school. So that about 1% of women in childbearing age will be disrupted of work for 3 days in a month because of work for that reason. Through this way 600

million work hours and economically 2 billion dollars is wasted annually in America (2, 3, 5).

It seems that increasing levels of prostaglandins (PGs), causes pain in dysmenorrhea. Progesterone decreases at the end of the luteal phase and this stimulates the enzymes and causes the release of arachidonic acid (AA) from phospholipids and activate the cyclooxygenase pathway (1, 6). Increasing levels of PGs lead to muscle contractions of the uterus, uterine ischemia and increased sensitivity to pain fibers and eventually causing pelvic pain (2, 4). Various treatments including non-invasive methods such as psychotherapy, yoga, hypnotic, massage, prescription vitamins and food supplements and aggressive treatments such as surgery, acupuncture and medical treatments such as PG synthetase inhibitors, NSAIDs and oral contraceptive drugs used to treat dysmenorrhea (5). Among these methods, the most commonly used are drugs, but given their side effects such as gastrointestinal problems and kidney failure (6), many people with dysmenorrhea are looking for alternative treatments like herbal and nutritional remedies. The beneficial effects of nutritional supplements such as vitamins B1, and E, fish oil, omega-3 fatty acids, low fat and vegetarian diet on dysmenorrhea has been reported (7,8). Although some studies have not found a significant relationship between menstrual pain and various types of fats, others have reported a significant positive correlation between saturated fatty acids (SFAs) and low intake of n-3 fatty acids with menstrual pain (9-11). The main role of n-3 fatty acids in the treatment of dysmenorrhea have expressed an inhibitory effect on PG synthesis, thereby relieve pain and may be other symptoms of dysmenorrhea (12,14,15). In addition, by production of anti-inflammatory compounds such as prostacyclin reduce myometrium and blood vessels contractions in uterine and subsequent reduce ischemia and pain (13).

Rosa damascena (RD) or damask rose is one of the most important species of the rosaceae family (16). Using RD to treat pain of abdomen and chest, strengthening the heart, also to treat menstrual bleeding, digestion problems and reducing inflammation, especially in the throat were common in traditional medicine (16, 17). Also animal studies have confirmed the anti-inflammatory effects of its flavonoid compounds (18) on the metabolism of AA in the enzymatic

peroxidation reactions (17). Association between rose gallica tea consumption and relief of menstrual pain and menstrual related stress was reported (19).

There are few studies that have been assessed the effects of concurrent consumption of supplements in dysmenorrhea (20). According to increasing evidence of the effects of n-3 fatty acid supplementation in combination with vitamins B₁₂, E (antioxidant effect) and with respect to the beneficial effects of an extract of rose in relief of menstrual pain, and because of possible synergistic effects due to the same mechanisms of actions; the purpose of this study was to investigate the effects of separate and concurrent supplementation of n-3 fatty acid and *Rosa damascena* extract (RDE) on some of primary dysmenorrhea complaints.

Materials and Methods

This double blind clinical trial designed to investigate concurrent effects of supplementation of FO and RDE on severity of pain, duration and amount of bleeding in girls with primary dysmenorrhea. The study design was explained to female college students in dormitories at the Tabriz University of Medical Sciences. Inclusion criteria were as follows: (1) primary menstrual pain in most recent years, without significant pathology, (2) having moderate and severe dysmenorrhea according to visual analogue scale (VAS); (3) regular menstrual cycles (21-35 day); (4) body mass index (BMI)=18.5-24.9 kg/m².

The severity of dysmenorrhea was determined with a 10-point visual analog scale. The second part of the questionnaires included visual analogue scale (VAS¹) to assess the severity of dysmenorrhea (1,3). At this method the classification was done according to the scores of the pain (mild: 1-3; moderate: 4-7; severe: 8-10).

Approval for this trial was granted by the ethical committee of Tabriz University of Medical Sciences and written consent was obtained from those who were willing to participate in the study. This study is registered at the Iranian Registry of Clinical Trials (IRCT registration number: IRCT201403105670N8). Subjects who agreed to participate were interviewed and requested to complete questionnaires including infor-

mation on demographic characteristics, frequency of major dietary resources of n-3 fatty acids consumption fish, nuts, fruit and vegetables (time/week) by Qualitative- Food Frequency Questionnaire and physical activity levels (PAL) by International Physical Activity Questionnaire (IPAQ). Some of menstrual characteristics including pain, duration of menstrual bleeding were evaluated by questionnaire (1,3).

