Original Article

Adjunctive Low-Dose Aspirin plus Omega-3 Fatty Acid versus Low-Dose Doxycycline on Chronic Periodontitis

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Abstract

Background and Aim: Host modulation therapy (HMT) has been considered as a new modality for treatment of periodontal disease. Omega-3 fatty acid has shown inhibitory and anti-inflammatory properties in treatment of inflammatory conditions such as periodontitis. This study compared the efficacy of omega-3 fatty acid and low - dose aspirin with doxycycline in treatment of chronic periodontitis.

Materials and Methods: Forty-five patients with chronic periodontitis were selected and their clinical periodontal parameters were measured. They received phase I of periodontal therapy and were randomly divided into three groups. Each group randomly received one of the following daily drug regimens: omega-3 fatty acid plus aspirin (80mg), doxycycline (20mg) and the placebo (control). Clinical parameters were measured again after six weeks. Wilcoxon test, paired t-test, Kruskal–Wallis test and one-way ANOVA were used to analyze the data.

Results: The mean values of bleeding on probing (BOP), periodontal pocket depth (PPD) and clinical attachment loss (CAL) in both test groups decreased significantly compared to the placebo group ($p<0.05$). The reductions in the omega-3 group were significantly greater than those in the doxycycline group ($p<0.05$).

Conclusion: Omega-3 fatty acid can improve clinical parameters of periodontal disease, even better than doxycycline, which is routinely used for HMT.

Key Words: Chronic periodontitis, Omega-3 fatty acid, Doxycycline

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Introduction

Periodontitis is among the most common chronic inflammatory diseases caused by bacterial infection due to complex activity of anaerobic Gram-negative microorganisms invading the tooth supporting structures [1, 2].

Its clinical manifestations include gingival edema, redness, bleeding, suppuration, periodontal pocket formation, gingival recession, bone loss and CAL [2].

Tissue destruction in periodontitis is secondary to inflammatory tissue injury caused by neutrophils later associated with monocyte infiltration and development of an acquired immunity response [3]. Periodontal disease is related to specific pathogenic microorganisms; however, previous studies on specific pathogens have revealed that most of the destruction is due to host response to infection and not directly related to infectious agents [4].

HMT is a new concept suggested for treatment of periodontal disease. Scaling and removal of dental plaque is the first step of treatment and must be followed by measures to cease the pathogenic process of periodontal disease i.e. decreasing the bacterial load. However, HMT is a treatment method targeting host-bacteria interactions with particular focus on the host. It has been revealed that tissue destruction, which is the clinical manifestation of periodontitis, is mainly due to the function of host immunity response. HMTs do not inhibit the natural defense system or inflammation but modulate the excessive inflammatory and pathologic response allowing wound repair and periodontal stability [5]. This treatment includes systemic administration or topical application of medications as part of periodontal treatment and as an adjunct to conventional periodontal therapy [6]. HMT aims to decrease tissue destruction and results in stabilization or even regeneration of periodontium via modulating or inhibiting host-related destructive agents and reinforcing the protective or regenerative responses [7].

Several medications have been evaluated as host modulators; among which, the tetracycline family and particularly low-dose doxycycline have yielded satisfactory results especially when combined with non-surgical treatments [8].

Tetracycline is effective for periodontal disease to some extent because its concentration in crevicular fluid reaches 2 to 10 times its serum level. Thus, a high concentration of drug is carried into the periodontal pockets.

Sub-antimicrobial doses of doxycycline inhibit matrix metalloproteinases [9]. Ashley et al. divided periodontitis patients into three groups receiving different treatment protocols. They found that after the first phase of periodontal therapy, 20 mg of doxycycline twice and once daily decreased collagenase activity. The greatest reduction was observed in the group receiving doxycycline twice daily [10]. Caton [11], Crout [12] and Golub [13] in similar studies demonstrated that treatment with 20 mg doxycycline twice daily for one, two and three months caused a significant reduction in collagenase concentration in gingival crevicular fluid.

