Comparison of the effect of omega-3 fatty acids and perforan (Hypericum perforatum) on severity of premenstrual syndrome (PMS): a randomized trial

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ABSTRACT
Premenstrual syndrome (PMS) encompasses a wide variety of cyclic and recurrent physical, emotional, and behavioral symptoms that occur before menstruation and has negative impact on activities of daily living, social activities, sexual functioning and quality of life. The aim of the present study was to compare the effect of omega-3 fatty acid and perforan (Hypericum perforatum) on severity of premenstrual syndrome (PMS). This study is a triple-blind clinical trial that was carried out across three groups with 150 students after considering inclusion and exclusion criteria. The subjects of this study were randomly divided into three groups include omega-3 fatty acid group, perforan group and control (placebo) group. Every subject in this study took drugs during three subsequent cycles so they took capsules daily in the first cycle for one month and in the second and third cycles they took them from eight days before menstruation to two days after and recorded the severity of premenstrual syndrome questionnaire. Statistical analyses were performed using SPSS version 17. The repeated measures ANOVA, chi-square and Wilcoxon tests were used to compare mean differences in three groups. The data showed that there were no significant differences between 3 groups before the intervention but 1, 2 and 3 month s after consumption of perforan and omega-3 capsules, the severity of PMS was significantly lower than that in control group (p<0.001). perforan and omega-3 significantly reduce the severity of PMS.

Key words: Omega-3 fatty acid, perforan (Hypericum perforatum), premenstrual syndrome (PMS).

Quick points:
• The mean scores for PMS were similar in three groups (omega-3 fatty acid group, perforan group and control (placebo) group) prior to the intervention.
• There was a substantial difference between these groups in mean scores for PMS, one, two and three months after the intervention. Results showed that the difference was caused by the difference between the placebo and drug groups.
• A significantly and similarly decreased PMS severity mean scores was observed during treatment cycles in both treatment groups (omega-3 fatty acid group and perforan group), but it did not change in placebo group.
• The mean scores for severity of mood symptoms, physical symptoms and behavioral symptoms were similar in three groups prior to the intervention, but there was a significant difference between these groups in mean scores for severity of these symptoms, one, two and three months after the intervention. The difference was caused by the difference between the placebo and drug groups.
• Success rates in both treatment groups were similar and we did not see any difference between two treatment groups PMS mean score, one, two and three months after the intervention.

INTRODUCTION
Premenstrual syndrome (PMS) encompasses a wide variety of cyclic and recurrent physical, emotional, and behavioral symptoms that occur before menstruation (1) and has negative impact on activities of daily living(2), interpersonal relationships, social activities, leisure activities, sexual functioning, occupation and quality of life(3). The prevalence of PMS has been reported in 20 to 32 % of premenopausal and 30-40% of the reproductive female
population(4). Although some surveys have suggested that over 80% of women report PMS, when strict diagnostic criteria are applied; the prevalence of severe PMS is estimated to be about 2-6% in women of reproductive age(5).

PMS cause criminal behavior, suicide attempt, work absences, hospital admissions and increase in accidents(6). It influence on person’s life and others and it comes with problems for example, anxiety, nutrition disorders and overweight(7). The women with PMS complain of cyclical mastalgia (breast pain)(8), menstrual migraine(9), sleep problems(10), stress and depression(11). Mastalgia occurring during the luteal phase(12) and leads to disturbance of the sexual function, physical and social activities(13). It was seen that in women with menstrual migraine the headaches, depression, irritability, anxiety and nausea will increase in the luteal phase (14, 15). Though the etiology of PMS is unknown(16), The causative factors include hormonal imbalances, abnormalities in thyroid hormones, low serotonin levels, nutritional deficiencies, increased inflammatory prostaglandins, cortisol, prolactin, β-endorphins and electrolytes(17). Many treatments for PMS have been tried over the years. These treatments include non-pharmacological (dietary modification, dietary supplement and regular physical activity) and pharmacological and they have varying outcomes (13, 18).

While PMS is a persistent condition(19), we must pay attention to side effects of medications(20). Recent research demonstrates that herbal medicines have been known as acceptable treatment because they have fewer side effects(21). Hypericum perforatum (perforan) is a plant that its extract has a great effect(22). Its effectiveness is proven through experimental investigations and clinical trials(23). Hypericum perforatum has traditionally been used to treat many diseases, especially depression over 2000 years ago (22, 24). Perforan prevent amino oxidize activity and reuptake of norepinephrine, serotonin and dopamine(25). Perforan is a good treatment for mild severity of PMS. University internal review board approval and ethics committee approval were obtained before the start of the research project.

