Efficacy of Omega-3 in Treatment of Recurrent Aphthous Stomatitis: A Randomised, Double-blind, Placebo-controlled Study

Tahereh NOSRATZEHI¹, Azadeh AKAR²

Objective: To evaluate the potential of omega-3 polyunsaturated fatty acid supplement as an effective, safe and inexpensive medicine for the treatment of recurrent aphthous stomatitis.

Methods: In this double-blind clinical trial, 50 patients with recurrent aphthous stomatitis were randomly divided into the omega-3 group and placebo group. Patients in the omega-3 group received 1000 mg omega-3 group capsules (Daroupaksh Company, Tehran, Iran) for 6 months; while those in the placebo group received placebo capsules with the same instructions. The pain, size, duration and recurrence rate of ulcers were recorded in each follow-up phase. Follow-up was done weekly in the first month of drug prescriptions and then monthly in the next 5 months. The data were analysed with SPSS-20 through the Mann-Whitney test to compare the groups with respect to each variable and the Wilcoxon and Friedman tests to compare the groups over time. Values were significant at P < 0.05.

Results: In the omega-3 group, pain was lessened from 4.96 to 3.04, irritation was reduced from 5.88 to 4.00 (P = 0.0627) and the size of ulcers was decreased from 2.30 to 1.48 mm (P = 0.062). No significant change was observed in the aforementioned variables in the placebo group. Moreover, the number of ulcers indicated a significant reduction in the fourth, fifth and sixth months in comparison with the placebo group (P = 0.00).

Conclusion: The recurrence of ulcers in the omega-3 group showed a significant decrease in the fifth and sixth months compared with the placebo group (P < 0.05). The current study indicated that omega-3 consumption decreased the symptoms of recurrent aphthous stomatitis.

Key words: omega-3, recurrent aphthous stomatitis, treatment


Recurrent aphthous stomatitis is a common disorder characterised by recurring ulcers confined to the oral mucosa in patients with no other signs of systemic disease. With a higher prevalence amongst women¹, this disease has been observed in 5 to 25% of the population².

Aphthous is a multifactorial ulcer, and the real cause has not been identified³. The aetiology of this disease includes bacterial infection, immunological disorders and the increased viscosity of the submucosal extracellular matrix⁴. In different sources, the predisposing factors for the development of aphthous have been thought to include psychological factors, hormonal changes, trauma and allergy³,⁵,⁶.

Recurrent aphthous stomatitis is divided into three classes of ulcerations including minor, major and herpetiform aphthous. These painful ulcers are formed singly or multiply, especially in non-keratinised oral mucosa. Except for major aphthous ulceration, these ulcers last for 1 to 2 weeks and are self-limited⁷,⁸. The goals of current therapeutic approaches include the management of pain and functional impairment, as well as reducing the duration and frequency of recurrences⁹,¹⁰. To achieve these goals, several topical medicaments
such as chlorhexidine, hyaluronic acid, amelexanx and some systemic drugs such as corticosteroids, levamisole and colchicine have been used\textsuperscript{11,12}. Recent studies have investigated the beneficial effects of fish oil, which is rich in omega-3, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus and chronic periodontitis\textsuperscript{13-15}. Several studies suggested that 1.5 g of DHA/EPA supplement per day would be enough to control the inflammatory processes, although some other studies advised higher doses (3.5 g/d)\textsuperscript{16}. Except El Khouli et al\textsuperscript{17}, rare studies have been carried out regarding the omega-3 in the treatment of recurrent aphthous stomatitis. The current study investigated the impact of omega-3 on patients with recurrent aphthous stomatitis.

\textbf{Materials and methods}

\textbf{Subjects}

In this double-blind clinical trial, the participants were selected from patients of the outpatient clinic of the Oral Medicine Department, Faculty of Dentistry at Zahedan University of Medical Sciences in Iran. The condition was evaluated by oral medicine specialists according to clinical symptoms, and those with inclusion and exclusion criteria were selected. After receiving enough explanations on the necessity of treatment, methodology and possible side effects, all patients signed a written consent regarding the treatment and 6-month follow-up, after they were enrolled in the study. The patients were visited from October 2013 and the follow-up was completed in December 2015. This study was confirmed by the Ethics Committee at Zahedan University of Medical Sciences. It was registered in the Iranian Registry of Clinical Trials with the number IRCT2015041620377N2.