Also, it has been demonstrated that omega-3 has beneficial anti-inflammatory effects on a number of body organs including gingiva and periodontal tissue [5]. Omega-3 acts as a substrate that later converts to a series of lipid mediators. These biochemically active mediators are responsible for the beneficial and protective properties of omega-3 in colitis, brain ischemia and periodontitis [5].

Kesavalu et al, in an animal model study showed that a nutritional regimen containing omega-3 enhanced the treatment of periodontal disease [14]. Naghavi et al. also stated that consumption of omega-3 decreased the prevalence of periodontitis [15].

Moreover, it has been demonstrated that omega-3, especially in combination with aspirin, shows significant protective effects via the reinforcement of production and activity of endogenous mediators through modulating the activity of cyclooxygenase 2 (COX2) [16]. Faizuddin et al. evaluated CAL in 162 patients under treatment with low dose aspirin for more than 6 months and concluded that low dose aspirin can decrease the risk of CAL [17].

Aspirin, in conjunction with omega-3 and in presence of omega-3 fatty acids such as DHA and EPA, produces a strong anti-inflammatory lipid mediator namely 18R-Resolvine. This compound affects the performance of polymorphonuclear leukocytes and prevents inflammation.

Also, aspirin plays a critical role in increasing the activity of stereoisomers via modulating COX2 activity [16]. Elkhouli et al. stated that omega 3 in conjunction with low dose aspirin as an adjunct decreased the inflammation, the mean pocket depth and CAL in patients with periodontitis [18].

To the best of our knowledge, no previous study has evaluated the efficacy of omega-3 in conjunction with low dose aspirin for chronic periodontitis in comparison with low dose doxycycline. Thus, the current study was conducted to assess the efficacy of adjunct treatment with low dose doxycycline in comparison with omega-3 associated with low dose aspirin in patients with chronic periodontitis.

Materials and Methods

This clinical trial (IRCT2013022511771N4) was conducted on 45 patients with mild to moderate chronic periodontitis (1-4mm CAL in at least 30% of the sites) selected among patients presenting to

the Periodontics Department of School of Dentistry Isfahan Khorasgan Islamic Azad University, Dental Branch in fall 2012. Sample size was calculated to be 15 subjects in each group using the formula:

$$n= \frac{(z_1+z_2)^2(2s^2)}{d^2}$$

Sampling was done during seven weeks in fall 2012. Follow up time for each patient was six weeks. All patients were briefed about the advantages and possible side effects of understudy medications based on previous studies and signed written informed consent forms. Patients had one week to decide on participating in the study and discussed it with their family members and physicians. Also, they were free to quit the study at any time.

The diagnosis of periodontitis was made based on the history, clinical examination and measurement of CAL using a periodontal probe by a periodontist. Patients with a systemic disease, those pregnant or nursing, those receiving any medication or having a history of antibiotic therapy in the past 6 months, patients allergic to antibiotics, those with a history of scaling or periodontal surgery in the past 6 months as well as smokers were excluded from the study. To match the oral hygiene practice of patients, selected subjects were physically healthy and in the age range of 25-45 years with a plaque index (PI) <30%. BOP, PPD, PI and CAL were calculated and recorded for each patient and the first phase of periodontal therapy namely scaling and root planning was done.

After oral hygiene instruction, each patient was allocated a code. Each group was randomly allocated 15 codes. Three groups of 15 subjects comprised the study population. Group one was given a 300mg Omega-3 tablet (Nature Made, Mission Hills, CA, USA) along with an 80mg aspirin tablet (Amin Pharmaceuticals, Isfahan, Iran) daily.

Group 2 was given a 20mg doxycycline capsule (Periostat, Alliance Pharma plc, Wiltshire UK) daily and group 3 (control) received a placebo tablet daily. The study had a double blind fashion and neither the patients nor the examiner were aware of the type of medications administered. After six weeks, the patients were evaluated by a clinician blinded to the group allocation of subjects and clinical parameters (BOP, PPD, CAL, PI) were recorded for them. Data were analyzed using Wilcoxon, paired t-test, Kruskal Wallis test and one-way ANOVA.

Results

ANOVA showed that the frequency distribution of gender was not significantly different in the three groups (p=0.91) (Table 1).