On the other hand, good nutrition is important for balance and mental health as well as physical health. In some countries poor nutrition is a factor for diseases(29, 30). Studies have shown that fat as a source of energy helps the body absorb vitamins and adequate fat intake is essential to growth and health(31). The body can make all fatty acids except two unsaturated fatty acid: linoleic acid (n-6) and alpha-linolenic acid (n-3)(32). Researchers have shown an abnormal metabolism of essential fatty acids in women with PMS(33). Omega-3 fatty acids produce anti-inflammatory prostaglandins: prostaglandin E1 and thromboxane A3 that reduce myometrial contractions, vasoconstriction and ischemia. This phenomenon reduces pain, nausea and vomiting (34-36). Omega-3 fatty acids significantly reduce mood disorders and improve mental health(37). Some epidemiological studies have shown the relationship between low levels of omega-3 fatty acids and an increased risk of depression(38).

There are a few studies about the effect of omega-3 fatty acids and perforan on severity of PMS and previous research did not compare omega-3 fatty acids with perforan. Since herbs and supplements can be safer and less expensive than chemical drugs and they are more accepted, and women have the right to have too many choices and choose something that is more affordable and has fewer side effects, we compared the effect of omega-3 fatty acids and perforan on severity of PMS.

**MATERIALS AND METHODS**

This study is triple-blind clinical trial that was conducted to compare the effect of omega-3 fatty acids and perforan on severity of PMS. University internal review board approval and ethics committee approval were obtained before the start of the research project. The study was conducted on students living in Isfahan university residence halls and included all unmarried students who were dormitory resident during the study period. Data was collected by using a questionnaire including 2 sections: demographic characteristics and statistical manual of mental disorders form (DSM-IV) that includes 19 symptoms of PMS (irritability, restlessness, impatience, anger, fear, depression, sadness, crying for no reason, loneliness, physical symptoms such as breast tenderness or swelling, headaches, back pain, abdominal pain, weight gain, swelling of the extremities, gastrointestinal disorders, behavioral symptoms include fatigue, lack of energy, sleep problems, difficulty in concentrating and appetite disorders). The inclusion criteria were predefined as follows: having regular menstrual cycles (arriving every 24-35 days), being single, not to take any drugs and herbal medicines, having no physical illness such as endocrine disorders, not to take medication for PMS, no alcohol consumption, having no history of relative dies in the last three months and having no surgery in the last three months. Exclusion criteria included: unwillingness to remain in the study, drug allergy or side effect, recognizing physical and psychiatric symptoms of any endocrine disorders and severe premenstrual syndrome. At the first stage of study, from among 700 students who were invited to participate in the study only 350 returned the...
DSM-IV form and following exclusion of participants with incomplete form (n = 170) resulted in 180 students who were completed DSM-IV at baseline. At the second stage of study, a form that was a daily schedule including 19 symptoms that experienced on days 1 to 35 on menstrual cycle were given to them for two months. The subjects were advised not to use any drugs even vitamins during this time and also caffeine and salt during the premenstrual period. The form was filled out in this way: absence of symptoms -0 points, mild symptoms that have no interfere with activities -1 points, moderate symptoms that interfere with daily activities -2 points and severe symptoms that interfere with daily tasks such as class absence or use of painkilling drugs -3 points. A student had PMS if she had at least five symptoms for a week before her menstruation until 3 days after. To analyze the severity of PMS, the total scores of 19 symptoms from a week before menstruation until 3 days after were added together. Then the cases were classified as: lack of PMS symptoms (0 scores), mild PMS (1-190 scores), moderate PMS (191-380 scores) and severe form of PMS (381-570 scores). At these stage, from among 180 subjects who were completed daily symptoms form following exclusion of participants with severe or lack of PMS (n = 30) resulted in 150 subjects. At the third stage of study these subjects randomly (random assignment) divided into three groups (omega-3 fatty acid -2000 mg per day, perforan -280 mg per day and placebo -2000 mg per day) and each group contains 50 students. Enough information was given subjects for taking drugs for three cycles. Thus, they take them for all days of the first menstrual cycle, and from 8 days before menstruation until 2 days after it for the next 2 months. Subjects recorded any symptoms experienced during the total study period on a daily basis using the daily symptoms form. 9 students were excluded due to weight gain and obesity in omega-3 fatty acid group (n=2), fear of dependence in perforan group (n=2) and gastrointestinal complications in placebo group (n=5) during the study period. Finally, the forms were collected and severity of symptoms were measured and analyzed separately for each group. We used descriptive statistics to describe the demographic characteristics of the sample, repeated measures ANOVA test for quantitative variables, chi-square test for relationships between categorical variables and Wilcoxon test for ranked variables. Normally distributed population was tested using Kolmogrov-Smirnov (k-s) test. All data analysis was performed using SPSS version 17.