After a primary examination, 120 women who met the above inclusion criteria were registered to participate in the present study. A diagnosis of dysmenorrhea was made by gynecologist. One hundred twenty university students were randomly allocated with equal size into two groups: one with one-gram soft gel capsule of fish oil (Dana pharmaceutical Co, Tabriz, Iran) containing 180 mg EPA, 120 mg of DHA (n=60) and other without it (n=60), then each group was randomly allocated with equal size into two groups: group one (n=30) received one-gram capsules containing 200 mg of RDE (Yashil pharmaceutical Co, Tabriz, Iran) and other (n=30) not given it. At the beginning of the study groups were not statistically different in terms of variables such as diet and physical activity. Pain intensity by VAS and menstrual duration and blood loss by valid questionnaires was measured begin, and 30th and 60th days after interventions. Blood loss was measured by Higham Pictorial blood loss assessment charts according pad used during menstrual bleeding. In this chart number 1 is for each lightly stained pad, number 5 is for each moderately solid pad and number 20 is for each completely saturated pad. With above calculation when bleeding is <50, scarce flow, 50-80 average flow and >80 abundant (21).

The influential variables were adjusted between two groups (one with one-gram capsules of RDE and other without it) in two sub-groups (one with one-gram soft gel capsule of fish oil and other without it) in 1st day before starting experimental. For quantitative data, normality was evaluated by Q-Q test and outlier data were removed, two ways ANCOVA repeated measured was used for comparing pain severity, bleeding days and quantity of bleeding between RDE factor and fish oil factor. For repeated measure data at first, Mauchly's *W* test was checked for identity covariance matrix, and repeated measure test was used by Minitab Software version 17. The results include four p-values,

the first was p-value group for comparing two RDE and non-RDE groups, the second was p-value treatment for comparing two fish oil and non-fish oil groups, the third was p-value interaction for recognizing interaction effect between RDE factor and fish oil factor and the final P-value Time for comparing variations in three times of intervention. Sidak tests was used for multiple comparison. The level of significance was set at 0.05 and all results was expressed as Mean±SEM (standard error of mean).

Results

Of the 120 girls who enrolled, 15 were lost to follow-up: 3 from group 1, 4 from group 2, 3 from group 3 and 5 from group 4 (Figure 1).

As shown in Table 1, no significant difference was observed in baseline characteristics including the mean pain severity score (p=0.069), BMI (p=0.88), menarche age (p=0.70), frequency of major dietary resources of n-3 fatty acids consumption: fish (p=0.98), nuts (p=0.67), fruit (p=0.24), and vegetables (time/week) (p=0.88) between groups. Mean of menstrual cycle days (p=0.12) and PAL (p=0.04) had significant difference between study groups. In statistical analyzes were adjusted for effect of confounder variables such as age, menarche age, BMI, menstrual cycle days, family history of dysmenorrhea, PAL, number of analgesic drugs such as gelofen-200, gelogen-400, acetaminophen-325, acetaminophen-500, acetaminophen codeine, mefenamic acid, suppository and frequency of fish, nuts, and fruit and vegetables consumption.

VAS was significantly reduced with fish oil (p=0.02), and RDE (p<0.01) but remained high among those who received both of fish oil and RDE (p=0.27).

After two months intervention the time were significant effect on pain severity (p=0.00) but about amount of bleeding (p=0.78) and bleeding days (p=0.92) does not changed significantly during the time (Table 2)

Separate supplementation with fish oil and RDE decreased bleeding days significantly (p<0.01), but concurrent use of them has not significant effect (p=0.75) on it. The amount of bleeding does not changed significantly in any supplements (Table 2).