The ulcers were diagnosed by an oral medicine specialist, based on clinical manifestations. The inclusion criteria included: age > 13 years, experiencing a recurrent aphthous ulcer in at least each month for the last year, and having one to three aphthous ulcers (developed in less than 48 h) not wider than 5 mm. Patients with systemic diseases and those who take drugs, patients who were pregnant women, smokers or those who smoke other types of substances, and patients already treated for oral ulcers during the last 3 months\textsuperscript{16}, were excluded from the study.

In total, 50 patients were selected and randomly divided into the two groups of case (omega-3) and control (placebo). Patients in the case group (25 subjects including 10 men and 15 women) received 1000 mg omega-3 capsules (Daroupakhsh Company, Tehran, Iran) three times a day for 6 months, and the control group including 25 subjects, 12 men and 13 women received placebo capsules (Daroupakhsh Company, Tehran, Iran) with the same prescription. A specialist who was blind to the received dose evaluated the patients. The pain and irritation of ulcers were recorded with the Visual Analog Scale from 0 to 10 before treatment and in each follow-up session. Before treatment and in each follow-up session, the sizes of ulcers were measured with a caliper, and the rate of recurrence was recorded. Follow-up was done weekly in the first month and monthly in the next 5 months.

\textbf{Data analysis and description}

The data were analysed with SPSS 20 (SPSS, Illinois, USA) using the Mann-Whitney test to compare the placebo group with the omega-3 group with respect to each variable and the Wilcoxon and Friedman tests to compare the groups over time. Values are significant at $P < 0.05$.

\textbf{Results}

Both groups consisted of 25 subjects: 12 males and 13 females in the placebo group and 10 males and 15 females in the omega-3 group. In the placebo group, the average age of the patients was 31.6 years, ranging from 14 to 49. It was 37.13 years in the omega-3 group, ranging from 16 to 54.

The ulcers were as wide as 2.3 mm at the beginning of treatment in the omega-3 group. After 6 months of treatment with omega-3, on average they were as wide as 1.48 mm. There was a significant difference between the sizes of the ulcers at the beginning and the end of treatment in the omega-3 group ($P < 0.05$). There was no significant difference between the two groups in terms of the sizes of ulcers at the beginning. After 6 months of intervention in the study groups, the ulcers in the omega-3 group were significantly smaller than the ulcers in the placebo group ($P < 0.05$) (Table 1).

The average pain was 4.44 at the beginning and 4.64 after 6 months of treatment with placebos in the control group showing no significant difference. The average pain was 4.96 at the beginning and reduced to 3.04 after 6 months of treatment with omega-3 in the case group. For this group a significant difference was found ($P < 0.05$). There was no significant difference between the two groups at the beginning, while after 6 months of intervention, the pain in the omega-3 group was
Table 1  Mean values of sizes of ulcers amongst the study groups at baseline and 6-month follow-up.

<table>
<thead>
<tr>
<th>Time</th>
<th>Omega-3 (Mean ± SD)</th>
<th>Placebo (Mean ± SD)</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.20 ± 1.57</td>
<td>2.30 ± 1.90</td>
<td>0.497</td>
</tr>
<tr>
<td>After 6 Months</td>
<td>2.66 ± 2.30</td>
<td>1.48 ± 0.86</td>
<td>0.010</td>
</tr>
<tr>
<td>P value*</td>
<td>0.062</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

*: Wilcoxon Test  
**: Mann-Whitney U Test

Table 2  Mean scores of the visual analogue scale amongst the study groups at baseline and 6-month follow-up.

<table>
<thead>
<tr>
<th>Time</th>
<th>Omega-3 (Mean ± SD)</th>
<th>Placebo (Mean ± SD)</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.44 ± 1.61</td>
<td>4.96 ± 1.21</td>
<td>0.162</td>
</tr>
<tr>
<td>After 6 Months</td>
<td>4.64 ± 1.78</td>
<td>3.04 ± 1.20</td>
<td>0.000</td>
</tr>
<tr>
<td>P value*</td>
<td>0.0627</td>
<td>0.0000</td>
<td></td>
</tr>
</tbody>
</table>

*: Wilcoxon Test  
**: Mann-Whitney U Test

Table 3  Mean values of monthly number of ulcers amongst the study groups at baseline and at 1-, 2-, 3-, 4-, 5- and 6-month follow-up.