RESULTS

Confounding factors that controlled through randomizing included: age, age at menarche, length of the menstrual cycle, duration of menstrual bleeding and body mass index.

Three groups were similar in age, age at menarche, length of the menstrual cycle, duration of menstrual bleeding and body mass index (table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Omega-3 fatty acid N=48 Mean±SD</th>
<th>Perforan N=48 Mean±SD</th>
<th>Placebo N=45 Mean±SD</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22.5±3.33</td>
<td>22.4±3.34</td>
<td>22.4±3.67</td>
<td>P=0.97</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td>13.56±1.39</td>
<td>13.70±1.30</td>
<td>13±1.22</td>
<td>P=0.26</td>
</tr>
<tr>
<td>Length of the menstrual cycle (days)</td>
<td>27.33±2.32</td>
<td>27.62±2.59</td>
<td>26.93±2.41</td>
<td>P=0.39</td>
</tr>
<tr>
<td>Duration of menstrual bleeding (days)</td>
<td>6.04±1.42</td>
<td>6.14±1.57</td>
<td>5.97±1.43</td>
<td>P=0.85</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>20.83±3.18</td>
<td>20.72±2.56</td>
<td>21.30±3.59</td>
<td>P=0.64</td>
</tr>
</tbody>
</table>

The mean scores for PMS were similar in three groups prior to the intervention, but there was a substantial difference between these groups in mean scores for PMS, one, two and three months after the intervention. Scheffe's test showed that the difference was caused by the difference between the placebo and drug groups (Table 2).

<table>
<thead>
<tr>
<th>Treatment cycles</th>
<th>Omega-3 fatty acid Mean±SD</th>
<th>Perforan Mean±SD</th>
<th>Placebo Mean±SD</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>prior to the intervention</td>
<td>106.32±45.63</td>
<td>119.63±45.66</td>
<td>109.94±42.75</td>
<td>P=0.32</td>
</tr>
<tr>
<td>1 month after the intervention</td>
<td>73.30±27.63</td>
<td>74.30±31.63</td>
<td>110.58±42.77</td>
<td>P=0.001</td>
</tr>
<tr>
<td>2 months after the intervention</td>
<td>70.36±26.91</td>
<td>71.64±30.46</td>
<td>110.66±43.02</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>3 months after the intervention</td>
<td>58.75±23.27</td>
<td>59.55±27.28</td>
<td>110.72±43.05</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

A significantly and similarly decreased PMS severity mean scores was observed during treatment cycles in both treatment groups, but it did not change in placebo group.
The mean scores for severity of mood symptoms, physical symptoms and behavioral symptoms were similar in three groups prior to the intervention, but there was a significant difference between these groups in mean scores for severity of these symptoms, one, two and three months after the intervention. Scheffe’s test showed that the difference was caused by the difference between the placebo and drug groups (Table 3).

Table 3: Comparison of the mean scores for severity of mood, physical and behavioral symptoms among three groups using one-way ANOVA and Kruskal-Wallis tests

<table>
<thead>
<tr>
<th>Treatment cycles</th>
<th>symptom</th>
<th>Omega-3 fatty acid Mean±SD</th>
<th>Perforan Mean±SD</th>
<th>Placebo Mean±SD</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>prior to the intervention</td>
<td>Mood</td>
<td>43.28±25.49</td>
<td>48.05±24.67</td>
<td>46.18±30.86</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>37.06±19.92</td>
<td>38.73±19.55</td>
<td>36.07±17.65</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Behavioral</td>
<td>25.97±20.44</td>
<td>32.83±19.04</td>
<td>27.06±18.75</td>
<td>0.18</td>
</tr>
<tr>
<td>1 month after the intervention</td>
<td>Mood</td>
<td>30.46±17.58</td>
<td>30.93±16.10</td>
<td>46.17±30.85</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>25.85±13.43</td>
<td>25.38±17.42</td>
<td>37.35±17.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Behavioral</td>
<td>18.33±11.50</td>
<td>17.99±10.80</td>
<td>27.06±18.75</td>
<td>0.02</td>
</tr>
<tr>
<td>2 months after the intervention</td>
<td>Mood</td>
<td>32.79±18.96</td>
<td>31.80±16.87</td>
<td>46.91±31.30</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>21.21±12.38</td>
<td>24.46±16.55</td>
<td>36.62±17.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Behavioral</td>
<td>16.35±10.79</td>
<td>15.38±10.02</td>
<td>27.06±18.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 months after the intervention</td>
<td>Mood</td>
<td>19.25±11.76</td>
<td>23.15±16.24</td>
<td>36.71±17.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>13.85±10.44</td>
<td>13.85±9.43</td>
<td>27.06±18.75</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 1: flow diagram of the study group