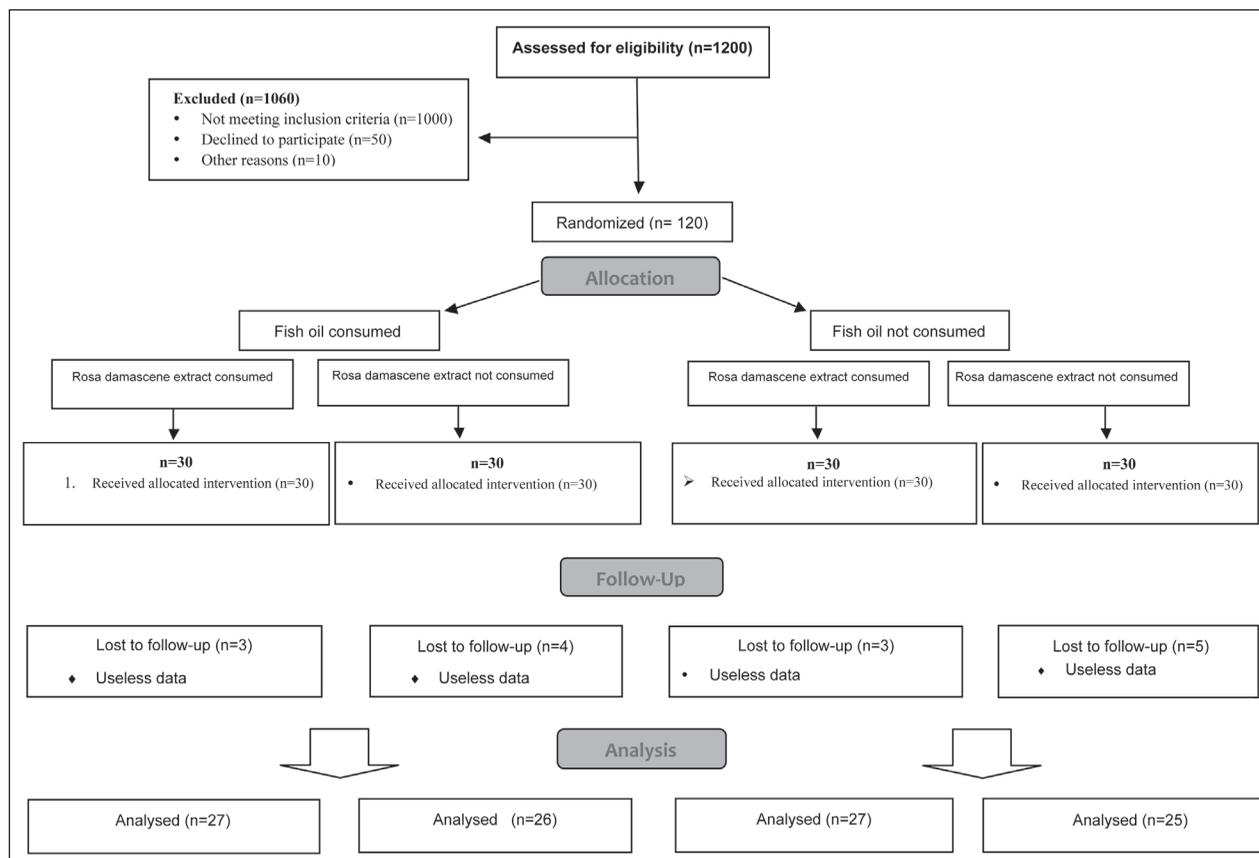


Figure 1. Flow diagram of study selection and data collection process

Table 1. Mean±SE of baseline characteristics in study groups

Fish oil	Yes		No		Pv
	Yes	No	Yes	No	
RDE					
Age (year)	21.96±0.56	21.15±0.40	22.63±0.47	22.08±0.39	0.150
BMI (kg/m ²)	20.97±0.46	21.30±0.46	21.35±0.43	21.45±0.43	0.880
PAL (1-3)	1.40±0.13	1.46±0.11	1.15±0.09	1.60±0.13	0.040
Menarche age (year)	13.00±0.23	13.08±0.27	13.19±0.26	13.40±0.24	0.700
Menstrual cycle (day)	29.56±0.52	28.65±0.38	27.37±0.53	28.88±0.43	0.010
Pain severity (VAS=0-10)	6.68±0.33	7.15±0.26	7.52±0.23	6.64±0.26	0.060
Fish (times/wk)	0.12±0.01	0.12±0.02	0.13±0.02	0.12±0.01	0.980
Nuts (times/wk)	0.19±0.07	0.15±0.04	0.23±0.05	0.22±0.05	0.670
Fruits (times/wk)	0.85±0.09	1.11±0.11	0.85±0.09	1.00±0.13	0.240
Vegetables (times/wk)	0.27±0.06	0.20±0.08	0.22±0.07	0.21±0.05	0.880

RDE= *Rosa damascena* extract; *One Way Anova test PAL=Physical activity level; VAS=Visual analogue scale

Table 2. Mean±SE of pain intensity and bleeding days and quantity of bleeding in study groups

Fish Oil Factor		Yes				
RDE Factor		Yes			No	
Time	begin	30th day	60th day	begin	30th day	60th day
Pain severity (VAS)	6.68±0.28	4.88±0.33	3.24±0.23	7.62±0.30	5.85±0.30	4.11±0.28
Bleeding days	5.60±0.21	5.48±0.25	5.52±0.23	6.40±0.19	6.33±0.23	6.33±0.23
Bleeding quantity	37.72±1.69	35.64±1.53	35.08±1.40	35.62±1.70	35.07±1.66	34.74±1.79