<table>
<thead>
<tr>
<th>Time (month)</th>
<th>Placebo (n = 25) (Mean ± SD)</th>
<th>Omega-3 (n = 25) (Mean ± SD)</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.96 ± 1.24</td>
<td>1.12 ± 0.00</td>
<td>0.547</td>
</tr>
<tr>
<td>2</td>
<td>1.28 ± 1.24</td>
<td>1.60 ± 0.96</td>
<td>0.188</td>
</tr>
<tr>
<td>3</td>
<td>1.44 ± 1.23</td>
<td>1.32 ± 0.80</td>
<td>0.887</td>
</tr>
<tr>
<td>4</td>
<td>1.40 ± 1.19</td>
<td>0.84 ± 0.62</td>
<td>0.045</td>
</tr>
<tr>
<td>5</td>
<td>1.36 ± 0.96</td>
<td>0.64 ± 0.49</td>
<td>0.001</td>
</tr>
<tr>
<td>6</td>
<td>1.32 ± 0.75</td>
<td>0.41 ± 0.20</td>
<td>0.000</td>
</tr>
<tr>
<td>P value*</td>
<td>0.17</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

*: Friedman Test  
**: Mann-Whitney Test

Table 4  Mean values of recurrence of ulcers amongst the study groups at baseline and at the 1-, 2-, 3-, 4-, 5- and 6-month follow-up.

<table>
<thead>
<tr>
<th>Time (month)</th>
<th>Placebo (n = 25) (Mean ± SD)</th>
<th>Omega-3 (n = 25) (Mean ± SD)</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.40 ± 0.76</td>
<td>1.52 ± 0.65</td>
<td>0.302</td>
</tr>
<tr>
<td>2</td>
<td>1.28 ± 0.74</td>
<td>1.48 ± 1.05</td>
<td>0.492</td>
</tr>
<tr>
<td>3</td>
<td>1.36 ± 0.86</td>
<td>1.28 ± 0.79</td>
<td>0.653</td>
</tr>
<tr>
<td>4</td>
<td>1.20 ± 1.00</td>
<td>1.04 ± 0.61</td>
<td>0.724</td>
</tr>
<tr>
<td>5</td>
<td>1.20 ± 1.04</td>
<td>0.60 ± 0.50</td>
<td>0.038</td>
</tr>
<tr>
<td>6</td>
<td>1.44 ± 1.04</td>
<td>0.41 ± 0.20</td>
<td>0.000</td>
</tr>
<tr>
<td>P value*</td>
<td>0.593</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

*: Friedman Test  
**: Mann-Whitney Test
The average irritation of ulcers was 5.28 and 5.16 at the beginning and the end of treatment in the control group. The average irritation of ulcers was 5.88 and 4.04 at the beginning and the end of 6 months of treatment with omega-3 in the case group, with a significant difference (\(P < 0.05\)). No significant difference was found between the irritation of ulcers in the omega-3 group and the placebo group at the beginning, while the irritation of ulcers in the omega-3 group was significantly lower than that of the placebo group after 6 months of treatment (\(P < 0.05\)).

The number of ulcers in the first, second, third, fourth, fifth and sixth months are demonstrated in Table 3. There was no significant difference in the first, second and third months in terms of the number of aphthous ulcers in both groups. However, the number of ulcers decreased significantly in the omega-3 group in the fourth, fifth, and sixth months in comparison with the placebo group (\(P < 0.05\)). Considering the recurrence of ulcers during 6-month treatment, there was no significant difference between the two groups in the first, second, third and fourth months in terms of the recurrence. However, there was a significant decrease in the recurrence of ulcers in the omega-3 group compared to the placebo group in the fifth and sixth months (\(P < 0.05\)) (Table 4).