Table 1. The frequency distribution of gender in the three groups

Gender	Omega-3+aspirin	Doxycycline	Placebo
	Number (%)	Number (%)	Number (%)
Female	8 (53.3)	9 (60)	8 (53.3)
Male	7 (46.7)	6 (40)	7 (46.7)
Total	15 (100)	15 (100)	15 (100)

The mean age of subjects was 40.90±6.20, 40.20±4.37 and 38.6±4.42 years in the three groups of Omega-3+ aspirin, doxycycline and placebo, respectively. ANOVA found no significant difference in this respect among the three groups (p=0.44).

Wilcoxon test showed that the mean BOP decreased in the three groups after the intervention compared to the baseline values (p<0.001). The reduction in BOP in the placebo group was the lowest followed by doxycycline and the Omega-3+aspirin (the highest) groups. The Kruskal Wallis test showed that before the intervention, the mean BOP was not significantly different among the three groups (p=0.68).

However, after the intervention, the mean BOP in the three groups was significantly different (p<0.001). Also, the Mann Whitney test showed that after the intervention, the mean BOP in the Omega-3+aspirin group was less than that in the doxycycline group (p=0.09)(with an error rate of 10%, this value was significant) and this value in the doxycycline group was less than that in the placebo group (p=0.024) (Table 2).

Paired t-test demonstrated that in the three groups, the mean PPD after the intervention significantly improved compared to the baseline value

(p<0.001). However, the improvement in the placebo group was less than that in the doxycycline and Omega-3+aspirin groups. ANOVA showed that before the intervention, the mean PPD was not significantly different in the three groups (p=0.91). But, after the intervention, the mean PPD in the three groups was significantly different (p<0.006). LSD test revealed that after the intervention, the mean PPD was not significantly different between the Omega-3+aspirin and doxycycline groups (p=0.08). But, this value in the Omega-3+aspirin group was significantly more desirable than that in the placebo (p=0.002). The same difference was found between the doxycycline and placebo group (p=0.03) (Table 3).

Table 2. The mean BOP before and after the intervention in the three groups

Group	Before the intervention	After the intervention	P.V
	Mean± SD	Mean± SD	
Omega-3+ aspirin	2.2 (0.9)	0.98 (0.6)	< 0.001
Doxycycline	2.1 (0.8)	1.27 (0.9)	< 0.001
Placebo	2.3 (0.8)	1.59 (0.71)	< 0.001
P value	0.68	< 0.001	-

Table 3. The mean PPD before and after the intervention in the three groups

Group	Before the intervention	After the intervention	P.V
	Mean± SD	Mean± SD	
Omega-3+ aspirin	3.4 (0.78)	2.1 (0.88)	< 0.001
Doxycycline	3.46 (0.69)	2.43 (0.81)	< 0.001
Placebo	3.5 (0.46)	2.9 (0.7)	< 0.001
P value	0.91	< 0.006	-

Paired t-test showed that the mean CAL after the intervention significantly improved compared to the baseline values in the three groups (p<0.001). However, the improvement in the placebo group was smaller than that in the doxycycline group and the improvement in the latter group was smaller than that in the Omega-3+aspirin group. ANOVA showed that before the intervention, the mean CAL was not significantly different among the three groups (p=0.92). But, after the intervention, the mean CAL was significantly different among the three groups (p<0.001). LSD test showed that after the intervention, the mean CAL in the Omega-3+ aspirin group was less than that in the doxycycline (p=0.04) and the value in the latter was less than that in the placebo group (p=0.01) (Table 4).

Table 4. The mean CAL before and after the intervention in the three groups

Group	Before the intervention	After the intervention	P.V
	Mean± SD	Mean± SD	
Omega-3+ aspirin	2 (0.69)	0.89 (0.63)	< 0.001
Doxycycline	2.15 (0.75)	1.21 (0.89)	< 0.001
Placebo	2 (0.63)	1.59 (0.51)	< 0.001
P value	0.92	< 0.001	-

Discussion

Periodontal disease is a periodic, progressive disease associated with tissue destruction due to host response to bacterial antigens and stimuli. Host response to bacterial invasion in the form of subgingival plaque plays an important role in severity of disease. Host response to bacterial plaque is influenced by the genetic, systemic and environmental factors [19]. A wide range of host modulating medications are available affecting different aspects of host immunity response.