Success rates in both treatment groups were similar and we did not see any difference between two groups PMS mean score, one, two and three months after the intervention (Table 4).
Table 4: Comparison of the mean scores for PMS among two treatment groups using independent t-test

<table>
<thead>
<tr>
<th>Treatment cycles</th>
<th>Omega-3 fatty acid Mean±SD</th>
<th>Perforan Mean±SD</th>
<th>P-value (95% Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>prior to the intervention</td>
<td>106.32±45.63</td>
<td>119.63±45.66</td>
<td>P=0.15 (-31.82-5.19)</td>
</tr>
<tr>
<td>1 month after the intervention</td>
<td>73.30±27.63</td>
<td>74.30±31.63</td>
<td>P=0.86 (-12.1-10.1)</td>
</tr>
<tr>
<td>2 months after the intervention</td>
<td>70.36±26.91</td>
<td>71.64±30.46</td>
<td>P=0.82 (-12.93-10.36)</td>
</tr>
<tr>
<td>3 months after the intervention</td>
<td>58.75±23.27</td>
<td>59.55±27.28</td>
<td>P=0.91 (-10.94-9.76)</td>
</tr>
</tbody>
</table>

DISCUSSION

Our study shows that omega-3 fatty acids and perforan significantly reduce the premenstrual symptoms and omega-3 fatty acids did not differ in effectiveness from perforan.

Some studies have reported that factors like: age(39), age at menarche(40), length of the menstrual cycle, duration of menstrual bleeding(39) and body mass index(41) are involved in the occurrence of PMS, we have controlled all of them through randomizing.

There are various hypotheses for the biological action of omega-3 fatty acid that leads to decreased PMS severity. Prior to menstruation we can see an increase in the level of arachidonic acid in the uterus and at the same time, cyclooxygenase, prostaglandin E2, prostaglandin F2α and leukotriene B4 which have role in inflammation, produce from arachidonic acid(42). Also arachidonic acid induces an increase in ischemia, myometrial contractions, menstrual cramps and gastrointestinal symptoms such as nausea, vomiting and flatulence (34). Omega-3 fatty acid contains alpha-linolenic acid that increases production of eicosapentaenoic and docosahexaenoic(43); both of these are eicosanoids precursors that compete with prostaglandin synthesis. Omega-3 fatty acids produce anti-inflammatory prostaglandins: prostaglandin E1 and thromboxane A3 that reduce myometrial contractions, vasoconstriction and ischemia. This phenomenon reduces pain, nausea and vomiting(44, 45). In this study, we found a significantly decreased PMS severity mean score during treatment cycle in Omega-3 fatty acid group. This is in line with the findings from Tofighiyan(46), Sohrabi (47), Kashanian(48), Fontani(49), Sampalis (50) and Deutch(51) works.

Perforan has traditionally been used to treat many diseases, especially depression (22, 24). Perforan prevent amino oxidize activity and reuptake of norepinephrine, serotonin and dopamine(25). Similar to results reported by Sabet-Birjandi(52), Ghazanfarpure(27), Ryoo (53), canning(54), Pakgohar(55) and Hicks(56), we observed that perforan significantly reduce the PMS.

As mentioned, omega-3 fatty acids did not differ in effectiveness from perforan. According on our investigation, no work has been found comparing the effect of omega-3 fatty acid and perforan on severity of PMS to this time.

The present study has a limitation. Although the researcher tried to call the students once a week during the study period and ensured that drugs are used correctly, they may not take the drugs and this was out of our control.

Despite this possible limitation, there are certain important aspects of the design of this study that may have enhanced the accuracy of the study. These include being triple-blind that reduce the bias to the extent possible and having a control group that enabled us to find out if the treatments really had effect.

According to this study omega-3 fatty acids and perforan significantly reduce the PMS. The cause of PMS is unknown and some people with this syndrome do not respond to conventional treatments, so new method is suggested in these cases. Herbal medicines and supplements have been known as acceptable treatment because they are affordable and have fewer side effects(21).

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REFERENCES