Fish Oil Factor		No				
RDE Factor		Yes			No	
Time	begin	30th day	60th day	begin	30th day	60th day
Pain severity (VAS)	6.88±0.26	5.15±0.33	3.88±0.40	8.08±0.30	6.56±0.33	6.00±0.52
Bleeding days	6.42±0.26	6.34±0.24	6.07±0.32	6.96±0.13	6.88±0.12	6.80±0.12
Bleeding quantity	36.96±2.49	35.34±1.63	33.84±1.55	36.68±2.26	34.72±1.76	34.52±2.06

Fish Oil Factor		Pv*		
RDE Factor	Fish Oil	RDE	interaction	Time
Time				
Pain severity (VAS)	0.020	0.001	0.268	0.000
Bleeding days	0.001	0.000	0.751	0.920
Bleeding quantity	0.708	0.106	0.323	0.780

SE= Standard Error; RDE= *Rosa damascena extract*; VAS=Visual analogue scale. *Via ANCOVA

Discussion

The results of our study suggest that RDE has analgesic effects. Given the common, side-effect-free uses of this plant in diets of Persians as flavoring agent in yogurt and as a laxative, this plant would be a good candidate for alternative and/or complementary medicine in the management of primary dysmenorrhea.

A few studies have been done about the effect of Rose on dysmenorrhea. For example, Tseng et al in a study had shown a significant positive effect of consumption of rose tea to relieve pain severity, stress and anxiety of dysmenorrhea (19). Bani et al in a cross-over study in two groups of 46 persons had suggested that

RDE and mefenamic acid had similar effects on pain intensity of primary dysmenorrhea (26). Gharabaghi et al have showed rosehip extract can be used in elective surgical patients without any significant side effects in order to improve pain (25).

The effects of RDE can be attributed to its compounds including flavonoid, geraniol, eugenol, terpene, saponin, and etc (16, 22-24). Studies have confirmed the anti-inflammatory effects of its flavonoid compounds (18) on the metabolism of AA in the enzymatic peroxidation reactions (17).

Daily administration of FO supplements markedly reduced dysmenorrheal pain severity and bleeding duration in our study. The omega-3 fatty acids present

in fish oils possess anti-inflammatory activities that might be exploited to relieve the symptoms of primary dysmenorrhea, presumably by influencing metabolism of PGs and other factors involved in pain and inflammation (29).

Many studies have been conducted previously on the health benefits of fish oil and its components; however, few studies have examined the effect of these substances on the symptoms of primary dysmenorrhea. Positive effects of omega-3 fatty acid supplementation in relieving dysmenorrhea have been shown in several studies. Wu et al suggested that conversion of linoleic acid to gamma linoleic acid in subjects with dysmenorrhea was slower when received supplements of omega-3 fatty acids (27). The omega-3 fatty acids present in fish oil possess anti-inflammatory activities that might be exploited to relieve the symptoms of primary dysmenorrhea, presumably by influencing metabolism of prostaglandins (PGs) and other factors involved in pain and inflammation (28).

Our literature review showed that few studies have been assessed the effects of concurrent consumption of n-3 fatty acid and other supplements in dysmenorrhea (20). Contrary to our hypothesis and despite evidence of synergistic effects of omega-3 fatty acids and vitamins, in this study concurrent supplementation of RDE and omega-3 fatty acids not only have no synergistic effects in reducing the symptoms of dysmenorrhea, but also may counteract each other as well. Explanation mechanisms of this interaction need more and detailed studies.

Our study showed RDE and omega-3 fatty acids have significant effect on reducing bleeding duration but bleeding quantity has no significant change in any group. To best of our knowledge, the effects of these supplements on the duration and amount of dysmenorrhea bleeding don't have investigated. Although not true for all individuals, increasing bleeding time with fish oil supplementation may be occurred due to competitive inhibition of AA production and thus decreased thromboxane A₂ (30).

The strengths of this study were control of potential confounding factors including age, BMI, menarche age, and intakes of major dietary sources of n-3 fatty acids and phytochemicals. Physical activity levels of subjects were significantly different between groups

that may be affect results. In the other hand the duration of study may also have influenced the results, so in a longer duration other results can be obtained. Small sample size was another limitation of our study. Further studies with wide range of age, BMI, and selecting subjects from different population groups can provide clear and real results.

In conclusion, based on our results, concurrent use of omega-3 fatty acids and RDE as nutritional supplements to alleviate pain severity of dysmenorrhea doesn't recommended, but their separate supplementation have beneficial effects on dysmenorrhea symptoms.

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