Scaling and plaque removal decrease the bacterial count while host modulators affect the host - bacteria interactions. It has been confirmed that tissue destruction, which is a clinical symptom of periodontitis, is due to the host response to microorganisms. HMT does not inhibit the inflammatory or defense mechanisms. It modulates excessive inflammatory response to allow wound healing and periodontal stability [20].

The therapeutic value of Omega-3 supplementation for decreasing alveolar bone loss is via reducing the activity of osteoclasts and decreasing gingival inflammation via its anti-inflammatory activity, which has been confirmed in several studies.

Omega-3 contains fatty acids such as arachidonic acid, DHA and EPA and is capable of producing anti-inflammatory mediators. Thus, it may be beneficial for treatment of periodontal and other

inflammatory diseases. These effects are similar to the effect of other host modulating medications like doxycycline with confirmed efficacy without the side effects of antibiotics [14, 15, 21-23]. The witnessed clinical improvement supports the role of aspirin in decreasing gingival inflammation, PPD and CAL and also as a specific modulating cytokine for enhanced periodontal wound healing. Thus, simultaneous use of Omega-3 and low dose aspirin has higher efficacy for periodontal disease. This finding has also been confirmed in some previous studies [18, 24].

At present, doxycycline is considered the gold standard of periodontal treatment. However, it has limitations such as increasing bacterial resistance, allergic reactions and photosensitivity. Also, to prevent relapse, doxycycline must be administered for long periods of time [25-27].

El-sharkawy et al, [24] in 2010 evaluated 80 patients with chronic periodontitis and used Omega-3 and low dose aspirin as an adjunct.

Evaluation of clinical parameters such as gingival index, PPD, BOP and CAL revealed that this adjunct treatment significantly improved the clinical parameters. Tuter et al [28]. Evaluated the effect of first phase of periodontal therapy with low dose doxycycline on chronic periodontitis and after six weeks, showed a significant improvement in gingival index and PPD in the test group compared to controls. Akalin et al, [29] in their study on 45 patients with chronic periodontitis evaluated the effect of systemic doxycycline and local doxycycline on clinical parameters and reported that after seven weeks, these medications significantly improved the clinical symptoms.

Elkhouli [18] discussed that Omega-3 in conjunction with low dose aspirin as an adjunct decreased inflammation, the mean PPD and CAL in periodontitis patients. The current study showed that use of Omega-3 along with low-dose aspirin compared to doxycycline, caused a greater reduction in BOP and more significantly improved CAL. But, Omega-3 and doxycycline were not different in improving the PPD and were equally effective for this purpose. Our findings are in accord with the results of above-mentioned studies. Both Omega-3 and doxycycline are effective in decreasing inflammatory mediators and by doing so improve clinical parameters. Thus, higher efficacy of Omega-3 along with low dose aspirin observed in the current study may be due to higher tendency of patients for regular intake of Omega-3 in comparison with doxycycline, and also the synergistic effects of Omega-3 and aspirin. Novak et al [30]. confiremd the satisfactory results of using sub-antibacterial doses of doxycycline as an adjunct for treatment of chronic periodontitis and reported that side effects such as photosensitivity limit the application of this drug. On the other hand, Omega-3 is taken by a large percentage of the population as a dietary supplement. Thus, in case of equal or higher efficacy of Omega-3 compared to that of doxycycline for modulating the host response in periodontal disease, it may be successfully used for prevention and treatment of periodontal disease.

Conclusion

Omega-3 may be more effective than doxycycline, the gold standard of periodontal treatment, for improving the clinical parameters in periodontitis patients and may help control the disease progression. However, our results were obtained after a 6-week course of treatment with Omega-3 and aspirin and the efficacy of Omega-3 treatment in shorter and longer courses must be evaluated and compared with that of doxycycline in this respect.

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