Discussion

The worldwide distribution, high frequency and decreased quality of life of recurrent aphthous stomatitis have resulted in a great deal of research into the aetiology and efficient therapy of this condition\(^2,5,10\). Therefore, various symptomatic treatments have been proposed for it, and there have been many side effects in some cases\(^12\). However, these agents cannot reduce the frequency of recurrence of the disease. Moreover, some studies have reported that stress management, relaxation and imagery training may also have additional therapeutic benefits. In other words, the aim of treatment was to reduce pain, irritation and the number and size of ulcers.

Omega-3 supplement is an effective compound and includes unsaturated fatty acids of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The helpful clinical effects of the omega-3 diet can be explained with the ability of EPA and DHA to change the cellular performance of polymorphonuclear leukocytes. This process is done through regulating the inflammatory cells and blocking the production of pro-inflammatory cytokines\(^18-20\). Omega-3 polyunsaturated fatty acids prevent the production of arachidonic acid through cyclooxygenase and lipoxygenase. This effect indicates the supervisory role of EPA and DHA in limiting tissue damage and helping the ulcers heal\(^21\).

Omega-3 can partially inhibit a number of aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression and leucocyte endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n-6 fatty acid arachidonic acid, production of inflammatory cytokines and T cell reactivity. Mechanisms underlying the anti-inflammatory actions of n-3 fatty acids include altered cell membrane phospholipid fatty acid composition, disruption of lipid rafts, inhibition of activation of the pro-inflammatory transcription factor nuclear factor kappa B therefore reducing expression of inflammatory genes, activation of the anti-inflammatory transcription factor NR1C3 and binding to the G protein coupled receptor GPR120\(^22\).

In this double-blind clinical trial, the results are consistent with the study conducted by El Khouli et al\(^17\) in 2014. They stated that consumption of omega-3 could lessen the pain in patients with recurrent aphthous stomatitis. Duffy et al indicated that consumption of omega-3 would significantly influence the systemic lupus erythematosus, a fact which is consistent with the results of the present study\(^13\). Abbasi et al stated that consumption of triamcinolone acetonide 0.1% and diclofenac 1.0% would significantly reduce the size of ulcers\(^23\). El Khouli Am et al believed that consumption of omega-3 would reduce the number of ulcers in patients with recurrent aphthous stomatitis\(^17\). Volkov\(^24\) et al believed that B12 is also effective.

In this study, the recurrence of ulcers in the omega-3 group decreased during the 6 months. Moreover, the number of ulcers were almost the same in the two groups in the first, second, third and fourth months. However, the number of ulcers in the omega-3 group were significantly decreased in the fifth and sixth months in comparison with the placebo group.

Vitamin E plays a helpful role in many actions such as prevention of PUFAs (Poly Unsaturated Fatty Acids) peroxidation in the intestine and cell membranes, prevention of vitamin A oxidation in the intestine, preservation of cell membranes by neutralising free radicals, and prevention of RBC hemolysis\(^25\). Vitamin E also exerts anti-oxidative properties; a fact which can justify its role as a detoxifier and antioxidant. This compound makes the use of PUFAs and the protection of other materials such as vitamin A, enzymes and hormones possible\(^26\).

It was reported that the serum levels of vitamin E in RAS patients are considerably lower than healthy
individuals. Kokcam compared the concentration of vitamin E in plasma and RBC amongst patients with Behçet’s disease and healthy individuals. This study indicated that the level of antioxidants decreased considerably in patients with Behçet’s disease.

In 2005, Saral indicated that the levels of vitamins A, E and C were considerably lower in serum and saliva of patients with oral aphthous compared with healthy individuals. Therefore, there was a strong and very significant correlation between the serum and salivary levels of vitamins A, E, C and malondialdehyde.

Various studies indicated the significant impact of vitamins and supplements such as A, E, C, B12 and minerals like zinc, iron and ferritin on symptoms of recurrent aphthous stomatitis. The results of the current study showed that consumption of omega-3 supplement would also decrease the symptoms of this disease significantly. It is recommended that more extensive studies should be conducted on larger samples over longer periods so that the treatments can be improved.

Conflicts of interest

The authors reported no conflicts of interest related to this study.

Author contribution

Dr Tahereh Nosratzehi for carrying out the research and writing the manuscript and Dr Azadeh Akar for his help.

(Received April 19, 2016; accepted June 06, 2016)

References


